Clinical Study Protocol

A Multicenter, Randomized, Active-Controlled Study to Evaluate the Efficacy and Safety of EXPAREL When Administered via Infiltration into the Transversus Abdominis Plane versus Standard of Care in Subjects Undergoing Elective Cesarean Section (CHOICE)

Protocol No.: 402-C-414
EudraCT No.: Not applicable
IND No.: 069,198
Study Phase: 4
Study Drug: EXPAREL® (bupivacaine liposome injectable suspension)
Original Protocol Date: 16-Aug-2018
Amendment 1 Date: 15-Nov-2018
Amendment 2 Date: 07-Feb-2019
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, Active-Controlled Study to Evaluate the Efficacy and Safety of EXPAREL When Administered via Infiltration into the Transversus Abdominis Plane versus Standard of Care in Subjects Undergoing Elective Cesarean Section (CHOICE)

Principal investigator: To be determined

Study Center(s): Multicenter study in North America

Publications (Reference): None

Objectives:

Primary objective: To compare total opioid consumption through 72 hours following EXPAREL infiltration into the transversus abdominis plane (TAP) with standard of care (SOC) in subjects undergoing an elective cesarean section (C-section).

Secondary objective: To assess efficacy and safety parameters and participant satisfaction.

Methodology:

This is a Phase 4, multicenter, randomized, active-controlled study in approximately 182 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 should be started at least 24 hours prior to the day of surgery in order to ensure ample time for the subject to review the informed consent form (ICF) and have all her questions answered by the investigator/study staff prior to providing informed consent. Screening procedures that are 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 ICF is signed, medical history, surgical history, physical examination (according to the investigational site's SOC), 12-lead electrocardiogram, vital sign measurements, alcohol breath test and urine drug screen, and clinical laboratory tests (hematology and chemistry) will be performed. The Surgical Fear Questionnaire (SFQ) will be administered during screening.

Day of Surgery

***Pre-operative medications**:* Use of pre-operative analgesics (e.g., opioid medications, Tylenol® [acetaminophen], non-

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steroidal anti-inflammatory drugs [NSAIDs]) is prohibited.

On Day 1, prior to the C-section, pulse oximetry will be measured and eligible subjects will be randomized in a 1:1:1 ratio into one of the three treatment groups listed below:

- **Group 1:** 150 mcg Duramorph® (SOC arm). No EXPAREL TAP infiltration following skin-incision closure.

  Subjects randomized to Group 1 will receive an intrathecal injection of 150 mcg preservative-free morphine for spinal injection (e.g., Duramorph) in conjunction with single-shot spinal anesthesia using 1.4 to 1.6 mL bupivacaine hydrochloride (HCl) 0.75% and 15 mcg fentanyl. Postoperative pain management will follow the multimodal pain regimen as defined in this protocol..
- **Group 2:** 50 mcg Duramorph + EXPAREL TAP infiltration following skin-incision closure + postoperative multimodal pain regimen as defined in this protocol.

  Subjects randomized to Group 2 will receive an intrathecal injection of 50 mcg preservative-free morphine for spinal injection (e.g., Duramorph) in conjunction with single-shot spinal anesthesia using 1.4 to 1.6 mL bupivacaine HCl 0.75%. If deemed necessary by the investigator, intrathecal fentanyl can be given prior to incision for the C-section. If intrathecal fentanyl is used, the dose of 15 mcg fentanyl, date, and time of the usage must be recorded. In addition, Group 2 subjects will receive EXPAREL TAP infiltration following skin-incision closure plus postoperative multimodal pain regimen.
- **Group 3:** EXPAREL TAP infiltration following skin-incision closure + postoperative multimodal pain regimen as defined in this protocol. No Duramorph.

  Subjects randomized to Group 3 will NOT receive Duramorph as a spinal injection. This group will receive single-shot spinal anesthesia using 1.4 to 1.6 mL bupivacaine HCl 0.75%. If deemed necessary by the investigator, intrathecal fentanyl can be given prior to incision for the C-section. If intrathecal fentanyl is used, the dose of 15 mcg fentanyl, date, and time of the usage must be recorded. In addition, Group 3 subjects will receive EXPAREL TAP infiltration following skin-incision closure plus postoperative multimodal pain regimen.

In all treatment groups, 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.

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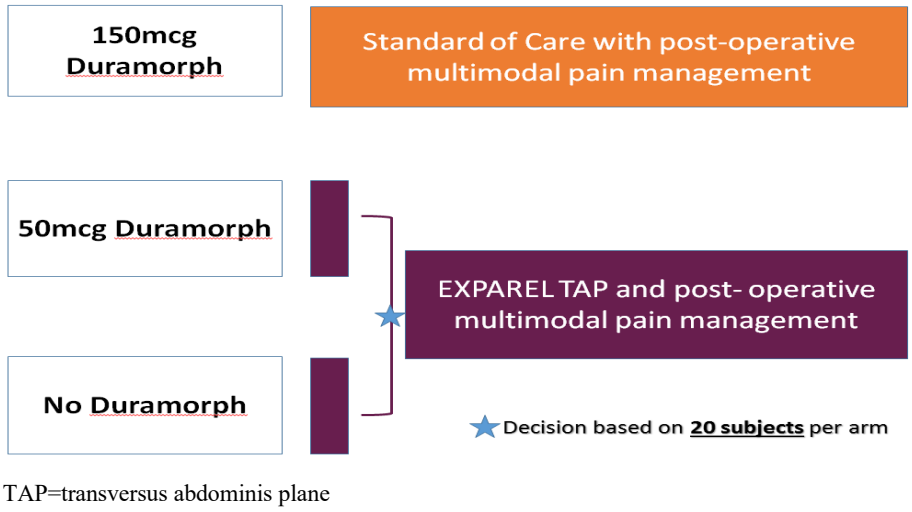
Study Schema



TAP=transversus abdominis plane

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

For Groups 2 and 3, 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 Pharmacy Binder), 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 image 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 (Groups 2 and 3): The TAP infiltration includes two steps: (1) TAP needle placement and saline hydrodissection and (2) study drug mixture infiltration into the TAP. Each step must be performed on 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.

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

The following multimodal pain regimens will be used for all treatment groups. The date, time, and dose of all standardized multimodal pain medications administered must be recorded.

All Subjects in Groups 1, 2, and 3:

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

- Intravenous (IV) ketorolac 30 mg (1 dose)
- IV acetaminophen 1000 mg (1 dose)

Beginning 6 hours after skin-incision closure:

- IV ketorolac 30 mg beginning 6 hours from the administration of IV ketorolac at the time of skin-incision closure and then every 6 hours (q6h) for the next 18 hours (i.e., total of 120 mg as four 30-mg doses over first 24 hours from the time of skin-incision closure)
- IV acetaminophen 1000 mg beginning 6 hours from the administration of IV acetaminophen at the time of skin-incision closure and then every 6 hours (q6h) for the next 18 hours (i.e., total of 4000 mg as four 1000-mg doses over first 24 hours from the time of skin-incision closure)
- Scheduled oral (PO) Tylenol® (acetaminophen) 975 mg beginning 6 hours from the administration of the last dose of IV acetaminophen and q6h for up to 72 hours or hospital discharge (whichever occurs first)
- Scheduled PO ibuprofen 600 mg beginning 6 hours from the administration of the last dose of IV ketorolac and then q6h for up to 72 hours or hospital discharge (whichever occurs first)

This multimodal 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 till hospital discharge.

Rescue Medication**:** When breakthrough pain occurs, the study staff or the floor nurses on duty will need to ensure that the study subject is strictly following the protocol-specific multimodal pain regimen schedule (q6h as defined in the protocol) before considering the use of the opioids as a rescue, especially in cases where the visual analog scale (VAS) score is relatively low. Subjects should receive opioid rescue pain medication only upon request for breakthrough pain.

Postsurgical rescue medication will comprise PO immediate-release oxycodone (initiated at 5 mg as needed [PRN]). If the 5 mg oxycodone is not sufficient for pain management, subject can receive a dose of 10 mg PRN. If a subject is unable to tolerate PO medication or fails the PO oxycodone rescue, IV morphine (initiated at 1 to 2 mg) or hydromorphone (initiated at 0.3 to 0.5 mg) may be administered 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 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 adverse events (AEs) of medications include the following (to 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

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- Metoclopramide 10 mg PO PRN for nausea and vomiting
- Nalbuphine IV 2.5 mg PRN for pruritus
- Naloxone IV 50 to 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
  - -Total opioid burden
  - -Time to first opioid use
- Date and time of first unassisted ambulation
- Pain intensity scores using a 10 cm VAS (see Appendix 1) at rest (general and site of injection)
- Discharge readiness (see Appendix 2)
- Opioid Related Symptom Distress scale (ORSDS; see Appendix 7)
- Date and time to first bowel movement
- Itching using Numeric Rating Scale (NRS) of 0 to 10 (see Appendix 10)
- Subject's satisfaction with postsurgical pain control (see Appendix 3)
- Recovery from Cesarean Section scale (RCSS; see Appendix 4)
- Calls to physician about pain (see Appendix 8)
- Total time in post-anesthesia care unit (PACU)
- Persistent opioid use at Day 30 (see Appendix 9)
- Emergency department visits

While in the hospital, subjects will be provided with an electronic patient-reported outcome (ePRO) device and will use the device 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 in general?" and "How much pain are you experiencing at the site of the incision"; 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 device, which the subjects will take home with them to continue to record study assessments at home.

At hospital discharge, the subject will be instructed to record in the device their daily pain intensity score (VAS) 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 worst pain at rest in the prior 24 hours by assessing "What was your worst pain since your last pain assessment?" (i.e., 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. AEs 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. On Day 30, a phone call will be made to ask the subjects about persistent opioid use.

Number of Subjects (Planned): Approximately 182 subjects are planned for enrollment into the study. Subjects who are withdrawn or discontinued prior to completing the study may be replaced.

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Eligibility Criteria:

Note: Based on the World Health Organization (WHO) Guidance: Breastfeeding and Maternal Medication, Recommendations for Drugs in the Eleventh WHO Model List of Essential Drugs, bupivacaine is compatible with breastfeeding; 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 Anesthesiologists 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 (e.g., multiple gestations, pregnancy resulting from in vitro fertilization, end-term prolonged bed rest required for medical reasons)
2. Subjects with an unstable pregnancy-induced medical condition or complication (e.g., gestational diabetes, hypertension, pre-eclampsia, chorioamnionitis)
3. Subjects with 3 or more prior C-sections (a subject is eligible if the index C-section is the third case for that subject)
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 (e.g., 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 (for example, serum creatinine level >2 mg/dL [176.8 µmol/L], blood urea nitrogen level >50 mg/dL [17.9 mmol/L], serum aspartate aminotransferase level >3 times the upper limit of normal [ULN], or serum alanine aminotransferase 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

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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 (e.g., 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 0.5% (Groups 2 and 3)

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

Dosage: See Pharmacy Binder

Lot Number: To be determined

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

Name: Duramorph® (150 mcg); Institutional site SOC

Duration of Subject Participation in Study:

Participation will begin upon signing of the ICF. No more than 30 days should pass between signing the ICF and surgery. The time from study drug administration through the end of participation is 30 ± 3 days. Therefore, each subject may participate in the study for a maximum of 66 days.

Efficacy Assessments:

The following efficacy measurements will be performed at the times specified after closure of the C-section skin incision:

- Date and time of administration, and amount of all postsurgical opioid rescue medication taken through Day 14
- Pain intensity scores at rest (general and at incision site) using a 10 cm VAS at 12, 24, 48, and 72 hours after surgery (see Appendix 1) and then once daily (at noon ± 4 hours) through Day 14

  Note 1: For pain intensity scores at 12, 24, 48, or 72 hours, if the subject is sleeping, do not wake her to assess pain. If she awakens within the assessment window (i.e., 1 hour for the 12- and 24-hour assessments, 2 hours for the 48-hour assessments, and 4 hours for the 72-hour assessments), a pain score may be collected then.

  Note 2: An unscheduled VAS score is also required immediately prior to administration of any rescue medication while in the hospital.

  Note 3: If a subject is discharged prior to any of the scheduled VAS assessments to be collected at 12 to 72 hours after surgery, a member of the study site staff will telephone the subject at the appropriate scheduled times (i.e., the time of each assessment scheduled to be collected that occurs after hospital discharge) to remind her to complete the VAS and to record the scheduled assessments in the ePRO device. This will ensure that, for any subjects 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.
- Total time in PACU
- Date and time of first unassisted ambulation

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- Date and time to first bowel movement
- Itching using an NRS of 0 to 10 (see Appendix 10)
- SFQ at screening (see Appendix 6)
- ORSDS questionnaire at 24, 48, and 72 hours after surgery (see Appendix 7)
- Subject satisfaction with postsurgical pain control using a 5-point Likert scale (see Appendix 3)
- RCSS at 24, 48, and 72 hours or at hospital discharge, whichever occurs first (see Appendix 4)
- Discharge readiness at 24, 48, and 72 hours, or at hospital discharge, or until the subject attains a score of 9, whichever occurs first (see Appendix 2)
- Unscheduled phone calls or office visits related to pain after discharge through Day 14
- Persistent opioid use at Day 30 (see Appendix 9)

Efficacy Endpoints:

Primary Efficacy Endpoint:

- Total postsurgical opioid consumption in morphine equivalents through 72 hours or hospital discharge

Secondary Efficacy Endpoints:

- Time to first postsurgical opioid rescue medication
- Percentage of opioid-free subjects through 72 hours or hospital discharge
- Incidence and severity of itching (NRS of 0 to 10)
- ORSDS at 24, 48, and 72 hours after surgery
- The VAS pain, general and at incision site (at rest), through 72 hours or hospital discharge prior to any physical therapy or physical activity/mobilization
- Proportion of subjects discharge-ready at 24, 48, and 72 hours, or at hospital discharge, or until the subject attains a score of 9, whichever occurs first
- Overall assessment of subject's satisfaction with pain control at 72 hours or at hospital discharge, whichever occurs first
- Integrated rank assessment using the VAS pain intensity score (at rest) and the total amount of postsurgical opioids consumed through 72 hours or hospital discharge

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

- Total opioid use from 72 hrs to Day 14
- Time to and date of first unassisted ambulation
- Length of hospital stay
- Number of unscheduled phone calls or office visits related to pain from discharge through Day 14
- Emergency department visits
- Persistent opioid use at Day 30

Safety Assessments:

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

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signs (blood pressure, heart rate, respiratory rate, and temperature) and pulse oximetry will be monitored and recorded.

Safety Endpoints:

Incidence of treatment-emergent AEs and SAEs will be assessed from 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 and safety endpoint analyses will be described in the SAP.

Determination of Sample Size:

Assuming a log-normal distribution for total opioid consumption with a 70% coefficient of variation, 5% alpha, an equal randomization ratio, and 80% power, a total of 77 subjects per treatment group will be sufficient to detect a 25% reduction in total opioid consumption. Assuming 5% of the subjects are not evaluable and one of the two EXPAREL groups will be dropped after interim analysis when a total of 60 subjects are treated, a total sample size of approximately 182 treated subjects is needed. This sample size will be re-evaluated after the interim analysis.

After approximately 20 subjects per treatment group are randomized and treated (i.e., a total of 60 patients are treated in this study), an interim analysis will be conducted to evaluate and compare the clinical efficacy/safety and health economics benefits between the two EXPAREL groups against the SOC control group. The primary purpose of this interim analysis is to select one EXPAREL treatment group out of the two EXPAREL treatment groups to continue for the rest of this study. The second purpose of this interim analysis is to evaluate the sample size assumptions and the selection of the primary/secondary endpoints. Full details on the planned or additional interim analysis will be covered in a prospective interim analysis plan.

Table 1. Assessment Schedule (Screening through 72 hours after Surgery)

Study Procedure	Within 30 days of scheduled surgery	Screening (up to 30 days prior to day of surgery)	Day 1			Hours after Surgery		
			OR	PACU	12 hr (± 1hr)	24 hr (± 1hr)	48 hr (± 2hr)	72 hr (± 4hr)
Explain study purpose and procedures; obtain signed ICF	X[1]	X[1]						
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, heart rate, respiratory rate, and temperature)		X[2]	X	X[11]		X	X	X[3]
Measure pulse oximetry per SOC[10]			←	———	→			
Physical examination (according to the investigational site's SOC)		X	X					
Drug screen/alcohol test		X						
Clinical laboratory tests (hematology and chemistry; Appendix 5)[4]		X						
12-lead electrocardiogram		X						
Explain ePRO device and expectations of the subject regarding the device		X						
Randomize subject and prepare study drug			X					
Administer intrathecal preservative-free morphine injection in conjunction with single-shot spinal anesthesia per the treatment group (Section 13.4)			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 (**per the treatment group)**				X				
Capture ultrasound image or video of the TAP needle placement after saline hydrodissection				X				
Perform 2-point classic TAP infiltration no more than 90 min after skin-incision closure of the C-section (**per the treatment group)**				X				
Take ultrasound image 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 opioid medications administered and doses			X					

Study Procedure	Within 30 days of scheduled surgery	Screening (up to 30 days prior to day of surgery)	Day 1			Hours after Surgery		
			OR	PACU	12 hr (± 1hr)	24 hr (± 1hr)	48 hr (± 2hr)	72 hr (± 4hr)
Record date, time in and out of the PACU				X				
Record SFQ (Appendix 6)		X						
Record **scheduled** 10 cm VAS pain intensity scores (General and Site of Incision) at rest through ePRO[5,6,7] (Appendix 1)					X	X	X	X
Record 10 cm VAS pain intensity (through ePRO) **immediately prior to any postsurgical opioid medication** administered while in the hospital (Appendix 1)				X	X	X	X	X
Record date, time, and dose of all postsurgical pain medication[8]				X	X	X	X	X
Record date, time, and dose of all standardized multimodal pain medications administered				X	X	X	X	X
Record date and time of first unassisted ambulation				X	X	X	X	X
Record date and time of first bowel movement				X	X	X	X	X
Assess itching (Numeric Rating Scale of 0 to 10)		X		X[11]	X	X	X	X
Record overall rating of subject's satisfaction with postsurgical pain control through ePRO (Appendix 3)								X[3]
Record RCSS through ePRO (Appendix 4)						X	X	X[3]
Record ORSDS through ePRO (Appendix 7)						X	X	X
Assess discharge readiness[9] (Appendix 2)						X	X	X
Record concomitant medications for treatment of AEs		X	X	X	X	X	X	X
Record AEs/SAEs (starting at signing of ICF)		X	X	X	X	X	X	X

1. 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 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.
2. Vital signs at screening will include height, weight, blood pressure, heart rate, respiratory rate, and temperature.
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 SOC, including direct bilirubin; either gamma-glutamyl transpeptidase and lactate dehydrogenase or alanine transaminase and aspartate transaminase; and either serum creatinine or blood urea nitrogen.
5. To assess pain intensity (VAS) general and at incision site 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. This assessment should not be completed immediately following assessment of ambulation.
6. If a subject is discharged prior to any of the scheduled VAS assessments (general and at incision site) to be collected at 12 to 72 hours after surgery, a member of the study site staff will contact the subject at the appropriate scheduled times (i.e., the time of each assessment scheduled to be collected that occurs after hospital discharge) to remind her to complete the VAS and ORSDS assessments and to record the scheduled assessments in the device. This will ensure that, for any subject discharged prior to 72 hours, all VAS and ORSDS assessments required for calculation of the study endpoints are captured. These phone calls will only be made if a subject is discharged prior to 72 hours.

Study Procedure	Within 30 days of scheduled surgery	Screening (up to 30 days prior to day of surgery)	Day 1			Hours after Surgery		
			OR	PACU	12 hr (± 1hr)	24 hr (± 1hr)	48 hr (± 2hr)	72 hr (± 4hr)

7. For pain intensity scores at 12, 24, 48, or 72 hours, if the subject is sleeping, do not wake her to assess pain. If she awakens within the assessment window (i.e., 1 hour for the 12- and 24-hour assessments, 2 hours for the 48-hour assessments, and 4 hours for the 72-hour assessments), a pain score may be collected then.
8. Subjects should only receive opioid pain medication (e.g., morphine, hydromorphone [Dilaudid], oxycodone) upon request for breakthrough pain.
9. Discharge readiness will be assessed at 24, 48, and 72 hours, or hospital discharge, or until the subject attains score of 9, whichever occurs first.
10. Pulse oximetry measured once prior to surgery and per your site's SOC from surgery end up to 24 hours.
11. Assess vital signs (blood pressure, heart rate, respiratory rate, and temperature) and itching in PACU prior to PACU discharge.

Note: No more than 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 skin-incision closure of the C-section wound (following delivery and prior to TAP infiltration).

AE=adverse event; C-section=cesarean section; ePRO=electronic patient-reported outcome; hr=hour(s); ICF=informed consent form; OR=operating room; ORSDS=Opioid Related Symptom Distress scale; PACU=post-anesthesia care unit; RCSS=Recovery from Cesarean Section scale; SAE=serious adverse event; SFQ=Surgical Fear Questionnaire; SOC=standard of care; TAP= transversus abdominis plane; VAS=visual analog scale

Table 2. Assessment Schedule (Hospital Discharge through Day 30)

Study Procedure	Hospital Discharge	Day 14 (±3 d) Call	Day 30 (±3 d) Call
Measure vital signs (blood pressure, heart rate, respiratory rate, and temperature)	X[1]		
Provide the ePRO device, addressed and stamped packaging material, and instructions for use	X		
Record **scheduled** 10 cm VAS pain intensity scores (general and site of incision) at rest through ePRO (Appendix 1)	X		
Record date, time, and dose of all standardized postsurgical pain medication through ePRO[4]	⟷	⟷	
Record date, time, and dose of all standardized multimodal pain medications administered	X		
Record overall rating of subject's satisfaction with postsurgical pain control through ePRO (Appendix 3)	X[1]		
Record RCSS[3] through ePRO (Appendix 4)	X[1]		
Assess discharge readiness[2] (Appendix 2)	X[1]		
Record date and time of hospital discharge	X		
Record persistent opioid use (see Appendix 9)			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 (Appendix 8)		X	
Remind subject to return the ePRO device in the provided addressed and stamped packaging material		X	
Record concomitant medications for treatment of AEs	X	X	
Record AEs/SAEs (starting at signing of ICF)	X	X	

1. At 72 hours postsurgery or prior to hospital discharge, whichever occurs first.
2. Discharge readiness will be assessed at 24, 48, and 72 hours, or hospital discharge, or until the subject attains score of 9, whichever occurs first.
3. RCSS at 24, 48, and 72 hours or at hospital discharge, whichever occurs first (see Appendix 4)
4. Following hospital discharge, the subject will record her daily use of pain medication, if any, in the ePRO.

Note: The end of surgery is defined as the time of skin-closure of the C-section wound (following delivery and prior to TAP infiltration).

AE=adverse event; C-section=cesarean section; d=day; ePRO=electronic patient-reported outcome; ICF=informed consent form; ORSDS=Opioid Related Symptom Distress scale; RCSS=Recovery from Cesarean Section scale; SAE=serious adverse event; VAS=visual analog scale

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4. LIST OF ACRONYMS/ABBREVIATIONS

AE	Adverse event
CFR	Code of Federal Regulations
CRF	Case report form
CSE	Combined spinal epidural
C-section	Cesarean section
d	Day
ePRO	Electronic patient-reported outcome
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCl	Hydrochloride
hr	Hour(s)
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
MMT	Multi-modal therapy
NRS	Numeric rating scale
NSAIDs	Non-steroidal anti-inflammatory drugs
q6h	Every 6 hours
OR	Operating room
ORSDS	Opioid Related Symptom Distress scale
PACU	Post-anesthesia care unit
PO	Oral
PRN	As needed
RCSS	Recovery from Cesarean Section scale
SAE	Serious adverse event
SAP	Statistical analysis plan
SFQ	Surgical Fear Questionnaire
SOC	Standard of care
TAP	Transversus abdominis plane
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
VAS	Visual analog scale
WHO	World Health Organization

5. ETHICS

5.1. Institutional Review Board/Independent Ethics Committee

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

5.2. Ethical Conduct of the Study

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

5.3. Subject Information and Consent

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

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

Effective postsurgical pain control is a critical element in 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 events (AEs), 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 the US 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 [PO] intake, etc.), and conserve healthcare resources. As such, the Joint Commission on Accreditation of Healthcare Organizations requires that all healthcare facilities practice adequate pain management and monitor opioid-related AEs (Apfelbaum 2003).

Opioid analgesics have long been established to be the most effective agents used for the management of moderate to severe 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. AEs related to opioid administration (e.g., nausea, vomiting, ileus, confusion); however, represent one important reason that there is a need to develop opioid-sparing strategies. Indeed, fear of gastrointestinal

AEs, 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 AEs often requires medical attention (e.g., opioid antagonists, antiemetic agents) and increased pharmacy/nursing time, which may raise healthcare expenses (Carroll 1994).

7.3. EXPAREL (Bupivacaine Liposome Injectable Suspension)

Bupivacaine is one of the longer-acting local anesthetics; however, it has a limited duration of action after local administration, usually 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.

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 hydrochloride [HCl]) administered by various routes: local infiltration into the surgical site, subcutaneous, perineural (or nerve block), and epidural. EXPAREL has been generally well tolerated and, in active comparator studies, AEs occurred at a similar rate as the corresponding bupivacaine HCl controls.

EXPAREL was initially approved by the US FDA in 2011 for single-dose administration into the surgical site to produce postsurgical analgesia. The indication was amended and approved by the US FDA in 2018 to read: "EXPAREL is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus block to produce postsurgical regional analgesia." Since its approval, EXPAREL has been administered to over 4 million patients in the US.

Following the initial approval of EXPAREL, numerous clinical studies were conducted in which EXPAREL was administered via various routes of administration, including infiltration into the transversus abdominis plane (TAP) (Sternlicht 2014, Feierman 2014).

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

8. OBJECTIVES

8.1. Primary Objective

To compare total opioid consumption through 72 hours following EXPAREL infiltration into the TAP with standard of care (SOC) in subjects undergoing an elective cesarean section (C-section).

8.2. Secondary Objectives

To assess efficacy and safety parameters and participant satisfaction.

9. OVERALL STUDY DESIGN AND PLAN

9.1. Study Design

This is a Phase 4, multicenter, randomized, active-controlled study in approximately 182 adult subjects. Subjects who are withdrawn or discontinued prior to completing the study may be replaced.

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 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 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 ICF is signed, medical history, surgical history, physical examination (according to the investigational site's SOC), 12-lead electrocardiogram, vital sign measurements, alcohol breath test and urine drug screen, and clinical laboratory tests (hematology and chemistry) will be performed. The Surgical Fear Questionnaire (SFQ) will be administered during screening.

Day of Surgery

Pre-operative medications: Use of pre-operative analgesics (e.g., opioid medications, Tylenol® (acetaminophen), non-steroidal anti-inflammatory drugs [NSAIDs]) is prohibited.

On Day 1, prior to the C-section, pulse oximetry will be measured and eligible subjects will be randomized in a 1:1:1 ratio into one of the three treatment groups listed below:

- **Group 1:** 150 mcg Duramorph® (SOC arm). No EXPAREL TAP infiltration following skin-incision closure.
  Subjects randomized to Group 1 will receive an intrathecal injection of 150 mcg preservative-free morphine for spinal injection (e.g., Duramorph) in conjunction with

single-shot spinal anesthesia using 1.4 to 1.6 mL bupivacaine HCl 0.75% and 15 mcg fentanyl. Postoperative pain management will follow the multimodal pain regimen as defined in this protocol.

- **Group 2:** 50 mcg Duramorph + EXPAREL TAP infiltration following skin-incision closure + postoperative multimodal pain regimen as defined in this protocol.
  Subjects randomized to Group 2 will receive an intrathecal injection of 50 mcg preservative-free morphine for spinal injection (e.g., Duramorph) in conjunction with single-shot spinal anesthesia using 1.4 to 1.6 mL bupivacaine HCl 0.75%. If deemed necessary by the investigator, intrathecal fentanyl can be given prior to incision for the C-section. If intrathecal fentanyl is used, the dose of 15 mcg fentanyl, date, and time of the usage must be recorded. In addition, Group 2 subjects will receive EXPAREL TAP infiltration following skin-incision closure plus postoperative multimodal pain regimen.
- **Group 3:** EXPAREL TAP infiltration following skin-incision closure + postoperative multimodal pain regimen as defined in this protocol. No Duramorph.
  Subjects randomized to Group 3 will NOT receive Duramorph as a spinal injection. This group will receive single-shot spinal anesthesia using 1.4 to 1.6 mL bupivacaine HCl 0.75%. If deemed necessary by the investigator, intrathecal fentanyl can be given prior to incision for the C-section. If intrathecal fentanyl is used, the dose of 15 mcg fentanyl, date, and time of the usage must be recorded. In addition, Group 3 subjects will receive EXPAREL TAP infiltration following skin-incision closure plus postoperative multimodal pain regimen.

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

For Groups 2 and 3, 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 Pharmacy Binder), 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 image 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 (Groups 2 and 3): The TAP infiltration includes two steps: (1) TAP needle placement and saline hydrodissection and (2) study drug mixture infiltration into the TAP. Each step must be performed on 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.

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

The following multimodal pain regimens will be used for all treatment groups. The date, time, and dose of all standardized multimodal pain medications administered must be recorded.

All Subjects in Groups 1, 2, and 3:

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

- Intravenous (IV) ketorolac 30 mg (1 dose)
- IV acetaminophen 1000 mg (1 dose)

Beginning 6 hours after skin-incision closure:

- IV ketorolac 30 mg beginning 6 hours from the administration of IV ketorolac at the time of skin-incision closure and then every 6 hours (q6h) for the next 18 hours (i.e., total of 120 mg as four 30-mg doses over first 24 hours from the time of skin-incision closure)
- IV acetaminophen 1000 mg beginning 6 hours from the administration of IV acetaminophen at the time of skin-incision closure and then every 6 hours (q6h) for the next 18 hours (i.e., total of 4000 mg as four 1000-mg doses over first 24 hours from the time of skin-incision closure)
- Scheduled PO Tylenol® (acetaminophen) 975 mg beginning 6 hours from the administration of the last dose of IV acetaminophen and q6h for up to 72 hours or hospital discharge (whichever occurs first)
- Scheduled PO ibuprofen 600 mg beginning 6 hours from the administration of the last dose of IV ketorolac and then q6h for up to 72 hours or hospital discharge (whichever occurs first)

This multimodal 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 till hospital discharge.

Rescue Medication**:** When breakthrough pain occurs, the study staff or the floor nurses on duty will need to ensure that the study subject is strictly following the protocol-specific multimodal pain regimen schedule (q6h as defined in the protocol) before considering the use of the opioids as a rescue, especially in cases where the visual analog scale (VAS) score is relatively low. Subjects should receive opioid rescue pain medication only upon request for breakthrough pain.

Postsurgical rescue medication will comprise PO immediate-release oxycodone (initiated at 5 mg as needed [PRN]). If the 5 mg oxycodone is not sufficient for pain management, subject

can receive a dose of 10 mg 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 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 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 AEs of medications include the following (to 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 to 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
  -total opioid burden
  -time to first opioid use
- Date and time of first unassisted ambulation
- Pain intensity scores using a 10 cm VAS (see Appendix 1) at rest (general and site of injection)
- Discharge readiness (see Appendix 2)
- Opioid Related Symptom Distress scale (ORSDS; see Appendix 7)
- Date and time to first bowel movement
- Itching using Numeric Rating Scale (NRS) of 0 to 10 (see Appendix 10)
- Subject's satisfaction with postsurgical pain control (see Appendix 3)
- Recovery from Cesarean Section scale (RCSS; see Appendix 4)
- Calls to physician about pain (see Appendix 8)
- Total time in post-anesthesia care unit (PACU)
- Persistent opioid use at Day 30 (see Appendix 9)
- Emergency department visits

While in the hospital, subjects will be provided with an electronic patient-reported outcome (ePRO) device and will use the device 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 in general?" and "How much pain are you experiencing at the site of the incision", 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 device, which the subjects will take home with them to continue to record study assessments at home.

At hospital discharge, the subject will be instructed to record in the device their daily pain intensity score (VAS) 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 worst pain at rest in the prior 24 hours by assessing "What was your worst pain since your last pain assessment?" (i.e., 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 made any unscheduled phone calls or office visits related to pain, experienced any hospital readmission, or experienced an emergency room visit since hospital discharge. AEs 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. On Day 30, a phone call will be made to ask the subjects about persistent opioid use.

9.1.1. Duration of the Study and Subject Participation

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

9.1.2. Study Stopping Rules

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

The Pacira Medical Monitor and Pharmacovigilance team review all SAEs reported from Pacira clinical studies on an ongoing basis and in real time (i.e., as the events are reported). The Medical Monitor is responsible for temporarily 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 performed. 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 indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia.

This Phase 4, multicenter, randomized active-controlled study will evaluate the efficacy and safety of EXPAREL+bupivacaine infiltration into the TAP compared to the active SOC in subjects undergoing elective C-section.

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 SOC 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 AEs. In some cases, such an approach may also reduce the average length of hospital stay (Elvir-Lazo 2010).

In addition, the dose-response relationship of intrathecal morphine for multimodal post-cesarean analgesia suggests that 50 mcg produces analgesia similar to that produced by either 100 mcg or 150 mcg (Berger 2016), which provides the scientific support for the current study design.

EXPAREL (liposomal bupivacaine injectable suspension) 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 block 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 (WHO) Guidance: Breastfeeding and Maternal Medication, Recommendations for Drugs in the Eleventh WHO Model List of Essential Drugs (WHO 2002), bupivacaine is compatible with breastfeeding; 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. American Society of Anesthesiologists 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 (e.g., multiple gestations, pregnancy resulting from in vitro fertilization, end-term prolonged bed rest required for medical reasons)
2. Subjects with an unstable pregnancy-induced medical condition or complication (e.g., gestational diabetes, hypertension, pre-eclampsia, chorioamnionitis)
3. Subjects with 3 or more prior C-sections (subject is eligible if the index C-section is the third case for that subject)
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 (e.g., 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 (for example, serum creatinine level >2 mg/dL [176.8 µmol/L], blood urea nitrogen level >50 mg/dL [17.9 mmol/L], serum aspartate transaminase level >3 times the upper limit of normal [ULN], or serum alanine transaminase 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 (e.g., 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 (e.g., excessive bleeding, acute sepsis), the subject should be withdrawn from the 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 device 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 AEs will receive appropriate treatment at the discretion of the investigator until resolution of the AE.

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 the 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 device 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 three treatment groups in this study. On Day 1, prior to the C-section, eligible subjects will be randomized in a 1:1:1 ratio into one of the three treatment groups listed below:

- **Group 1:** 150 mcg Duramorph® (SOC arm). No EXPAREL TAP infiltration following skin-incision closure.
  Subjects randomized to Group 1 will receive an intrathecal injection of 150 mcg preservative-free morphine for spinal injection (e.g., Duramorph) in conjunction with single-shot spinal anesthesia using 1.4 to 1.6 mL bupivacaine HCl 0.75% and 15 mcg fentanyl. Postoperative pain management will follow the multimodal pain regimen as defined in this protocol.
- **Group 2:** 50 mcg Duramorph + EXPAREL TAP infiltration following skin-incision closure + postoperative multimodal pain regimen as defined in this protocol.
  Subjects randomized to Group 2 will receive an intrathecal injection of 50 mcg preservative-free morphine for spinal injection (e.g., Duramorph) in conjunction with single-shot spinal anesthesia using 1.4 to 1.6 mL bupivacaine HCl 0.75%. If deemed necessary by the investigator, intrathecal fentanyl can be given prior to incision for the C-section. If intrathecal fentanyl is used, the dose of 15 mcg fentanyl, date and time of the usage must be recorded. In addition, Group 2 subjects will receive EXPAREL TAP infiltration following skin-incision closure plus postoperative multimodal pain regimen.
- **Group 3:** EXPAREL TAP infiltration following skin-incision closure + postoperative multimodal pain regimen as defined in this protocol. No Duramorph.
  Subjects randomized to Group 3 will NOT receive Duramorph as a spinal injection. This group will receive single-shot spinal anesthesia using 1.4 to 1.6 mL bupivacaine HCl 0.75%. If deemed necessary by the investigator, intrathecal fentanyl can be given prior to incision for the C-section. If intrathecal fentanyl is used, the dose of 15 mcg fentanyl, date and time of the usage must be recorded. In addition, Group 3 subjects will receive EXPAREL TAP infiltration following skin-incision closure plus postoperative multimodal pain regimen.

In all treatment groups, 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.

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

For Groups 2 and 3, 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 Pharmacy Binder), 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 image 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 (Groups 2 and 3): The TAP infiltration includes two steps: (1) TAP needle placement and saline hydrodissection and (2) study drug mixture infiltration into the TAP. Each step must be performed on 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.

11.1.1. 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 (as specified in the Pharmacy Binder) 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.

The maximum dosage of EXPAREL should not exceed 266 mg.

11.1.2. Intrathecal Morphine Administration Considerations

The most serious adverse effects encountered during administration of intrathecal morphine/hydromorphone are respiratory depression and/or respiratory arrest, which 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 therapy is being initiated.

Intrathecal morphine 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 (DepoFoam drug delivery system). Bupivacaine is present at a nominal concentration of 13.3 mg/mL. For the purpose 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 at 2°C to 8°C (36°F to 46°F).

11.2.2. Description of Reference Product

Duramorph® (150 mcg): Institutional site SOC.

11.3. Method of Assigning Subjects to Treatment

11.3.1. Randomization Scheme

This is an open-label study. Subjects will be randomized in a 1:1:1 ratio into one of three treatment groups. 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 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 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 (e.g., Duramorph) is commonly used during C-section, usually at a dose between 0.1 mg and 0.2 mg. 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 AEs, such as nausea and vomiting (which may increase with a higher dose). The study dose of 0.15 mg (150 mcg) of intrathecal morphine is also supported by a recent dose-finding study that sought to determine the effective analgesic dose for 90% of patients for both intrathecal morphine and hydromorphone in patient undergoing C-section (Sviggum 2016).

11.5. Prior and Concomitant Therapy and Medications

11.5.1. 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) within 3 days, or Tylenol® (acetaminophen) or any opioid medication within 24 hours.

11.5.2. Restricted Therapy and Medications During Surgery

As described in the EXPAREL Full Prescribing Information (2018), no agents are to be admixed with EXPAREL (e.g., 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 should not be allowed to come in contact with each other (e.g., the area must be dry before EXPAREL is administered). Upon discovering use of any prohibited therapy and/or medication during or after surgery, the investigator should document all events that led to the deviation, write a note to file, and notify the Pacira Medical Monitor accordingly.

11.5.3. Permitted Therapy or Medications after Surgery

Patient-controlled analgesia is not permitted.

The following multimodal pain regimens will be used for all treatment groups. The date, time, and dose of all standardized multimodal pain medications administered must be recorded.

All Patients in Groups 1, 2, and 3:

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

- Intravenous (IV) ketorolac 30 mg (1 dose)
- IV acetaminophen 1000 mg (1 dose)

Beginning 6 hours after skin-incision closure:

- IV ketorolac 30 mg beginning 6 hours from the administration of IV ketorolac at the time of skin-incision closure and then every 6 hours (q6h) for the next 18 hours (i.e., total of 120 mg as four 30-mg doses over first 24 hours from the time of skin-incision closure)
- IV acetaminophen 1000 mg beginning 6 hours from the administration of IV acetaminophen at the time of skin-incision closure and then every 6 hours (q6h) for the next 18 hours (i.e., total of 4000 mg as four 1000-mg doses over first 24 hours from the time of skin-incision closure)
- Scheduled PO Tylenol® (acetaminophen) 975 mg beginning 6 hours from the administration of the last dose of IV acetaminophen and q6h for up to 72 hours or hospital discharge (whichever occurs first)
- Scheduled PO ibuprofen 600 mg beginning 6 hours from the administration of the last dose of IV ketorolac and then q6h for up to 72 hours or hospital discharge (whichever occurs first)

This multimodal 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 till hospital discharge.

***Rescue Medication*:** When breakthrough pain occurs, the study staff or the floor nurses on duty will need to ensure that the study subject is strictly following the protocol-specific multimodal pain regimen schedule (q6h as defined in the protocol) before considering the use of the opioids as a rescue. Subjects should receive opioid rescue pain medication only upon request for breakthrough pain.

Postsurgical rescue medication will comprise PO immediate-release oxycodone (initiated at 5 mg PRN). If a subject is unable to tolerate PO medication or fails the PO oxycodone rescue, IV morphine (initiated at 1 to 2 mg) or hydromorphone (initiated at 0.3 to 0.5 mg) may be administered PRN. If the 5 mg oxycodone is not sufficient for pain management, subject can receive a dose of 10 mg PRN. If a subject is unable to tolerate PO medication or fails the PO oxycodone rescue, IV morphine (initiated at 1to 2 mg) or hydromorphone (initiated at 0.3 to 0.5 mg) may be administered 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 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 AEs of medications include the following (to 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 to 100 mcg PRN for pruritus

11.6. Treatment Compliance

Study drug will be administered by the study staff; therefore, treatment compliance is ensured.

11.7. 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 (e.g., pharmacist) in maintaining current and accurate inventory records. At a minimum, the investigator or designee will maintain accurate records demonstrating dates and units of drug received, lot numbers, subjects to whom drug was administered, and accounts of any drug destroyed accidentally or deliberately. The investigator must retain vials containing used, unused, or expired EXPAREL for return or destruction, as instructed by Pacira, following confirmation of drug accountability data by a study monitor. A record of drug return or destruction will be maintained and provided to Pacira. Inventory records must be readily available for inspection by the study monitor and/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 performed at the times specified after closure of the C-section skin incision:

- Date, time of administration, and amount of all postsurgical opioid rescue medication taken through Day 14
- Pain intensity scores at rest (general and site of incision) using a 10 cm VAS at 12, 24, 48, and 72 hours after surgery (see Appendix 1) and then once daily (at noon ± 4 hours) through Day 14

  Note 1: For pain intensity scores at 12, 24, 48, or 72 hours, if the subject is sleeping, do not wake her to assess pain. If she awakens within the assessment window (i.e., 1 hour for the 12- and 24-hour assessments, 2 hours for the 48-hour assessments, and 4 hours for the 72-hour assessments), a pain score may be collected then.

  Note 2: An unscheduled VAS score is also required immediately prior to administration of any rescue medication while in the hospital.

  Note 3: If a subject is discharged prior to any of the scheduled VAS assessments to be collected at 12 to 72 hours after surgery, a member of the study site staff will telephone the subject at the appropriate scheduled times (i.e., the time of each assessment scheduled to be collected that occurs after hospital discharge) to remind her to complete the VAS and to record the scheduled assessments in the ePRO device. This will ensure that, for any subjects 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.
- Total time in PACU
- Date and time of first unassisted ambulation
- Date and time of first bowel movement
- Itching using an NRS of 0 to 10 (see Appendix 10)
- SFQ at screening (see Appendix 6)
- ORSDS at 24, 48, and 72 hours after surgery (see Appendix 7)
- Subject satisfaction with postsurgical pain control using a 5-point Likert scale (see Appendix 3)
- RCSS at 24, 48, and 72 hours or at hospital discharge, whichever occurs first (see Appendix 4)

- Discharge readiness at 24, 48, and 72 hours, or at hospital discharge, or until the subject attains a score of 9, whichever occurs first (see Appendix 2)
- Unscheduled phone calls or office visits related to pain after discharge through Day 14
- Persistent opioid use at Day 30 (see Appendix 9)

12.2. Efficacy Endpoints

12.2.1. Primary Efficacy Endpoint

- Total postsurgical opioid consumption in morphine equivalents through 72 hours or hospital discharge

12.2.2. Secondary Efficacy Endpoints

- Time to first postsurgical opioid rescue medication
- Percentage of opioid-free subjects through 72 hours or hospital discharge
- Incidence and severity of itching (NRS of 0 to 10)
- ORSDS at 24, 48, and 72 hours after surgery
- The VAS pain, general and at incision site (at rest) through 72 hours or hospital discharge prior to any physical therapy or physical activity/mobilization
- Proportion of subjects discharge-ready at 24, 48, and 72 hours or at hospital discharge, or until the subject attains a score of 9, whichever occurs first
- Overall assessment of subject's satisfaction with pain control at 72 hours or at hospital discharge, whichever occurs first
- Integrated rank assessment using the VAS pain intensity score (at rest) and the total amount of postsurgical opioids consumed through 72 hours or hospital discharge

12.2.3. Exploratory Efficacy Endpoints

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

- Total opioid use from 72 hrs to Day 14
- Time to and date of first unassisted ambulation
- Length of hospital stay
- Number of unscheduled phone calls or office visits related to pain from discharge through Day 14.
- Emergency department visits
- Persistent opioid use at Day 30

12.3. Safety Assessments

Adverse events (AEs/SAEs) will be monitored and recorded from the time the ICF is signed through Day 14. Vital signs (blood pressure, heart rate, respiratory rate, and temperature) and pulse oximetry will be monitored and recorded.

12.4. Safety Endpoints

Incidence of treatment-emergent AEs (TEAEs) and SAEs will be assessed from the start of anesthesia 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 the completion of the last C-section skin-incision stitch (i.e., time of skin-incision closure of the C-section wound following delivery and prior to the TAP infiltration). 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 skin incision. 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 ePRO device. Additionally, the subject will record a daily (at noon ± 4 hours) 10 cm VAS pain score at rest in the device daily from hospital discharge through Day 14. This assessment should capture her worst pain at rest in the prior 24 hours by assessing, "What was your worst pain since your last pain assessment?" (i.e., 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 packaging material in which the device will be returned by the subject to the investigator.

13.1.1. Electronic Patient Reported Outcome Device

An ePRO device will be given to the subject at the first scheduled assessment; the option for the subject to record this event via a mobile app will also be provided. While in the hospital, the subject will use the device to record all scheduled VAS (general and incision site) (i.e., at 12, 24, 48, and 72 hours) and ORSDS (i.e., at 24, 48, and 72 hours) assessments. She will also use the device 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 to be collected at 12 to 72 hours after surgery or a scheduled ORSDS assessment to be collected at 24 to 72 hours after surgery, a member of the study site staff will contact the subject at the appropriate scheduled times (i.e., the time of each assessment scheduled to be collected that occurs after hospital discharge) to remind her to complete the VAS and ORSDS assessments and to record the scheduled assessments in the device, 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 ORSDS assessments required for calculation of the study endpoints are captured. These phone calls will only be made if a subject is discharged prior to 72 hours.

At hospital discharge, study personnel will use the device 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 device.

At home, the subject will assess pain intensity at rest each day at noon (± 4 hours). This assessment should capture her worst pain at rest in the prior 24 hours by assessing, "What was your worst pain since your last pain assessment?" (i.e., 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 12, 24, 48, and 72 hours (see Appendix 1) and once daily (at noon ± 4 hours) through Day 14.

For pain intensity scores at 12, 24, 48, or 72 hours, if the subject is sleeping, do not wake her to assess pain. If she awakens within the assessment window (i.e., 1 hour for the 12- and 24-hour assessments, 2 hours for the 48-hour assessments, and 4 hours for the 72-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 to 5 minutes before entering the pain score.

13.1.3. Itching Assessments

Subjects will be asked to rate the intensity of any itching they may have on a Numeric Rating Scale (NRS) from 0 to 10; 0 being no itching and 10 being worst itch (see Appendix 10). Itching assessments will be performed at screening, in the PACU prior to PACU discharge, and at 12 hours (±1 hour), 24 hours (±1 hour), 48 hours (±2 hours), and 72 hours (±4 hours).

13.1.4. Subject Satisfaction with Postsurgical Pain Control

Subject satisfaction with postsurgical pain control will be assessed using a 5-point Likert scale at 72 hours or at hospital discharge, whichever occurs first (see Appendix 3).

13.1.5. Recovery from Cesarean Section Scale

Recovery from the C-section procedure will be assessed using the RCSS at 24, 48, and 72 hours or hospital discharge, whichever occurs first (see Appendix 4)

13.1.6. Discharge Readiness

The subject's discharge readiness will be assessed using the Modified Post Anesthesia 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 at hospital discharge or until the subject attains a score of 9, whichever occurs first.

13.1.7. Opioid Related Symptom Distress scale (ORSDS)

The subject's opioid related symptom distress will be assessed using the ORSDS scale at 24, 48, and 72 hours (see Appendix 7). See Section 13.1.1 regarding subjects discharged prior to 72 hours.

13.1.8. Surgical Fear Questionnaire (SFQ)

The subject's attitudes toward pain prior to surgery will be recorded during screening or baseline (see Appendix 6).

13.1.9. Calls to Physician

Participants will record the number of calls made to their physician after discharge, for pain related to their surgery, to be collected on Day 14 (see Appendix 8).

13.1.10. Persistent Opioid Use

Participants will be asked if they are still taking opioids on Day 30 (see Appendix 9).

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 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:

- 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 an ePRO device while in the hospital and that she will be expected to capture specific information in the device while in the hospital
- Explain to the subject that she will be expected to capture specific information in the device after discharge through Day 14

To be completed in the hospital

- Measure vital signs (blood pressure, height, weight, heart rate, respiratory rate, and temperature)
- Perform physical examination according to the investigational site's SOC
- Perform 12-lead electrocardiogram
- Conduct urine drug screen and breath alcohol test
- Clinical laboratory tests in accordance with the investigator's SOC including (Appendix 5):
    1. Direct bilirubin
    2. Gamma-glutamyl transpeptidase and lactate dehydrogenase
       or
       Alanine transaminase and aspartate transaminase
    3. Serum creatinine
       or
       Blood urea nitrogen
- Record SFQ (Appendix 6)
- Assess itching (NRS of 0 to 10) (Appendix 10)
- Record AEs/SAEs 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, heart rate, respiratory rate, and temperature)
- Record pulse oximetry
- Perform physical examination according to the investigational site's SOC
- Randomize subject and prepare study drug
- Administer intrathecal preservative-free morphine injection in conjunction with single-shot spinal anesthesia per the treatment group. 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 skin incision)
- Record intraoperative opioids and other intraoperative medications administered and their 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 using up to 10 mL normal saline (per the treatment group)
- Capture ultrasound image or video 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 or video of 2-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 time out of the PACU
- Measure vital signs (blood pressure, heart rate, respiratory rate, and temperature) prior to PACU discharge
- Record an unscheduled VAS pain intensity score before any postsurgical opioid medication while in the hospital

- Record pulse oximetry per SOC
- Record date, time, and dose of all postsurgical opioid and other pain medication. Note: Subjects should only receive opioid pain medication (e.g., morphine, hydromorphone [Dilaudid], oxycodone) upon request for breakthrough pain.
- Record date, time, and dose of all standardized multimodal pain medications administered
- Record date and time of first unassisted ambulation
- Record date and time of first bowel movement
- Assess itching (NRS of 0 to 10) prior to PACU discharge (see Appendix 10)
- Record any AEs or SAEs
- Record concomitant medications for treatment of AEs

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

- Provide the ePRO device to the subject prior to the first assessment scheduled to be recorded in the ePRO device (i.e., 12 hr VAS assessment).
- Record scheduled pain intensity scores at rest using a 10 cm VAS (see Appendix 1) at 12, 24, 48, and 72 hours. If the subject is sleeping at 12, 24, 48, and 72 hours, do not wake her to assess pain. If she awakens within the assessment window (i.e., 1 hour for the 12-hour and 24-hour assessments, 2 hours for the 48-hour assessments, and 4 hours for the 72-hour assessments), a pain score may be collected. See Section 13.1.1 regarding subjects discharged prior to 72 hours.
- Record pulse oximetry per SOC up to 24 hours
- Record vital signs at 24, 48, and 72 hours or at the time of discharge, whichever occurs first
- Record date, time, and dose of all standardized multimodal pain medications administered
- Record an unscheduled VAS pain intensity score (general and site of incision) 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 date and time of first bowel movement
- Assess itching (NRS of 0 to 10) (Appendix 10)

- Record ORSDS (see Appendix 7) 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 at hospital discharge, whichever occurs first
- RCSS at 24, 48, and 72 hours or at hospital discharge, whichever occurs first (see Appendix 4)
- Provide the stamped packaging material and instructions for use at the hospital discharge
- 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

- Subjects will record VAS pain intensity scores at rest (see Appendix 1) in the device at noon (± 4 hours) each day through Day 14. This assessment should capture the subject's worst pain at rest in the prior 24 hours by assessing, "What was your worst pain since your last pain assessment?" (i.e., from noon on the previous day to the current assessment).
- Subjects will record the use of pain medication, if any, in the device 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 device in the provided addressed and stamped packaging material

13.10. Day 30 Phone Call

Document whether the subject reports continued use of opioids.

14. ADVERSE EVENT REPORTING

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

The concepts of AEs and SAEs represent regulatory instruments used to evaluate and monitor the safety of clinical study subjects. Therefore, these terms only apply in light of their regulatory definition. The term serious, in a regulatory sense, does not necessarily mean severe. The SAE concept is 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 of Adverse Event

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

An AE can be any unfavorable and unintended change in a body structure or body function. Adverse events include any clinically significant deterioration of a subject's medical status. The AE may involve any organ or system and can be represented by the new onset or 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 (e.g., 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. An AE that occurs after the administration of a study treatment is considered a TEAE.

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.

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

14.1.2. Recording Adverse Events

It is the responsibility of the investigator to document all AEs (i.e., pretreatment AEs 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; i.e., lined through and initialed). Whenever possible, abnormal laboratory results should be reported as their clinical corollary (e.g., low potassium should be recorded as hypokalemia).

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

Any condition noted before the subject signs the ICF will be listed as medical history and is considered a pre-existing condition. If a pre-existing condition changes (i.e., becomes more severe or more frequent) at any time after the ICF is signed, or after study drug administration, it is considered an AE. Note: A change in treatment for a pre-existing condition (e.g., new high blood pressure medication) does not necessarily indicate an AE.

Information recorded on the AE CRF will include the AE term, the date and time of onset, severity, seriousness, relationship to study drug, action taken with 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 (e.g., based on the temporal sequence, absence of a reasonable pathophysiological mechanism, or direct evidence of actual cause)

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

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

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

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

14.1.5. Outcome of Adverse Events

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

Recovered/Resolved:	The event resolved and the subject recovered from the AE
Recovered/Resolved with Sequelae:	The initial event resolved, but has a continuing abnormal condition as a result of the AE
Not Recovered/ Not Resolved:	At the time of last assessment, the event was ongoing, with an undetermined outcome. Note: ongoing AEs are not to be considered resolved as a result of death.
Recovering/Resolving:	At the time of last assessment, the event was decreasing in frequency, severity, etc., and a resolution was expected
Fatal:	The AE directly caused death

Unknown: There was an inability to access the subject or the subject's records to determine the outcome (e.g., subject withdrew consent or was lost to follow-up)

14.1.6. Action Taken with Subject Because of an Adverse Event

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

- 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 AE[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 cases of preplanned hospitalizations for a pre-existing condition that did not worsen during the study. However, any medical condition that delays a subject's discharge from the hospital (i.e., prolonged hospitalization) or requires the subject to be readmitted should be reported as an SAE.

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

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

14.2.2. Reporting Serious Adverse Events

Any SAE or death that occurs at any time after the subject signs the ICF through Day 14, whether or not related to EXPAREL, must be reported by the investigator or designee to Pacira Drug Safety either via 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, PRN.

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 infiltration into the TAP with SOC in subjects undergoing an 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

Assuming a log-normal distribution for total opioid consumption with a 70% coefficient of variation, 5% alpha, an equal randomization ratio, and 80% power, a total of 77 subjects per treatment group will be sufficient to detect a 25% reduction in total opioid consumption. Assuming 5% of the subjects are not evaluable and one of the two EXPAREL groups will be dropped after interim analysis when a total of 60 subjects are treated, a total sample size of approximately 182 treated subjects is needed. This sample size will be re-evaluated after the interim analysis.

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 the actual treatment 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 the actual treatment 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 SAP will be developed for this study. Efficacy endpoint analyses will be conducted on the efficacy analysis set. The primary efficacy endpoint will also be analyzed using the per-protocol analysis set as a sensitivity analysis.

Summary statistics (number, mean, median, standard deviation, minimum, and maximum) will be shown for each continuous measure of efficacy by treatment group. The 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 the first dose of trial drug unless otherwise specified.

All assessments will be listed in subject data listings.

The analyses of the primary, secondary, and exploratory 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. 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.

Vital signs and pulse oximetry results will be summarized by treatment group at each assessment timepoint. Summaries will present both actual and change-from-baseline results. Vital signs and pulse oximetry results will also be assessed for potentially clinically significant abnormal values. The number and percentage of subjects satisfying the potentially clinically significant abnormal criteria at any time during the study and at each assessment timepoint will be tabulated by treatment and overall treatments. Details will be described in the SAP.

15.7. Significance Testing

Significance testing will be described in the SAP.

15.8. Interim Analyses

After approximately 20 subjects per treatment group are randomized and treated (i.e., a total of 60 subjects are treated in this study), an interim analysis will be conducted to evaluate and compare the clinical efficacy/safety and health economics benefits between the two EXPAREL groups against the SOC control group. The primary purpose of this interim analysis is to select one EXPAREL treatment group out of the two EXPAREL treatment groups to continue for the rest of the study. The second purpose of this interim analysis is to evaluate the sample size assumptions and the selection of the primary/secondary endpoints. Full details on the planned or additional interim analysis will be covered in a prospective interim analysis plan.

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17. INVESTIGATOR AGREEMENT

Printed Name of investigator: _____

Printed Title/Position: _____

Printed Institution Address: _____

_____

_____

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

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

_____ _____

Signature of investigator Date

18. APPENDICES

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

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

If a subject is discharged prior to any of the scheduled VAS assessments to be collected at 12 to 72 hours after surgery, a member of the study site staff will contact the subject at the appropriate scheduled times (i.e., the time of each assessment scheduled to be collected from 12 to 72 hours that occurs after hospital discharge) to remind her to complete the VAS assessment and to record the scheduled assessment in the device. 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 be made if a subject is discharged prior to 72 hours.

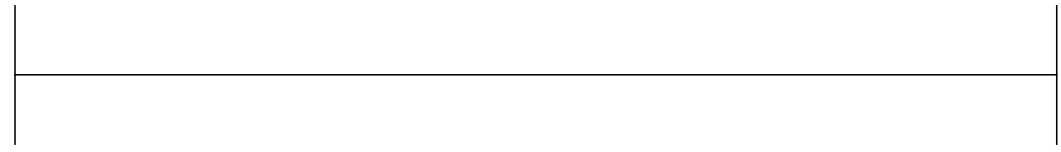
While in the hospital, subjects will also record an unscheduled VAS pain score immediately before any requested opioid pain medication.

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 to 5 minutes before recording the pain score.

While in the hospital, subjects are to assess, "How much pain are you experiencing right now in general?" and "How much pain are you experiencing right now at the site of the incision?" They are advised to place a vertical mark on the line below to indicate the level of pain experienced at the time of assessment, with a line closer to the left meaning little or no pain and a line closer to the right meaning much pain or pain as bad as it can be. This should be completed for both the general pain and pain at the site of incision (i.e., two VAS scales).

At home, the subject will assess pain intensity at rest each day at noon (± 4 hours). This assessment should capture her worst pain at rest in the prior 24 hours by assessing, "What was your worst pain since your last pain assessment?" (i.e., from noon on the previous day to the current assessment) through Day 14.

Visual Analog Scale (VAS)



No Pain

Pain as bad as it could possibly be

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

18.2. Appendix 2: Discharge Readiness

The subject's discharge readiness will be assessed using the Modified Post Anesthesia 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 at 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 Post Anesthesia 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

18.3. Appendix 3: Subject Satisfaction with Postsurgical Pain Control

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

18.4. Appendix 4: Recovery from Cesarean Section Scale (RCSS)

The RCSS will be assessed at 24, 48 and 72 hours after surgery (or at hospital discharge, whichever occurs first).

Please answer the following questions about your Recovery from Cesarean section by circling the number that most applies to you.

1 indicates strongly disagree, 7 indicates strongly agree.

1. I recovered quickly from my cesarean

   1 2 3 4 5 6 7

2. I was able to get out of bed soon after my cesarean

   1 2 3 4 5 6 7

3. My mobility was seriously affected by the cesarean

   1 2 3 4 5 6 7

4. The cesarean interfered with my ability to care for my baby

   1 2 3 4 5 6 7

5. The cesarean prevented me from feeding my baby

   1 2 3 4 5 6 7

6. I was able to change my baby soon after the cesarean

   1 2 3 4 5 6 7

7. I was able to care for my own hygiene needs soon after surgery

   1 2 3 4 5 6 7

8. The pain from the surgery prevented me from doing what I wanted

   1 2 3 4 5 6 7

9. I was tired for a long time after surgery

   1 2 3 4 5 6 7

18.5. Appendix 5: Clinical Laboratory Tests

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

1. Direct bilirubin
2. Gamma-glutamyl transpeptidase and lactate dehydrogenase
   or
   Alanine transaminase and aspartate transaminase
3. Serum creatinine
   or
   Blood urea nitrogen

18.6. Appendix 6: Surgical Fear Questionnaire (SFQ)

The SFQ will be completed at screening/baseline.

Patient instructions:

This questionnaire assesses how afraid you are for various aspects related to the surgical procedure you are about to undergo. Please circle the number that best reflects how you feel right now.

1. I am afraid of the operation

0	1	2	3	4	5	6	7	8	9	10
not at all afraid										very afraid

2. I am afraid of the anaesthesia

0	1	2	3	4	5	6	7	8	9	10
not at all afraid										very afraid

3. I am afraid of the pain after the operation

0	1	2	3	4	5	6	7	8	9	10
not at all afraid										very afraid

4. I am afraid of the unpleasant side effects (like nausea) after the operation

0	1	2	3	4	5	6	7	8	9	10
not at all afraid										very afraid

5. I am afraid my health will deteriorate because of the operation

0	1	2	3	4	5	6	7	8	9	10
not at all afraid										very afraid

6. I am afraid the operation will fail

0	1	2	3	4	5	6	7	8	9	10
not at all afraid										very afraid

7. I am afraid that I won't recover completely from the operation

0	1	2	3	4	5	6	7	8	9	10
not at all afraid										very afraid

8. I am afraid of the long duration of the rehabilitation after the operation

0	1	2	3	4	5	6	7	8	9	10
not at all afraid										very afraid

18.7. Appendix 7: Opioid Related Symptom Distress Scale (ORSDS)

The ORSDS will be assessed at 24, 48, and 72 hours after surgery.

We have listed 10 symptoms below. Read each one carefully. If you have had the symptoms during the past 24 hours, mark how OFTEN you had it, how SEVERE it was usually and how much it DISTRESSED or BOTHERED you by placing an "X" in the appropriate box. If you DID NOT HAVE the symptoms, please place an "X" in the box marked "Did not have."

For the symptoms "retching/vomiting" below, you will indicate the actual **number** of episodes you experienced.

During the last 24 hours, did you have any of the following?

Symptoms	Did not have	(If yes), how often did you have it?				(If yes), how severe was it usually?				(If yes), how much did it distress or bother you?				
		Rarely	Occasionally	Frequently	Almost Constantly	Slight	Moderate	Severe	Very Severe	Not at all	A little Bit	Somewhat	Quite a Bit	Very Much
Fatigue	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Drowsiness	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Inability to concentrate	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Nausea	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Dizziness	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Constipation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Itching	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Difficulty with urination	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Confusion	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Retching/vomiting	☐	_ _ # of episodes				☐	☐	☐	☐	☐	☐	☐	☐	☐

18.8. Appendix 8: Calls to Physician (Single Question)

To be collected at Day 14 as part of the Day 14 phone call.

Since being discharged from the hospital, how many times have you called your physician about pain ***related to your surgery***?

1. 0 (I have not called my doctor)
2. 1-2 times
3. 3-5 times
4. More than 5 times

18.9. Appendix 9: Persistent Opioid Use

To be collected at Day 30 as part of the Day 30 phone call. The following question will be asked to the subject:

1. Are you currently taking opioids for pain?
    a. Yes
    b. No

18.10. Appendix 10: Numeric Rating Scale

Subjects will be asked to rate the intensity of any itching they may have on a Numeric Rating Scale (NRS) from 0 to 10; 0 being no itching and 10 being worst itch.

Itching assessments are to be performed at screening, in the PACU prior to PACU discharge, and at 12 hours (±1 hour), 24 hours (±1 hour), 48 hours (±2 hours), and 72 hours (±4 hours).