Pacira Pharmaceuticals, Inc.
EXPAREL

Document:	Clinical Study Protocol
Official Title:	A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Dose Ranging Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Single Injection Femoral Nerve Block With Liposome Bupivacaine for Postsurgical Analgesia in Subjects Undergoing Total Knee Arthroplasty
NCT Number:	NCT01683071
Document Date:	April 19, 2013

Clinical Study Protocol
Amendment 2

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Single Injection Femoral Nerve Block with Liposome Bupivacaine for Postsurgical Analgesia in Subjects Undergoing Total Knee Arthroplasty

Protocol No.:	402-C-323
EudraCT No.:	N/A
IND No.:	69,198
Study Phase:	2/3
Study Drug:	Liposome bupivacaine
Date:	19 April 2013 (Amendment 2)
	04 September 2012 (Amendment 1)
	03 August 2012 (original)
Study Sites:	Up to 40 sites in the United States
Sponsor:	Pacira Pharmaceuticals, Inc. 10450 Science Center Drive San Diego, CA 92121 Tel: (858) 625-2424

SUMMARY OF CHANGES

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

Section 2 (Synopsis)

- Methodology:
  - The second postsurgical rescue medication (PCA and/or opioid) text was changed

    ***from**:* "The second rescue medication will be PCA-administered opioid (morphine or hydromorphone). The PCA pump will be programmed to deliver either: (1) on-demand morphine boluses of 1.5 mg with a lockout interval of 6 minutes and an initial maximum hourly dose of 15 mg or (2) on-demand hydromorphone boluses of 0.2 mg with a lockout interval of 10 minutes and an initial maximum hourly dose of 1.2 mg."

    ***to**:* "The second rescue medication will be an on-demand PCA-administered opioid (morphine or hydromorphone). The PCA pump will be programmed to deliver either on-demand morphine or on-demand hydromorphone boluses at a dose and lockout interval in accordance with the site's standard practice."
  - The opioid-related adverse events (ORAE) questionnaire was removed from the Part 2 study assessments as well as from the study endpoints as there is no validated outcomes instrument available.
  - Text was clarified regarding follow-up procedures for discontinued subjects and the analgesic use during the 72-hour observation period. The text was changed

    from: "Subjects who do not receive adequate pain control with this regimen are to be withdrawn from the study and followed for safety only. No other analgesic agents, including non-steroidal anti-inflammatory agents (NSAIDs), are allowed during the 72-hour observation period."

    to: "Subjects who do not achieve adequate pain control with this regimen are to be withdrawn from the study and followed for AEs only. No other analgesic agents, including non-steroidal anti-inflammatory agents (NSAIDs), are allowed during the 72-hour observation period or until the subject is withdrawn from the study, whichever is sooner."
- Eligibility Criteria:
  - Exclusion criterion #5 was changed

    ***from**:* "Use of selective serotonin reuptake inhibitors (SSRIs), gabapentin, pregabalin (Lyrica®), or duloxetine (Cymbalta®) within 3 days of surgery."

    ***to**:* "Initiation of treatment with any of the following medications within 1 month of study drug administration or if the medication(s) are being given to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinepherine reuptake inhibitors (SNRIs), gabapentin, pregabalin (Lyrica®), or duloxetine (Cymbalta®).

- Eligibility Criteria (Cont.)
  - Exclusion criterion #8 was changed

    from: "Contraindication to any of the pain-control agents planned for postsurgical use (e.g., morphine, hydromorphone, oxycodone, bupivacaine)."

    to: "Contraindication to hydromorphone, oxycodone, or bupivacaine."
  - The following exclusion criterion was added: "Use of dexmedetomidine HCl (Precedex®) within 3 days of surgery."

Section 4 (List of Abbreviations)

SNRI and SSRI were added.

Table 1 (Time and Events Schedule of Study Procedures)

- "Part 1 only" was added to the row for the predefined ORAE assessment.
- ORAE was defined in the table footnote.

Sections 9, 10, 11, 12, and 13

The changes made in the Synopsis (listed above) were made to Sections 9 though 13.

Sections 10.3 (Removal of Subjects from Therapy or Assessment

Safety assessments (the neurological examination, cold test, 20-meter walk test, and collection of a blood sample for pharmacokinetic analysis, if possible) were specified in the early termination procedures.

Section 11.4 (Selection of Doses in the Study)

For clarification, "or placebo" was added to the end of the first sentence in the second paragraph.

Section 11.5.1 (Blinding Procedures)

The blinding procedures were modified.

Section 11.6.1 (Prior and Concomitant Therapy and Medications)

The text in this section was clarified and modified based on the changes made in the eligibility criteria.

Section 11.6.2 (Permitted or Restricted Therapy and Medication During Surgery)

For completeness, the following text was added: "Prophylactic antiemetics or planned postsurgical antiemetics given without regard to the subject's emesis needs is prohibited."

Section 11.6.3 (Permitted or Restricted Therapy and Medication After Surgery through 72 Hours After Surgery)

Dexmedetomidine HCl (Precedex) was added to the prohibited medications.

Section 13.6 (Additional Procedures at Withdrawal if Prior to 72 Hours)

For clarification, this section was added.

Section 18 (Appendices)

Minor revisions were made to some of the appendices.

"Part 1 only" was added to the ORAE questionnaire in Appendix 6.

SIGNATURE PAGE

Erol Onel, MD Executive Medical Director	22 April 2013 Date
Gary Patou, MD Chief Medical Officer	23 April 2013 Date
Patricia Mills, RN Sr. Director, Drug Safety and Pharmacovigilance	23 April 2013 Date

2. SYNOPSIS

Name of Sponsor/Company: Pacira Pharmaceuticals, Inc. 10450 Science Center Drive San Diego, CA 92121 (858) 625-2424	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Liposome Bupivacaine		
Name of Active Ingredient: Bupivacaine, 13.3 mg/mL		

Title of Study: A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Single Injection Femoral Nerve Block with Liposome Bupivacaine for Postsurgical Analgesia in Subjects Undergoing Total Knee Arthroplasty

Principal Investigators: To be determined.

Study Center(s): Up to 40 sites in the United States.

Publications (Reference): None.

Objectives:

Primary Objectives:

Part 1: The primary objectives of Part 1 are to (1) evaluate three dose levels of liposome bupivacaine versus placebo with respect to the magnitude and duration of the analgesic effect achieved following single dose injection femoral nerve block with liposome bupivacaine, and (2) select a single therapeutic dose of liposome bupivacaine from the three dose levels to be tested in Part 2.

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

Secondary Objectives:

The secondary objectives are to evaluate additional efficacy parameters, characterize the pharmacokinetic (PK) profile of liposome bupivacaine when administered as a femoral nerve block, and further assess the safety profile of liposome bupivacaine.

Methodology:

This is a Phase 2/3, multicenter, randomized, double-blind, parallel-group, placebo-controlled, dose-ranging study in subjects undergoing primary unilateral total knee arthroplasty (TKA) under general or spinal anesthesia. Note: Bupivacaine cannot be used as the spinal anesthetic.

On Day 1, eligible subjects will be randomized to receive a single dose of study drug administered in a blinded manner within 2 hours prior to the surgical procedure as a femoral nerve block. At the conclusion of the block, a femoral nerve catheter is to be left in place and hep-locked (see "Postsurgical Rescue Medication" below). Additionally, a patient-controlled analgesia (PCA) pump will be established prior to the completion of the surgery. *The PCA pump will not be loaded at this time*. The use of fentanyl will be permitted during surgery. However, intraoperative administration of morphine or any other analgesics (including intrathecal opioids), local anesthetics, or anti-inflammatory agents is prohibited, unless needed to treat an adverse event (AE).

All subjects will be required to remain in the study site for a minimum of 72 hours after the end of surgery for postsurgical assessments. The study staff will ensure adequate safety precautions are in place in order to prevent falls (e.g., use of support devices during ambulation, such as a knee immobilizer and walker/crutches), as needed.

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Methodology (Cont):

Part 1

During Part 1 of the study, approximately 100 subjects (25 per treatment arm) will be randomized to receive a single dose injection femoral nerve block with either one of three doses of liposome bupivacaine (67, 133, or 266 mg) or placebo in 20 mL under ultrasound guidance. Preservative-free normal saline will be added to the 67 mg and 133 mg doses of study drug to achieve a volume of 20 mL.

After all subjects have completed the 72-hour assessments in Part 1, an analysis will be conducted in order to select a single therapeutic dose from the three liposome bupivacaine dose levels tested. An unblinded dose selection committee will review at least the results from the following assessments conducted during Part 1: (1) the area under the curve (AUC) of the numeric rating scale (NRS) at rest (NRS-R) pain intensity scores through 72 hours; (2) total postsurgical opioid consumption; (3) the time to first opioid rescue; and (4) safety data. Based on a clinical evaluation of the data, the committee will determine the apparent efficacy and safety of each of the three liposome bupivacaine dose levels tested and will recommend a dose level for Part 2 of the study. Statistical significance will not be required in order to recommend a dose level for Part 2. The unblinded dose selection committee also will recommend whether the sample size for Part 2 should be increased.

Part 2

In Part 2 of the study, approximately 180 subjects (randomized 1:1, resulting in approximately 90 liposome bupivacaine subjects and 90 placebo subjects) will receive a single dose injection femoral nerve block with the selected dose level of liposome bupivacaine (i.e., 67, 133, or 266 mg) or placebo in 20 mL under ultrasound guidance.

Postsurgical Rescue Medication

Subjects should only receive rescue medication upon request for pain control, as needed.

The first rescue medication will be intravenous (IV) hydromorphone 0.5 mg, which will be administered once via bolus only. At this time, the PCA should be loaded with opioid (morphine or hydromorphone only).

The second rescue medication will be an on-demand PCA-administered opioid (morphine or hydromorphone). The PCA pump will be programmed to deliver either on-demand morphine or on-demand hydromorphone boluses at a dose and lockout interval in accordance with the site's standard practice. A continuous infusion (background or basal rate) of morphine or hydromorphone is not permitted. If the subject's pain is excessive or pain control is inadequate, then the bolus dose may be adjusted according to local hospital practices; however, **adding a basal rate is prohibited**. Once a subject is tolerating oral (PO) medication, PO immediate-release oxycodone may be administered (but not more than 10 mg every 4 hours).

If a subject's pain is inadequately controlled by opioids, a third rescue medication consisting of conventional bupivacaine HCl at a concentration of 0.125% (1.25 mg/mL) at a rate of 8 mL per hour for up to 12 hours may be administered via the previously placed femoral nerve catheter.

Subjects who do not achieve adequate pain relief with this regimen will be withdrawn from the study and followed for AEs only. No other analgesic agents, including non-steroidal anti-inflammatory agents (NSAIDs), are allowed during the 72-hour observation period or until the subject is withdrawn from the study, whichever is sooner.

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Methodology (Cont.)

Postsurgical Assessments: Postsurgical assessments will include pain intensity scores using the 0-10 point NRS-R and NRS with activity (NRS-A) (where the prescribed activity is active knee flexion up to 45 degrees) (see Appendix 1); use of supplemental opioid pain medication; neurological assessment (see Appendix 2); cardiac assessment (i.e., ECG recordings); sensory function assessment (i.e., cold test); motor function assessment (i.e., 20-meter walk test); vital signs; overall benefit of analgesia score (OBAS) questionnaire (see Appendix 3); subject satisfaction with postsurgical pain control (see Appendix 4); physician satisfaction with return of sensory/motor function (see Appendix 5); and an opioid-related AE questionnaire during Part 1 only (see Appendix 6). Adverse events will be recorded through Day 30. If a cardiac or neurological event occurs during Part 1 or Part 2 of the study that the Investigator believes may be associated with high levels of systemic bupivacaine, an unscheduled PK blood sample should be collected at the time that the event is noted.

Safety and efficacy assessments will be conducted at pre-specified time points *after the end of surgery* (defined as the time of the last suture/staple).

A follow-up visit will be scheduled for all subjects on Day 30.

Pharmacokinetic Assessments (Part 1 only): Blood samples for PK analysis will be obtained from subjects at specific sites during Part 1 of the study at baseline, 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours *after the beginning of study drug administration*. Blood samples for PK analysis should be collected even if the subject is not yet in surgery or is still in surgery. Placebo samples will be collected to maintain the treatment double-blind but will not be analyzed. Samples from subjects receiving bupivacaine nerve block rescue will not be analyzed. (Note: At time points when the PK and NRS pain intensity assessments coincide, the NRS pain intensity assessments will be conducted before the blood draw.)

Number of Subjects (Planned):

Approximately 280 subjects are planned for enrollment in this study: 100 subjects (25 per treatment arm) in Part 1 and 180 subjects (approximately 90 liposome bupivacaine subjects and 90 placebo subjects) in Part 2. The number of subjects in Part 2 may be increased after review of the Part 1 data.

Eligibility Criteria:

Inclusion Criteria:

1. Male or female, ≥18 years of age.
2. Scheduled to undergo primary unilateral TKA under general or spinal anesthesia.
3. American Society of Anesthesiology (ASA) Physical Status 1, 2, or 3.
4. Able to demonstrate motor function by performing a 20-meter walk unassisted with the optional use of a 4-legged walker, and sensory function by exhibiting sensitivity to cold.
5. Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments.

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Exclusion Criteria:

1. Currently pregnant, nursing, or planning to become pregnant during the study or within 1 month after study drug administration. Female subjects must be surgically sterile, at least 2 years menopausal, or using an acceptable method of birth control. If of childbearing potential, must have a documented negative pregnancy test within 24 hours before surgery.
2. Planned concurrent surgical procedure (e.g., bilateral TKA).
3. Use of any of the following medications within the times specified before surgery: long-acting opioid medication, NSAIDs, or aspirin (except for low-dose aspirin used for cardioprotection or acetaminophen) within 3 days, or any opioid medication within 24 hours.
4. Concurrent painful physical condition that may require analgesic treatment (such as an NSAID or opioid) in the postsurgical period for pain that is not strictly related to the TKA surgery and which may confound the postsurgical assessments (e.g., significant pain from other joints including the non-index knee joint, chronic neuropathic pain, concurrent or prior contralateral TKA, concurrent foot surgery).
5. Initiation of treatment with any of the following medications within 1 month of study drug administration or if the medication(s) are being given to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinepherine reuptake inhibitors (SNRIs), gabapentin, pregabalin (Lyrica®), or duloxetine (Cymbalta®).
6. Current use of systemic glucocorticosteroids within 1 month of enrollment in this study.
7. Body weight < 50 kg (110 pounds) or a body mass index ≥ 40 kg/m^2.
8. Contraindication to hydromorphone, oxycodone, or bupivacaine.
9. Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study.
10. Previous participation in a liposome bupivacaine study.
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. Failure to pass the urine drug screen.
13. Uncontrolled anxiety, schizophrenia, or other psychiatric disorder that, in the opinion of the Investigator, could interfere with study assessments or compliance.
14. Malignancy in the last 2 years, with the exception of non-metastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.
15. Current or historical evidence of any clinically significant disease or condition, especially cardiovascular or neurological conditions that, in the opinion of the Investigator, may increase the risk of surgery or complicate the subject's postsurgical course.
16. Significant medical conditions or laboratory results that, in the opinion of the Investigator, indicate an increased vulnerability to study drugs and procedures.
17. Subjects who are planned to receive Entereg® (alvimopan).
18. Subjects who will receive prophylactic antiemetics or planned postsurgical antiemetics given without regard to the subject's emesis needs.
19. Use of dexmedetomidine HCl (Precedex®) within 3 days of surgery.

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Name of Active Ingredient: Bupivacaine, 13.3 mg/mL		

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

Name: Liposome bupivacaine.

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

Dosage: Single administration of 67, 133, or 266 mg. Preservative-free normal saline will be added to the 67 mg and 133 mg doses of study drug to achieve a volume of 20 mL.

Lot Number: To be determined.

Mode of Administration: Ultrasound-guided femoral nerve block prior to the surgical procedure.

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

Name: Placebo (preservative-free normal saline for injection).

Dosage: Single administration in a volume of 20 mL.

Lot Number: To be determined.

Mode of Administration: Ultrasound-guided femoral nerve block prior to the surgical procedure.

Duration of Subject Participation in Study:

Each subject's participation in this study could be up to 64 days (up to 30 days for the screening period and up to 34 days for post-dosing follow-up).

Efficacy Assessments:

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

- Pain intensity scores using the NRS-R at baseline (prior to the nerve block), and 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours, and at first request for rescue pain medication.
- Pain intensity scores using the NRS-A (where the prescribed activity is actively flexing the involved knee up to 45 degrees) at baseline (prior to the nerve block), and 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours, and at first request for rescue pain medication.
- Time of first opioid rescue.
- Opioid use.
- Conventional bupivacaine HCl use.
- Sensory function assessment (i.e., cold test) at baseline, when the subject wakes up after surgery (general anesthesia subjects only), and at 2, 4, 12, 24, 36, 48, 60, and 72 hours after surgery, or until the subject's sensitivity to cold is demonstrated on two consecutive evaluations.
- Overall benefit of analgesia score questionnaire at 24, 48, and 72 hours.
- Subject satisfaction with postsurgical pain control at 72 hours and Day 30 using a 5-point Likert scale.
- Predefined treatment-emergent opioid-related AEs at 72 hours following surgery during Part 1 only.

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Efficacy Endpoints:

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

Primary Endpoint

The primary efficacy endpoint is the AUC of the NRS-R pain intensity scores through 72 hours.

Secondary Endpoints

The following secondary endpoints will be analyzed using a hierarchical testing procedure.

- Total postsurgical opioid consumption (in mg) through 72 hours.
- Time to first opioid rescue.

Tertiary Endpoints

- Total postsurgical opioid consumption (in mg) through 24, 36, 48, and 60 hours.
- Overall benefit of analgesia score questionnaire at 24, 48, and 72 hours.
- Subject satisfaction with postsurgical pain control at 72 hours and Day 30.
- The NRS-R and NRS-A pain intensity scores at each assessed time point.
- The AUC of the NRS-R pain intensity scores through 24, 36, 48, and 60 hours.
- The AUC of the NRS-A pain intensity scores through 24, 36, 48, 60, and 72 hours.
- The AUC of the NRS-R pain intensity scores from 24-48 and 48-72 hours.
- Proportion of subjects who are pain free (defined as an NRS pain intensity score of 0 or 1) at each assessed time point.
- Proportion of subjects who receive the following rescue medication(s):
  - Subjects who receive no rescue medications (i.e., opioid or conventional bupivacaine HCl).
  - Subjects who only receive IV hydromorphone bolus.
  - Subjects who receive IV hydromorphone bolus and a second opioid medication.
  - Subjects who receive IV hydromorphone bolus, a second opioid medication, and conventional bupivacaine HCl.
- Proportion of subjects at each time point with sensitivity to cold in one of the dermatomes.

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Pharmacokinetic Endpoints (Part 1 only):

Pharmacokinetic parameters will be estimated from plasma bupivacaine measurements using non-compartmental analysis, based on the sampling schedule described above (at baseline, 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours *after the beginning of study drug administration*). The following parameters will be determined:

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

Safety Assessments:

The following safety measurements will be conducted at the specified time points:

- Adverse events from the time of randomization through Day 30.
- Vital signs (resting heart rate and blood pressure) at baseline, 30 minutes, 1 hour, and 2 hours after surgery.
- Neurological assessment at baseline, 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 60, and 72 hours after surgery.
- Cardiac assessment (i.e., ECG recordings) at baseline (beginning approximately 1 hour prior to study drug administration) through the first 72 hours after study drug administration. Electrocardiogram changes will be examined using the ECG data closest to the median T_{max} from each dose group.
- Motor function assessment (i.e., ability to perform a 20-meter walk, unassisted with the optional use of a 4-legged walker) at 24 hours and 72 hours after surgery and on Day 30.
- Physician satisfaction with return of sensory/motor function at 72 hours and on Day 30.

Safety Endpoints:

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

- Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) through Day 30.
- Change from baseline in vital signs (resting heart rate and blood pressure) at each assessed time point.
- Summary of neurological assessments (proportion of subjects who are oriented, and proportion of subjects who have any of the neurologic events).
- Change from baseline in ECG data closest to the median $T_{max.}$
- Proportion of subjects able to walk 20 meters, unassisted, at 24 hours, 72 hours, and on Day 30.
- Rating of physician satisfaction with return of sensory/motor function at 72 hours and on Day 30.

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Statistical Methods:

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

The efficacy results from Part 1 and Part 2 will not be combined.

Part 1

At the end of Part 1, an unblinded dose selection committee will review at least the results from the following assessments conducted during Part 1: (1) the AUC of the NRS-R pain intensity scores through 72 hours; (2) total postsurgical opioid consumption; (3) the time to first opioid rescue, and (4) safety data. Based on a clinical evaluation of the data, the committee will determine the apparent efficacy and safety of each of the three liposome bupivacaine dose levels tested and will recommend a dose level to be tested during Part 2 of the study.

Descriptive summaries will be provided by treatment group. Each dose of liposome bupivacaine will be compared to placebo using analysis of covariance (ANCOVA) with treatment as the main effect and the baseline NRS-R pain intensity score as a covariate for AUC of the NRS-R pain intensity scores through 72 hours, using analysis of variance (ANOVA) after a natural logarithm transformation for total postsurgical opioid consumption, and using a log-rank test for time to first opioid rescue. Summary statistics will be provided by treatment group for the safety assessments.

Adverse events and SAEs will be summarized by treatment group.

At the end of the study, descriptive summary statistics, without statistical tests, will be provided by treatment group for the other efficacy endpoints.

Part 2

The efficacy results from Part 2 will not include data from Part 1. Descriptive summaries will be provided by treatment group. Liposome bupivacaine will be compared to placebo using ANCOVA with treatment as the main effect and the baseline NRS-R pain intensity score as a covariate for AUC of the NRS-R pain intensity scores through 72 hours, using ANOVA after a natural logarithm transformation for total postsurgical opioid consumption, and using a log-rank test for time to first opioid rescue. For analyzing the two secondary endpoints a hierarchical testing procedure will be used. First the total postsurgical opioid consumption will be tested. If the test is significant at the 0.05 level then, and only then, time to first opioid rescue will be tested. This result will be declared statistically significant at the 0.05 significance level.

Safety data from Part 1 and Part 2 will be combined and summarized by treatment group.

Table 1. Time and Events Schedule of Study Procedures

	Screen Visit	Day-1 to Day 1[1]	15min	30min	1h	2h	4h	8h	12h	18h	24h	30h	36h	42h	48h	54h	60h	72h	Day 30
Time Window	**Within 30 days**		**±5 min**	**±5 min**	**±5 min**	**±15 min**	**±15 min**	**±30 min**	**±30 min**	**±1h**	**±1h**	**±1h**	**±1h**	**±2h**	**±2h**	**±2h**	**±2h**	**±4h**	**±4d**
Obtain signed informed consent	X																		
Assess/confirm eligibility	X	X																	
Medical/surgical history	X	X																	
Demographics and baseline characteristics	X																		
Pregnancy test (for women of childbearing potential only)		X																	
Urine drug screen		X																	
Physical examination		X																	
Vital signs[2]	X	X		X	X	X													
Perform neurological assessment[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Perform cardiac assessment (electrocardiogram recordings)[4]		◄----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	---►	
Perform sensory function assessment (cold test)[5]		X				X	X		X		X		X		X		X	X	
Perform motor function assessment (20-meter walk test)	X										X							X	X
Randomize subject and prepare study drug		X																	
Administer study drug within 2 hours of surgery; record start and stop time		X																	
Record intraoperative opioids administered and dose		X																	
Place femoral nerve catheter and install PCA pump (prior to the completion of surgery)		X																	
Conduct pain intensity assessments (NRS-R, NRS-A)[6]		X				X	X	X	X		X		X		X		X	X	
Record times and amounts of rescue medication administered		◄----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	---►	
Complete OBAS questionnaire											X				X			X	
Part 1 only (specific sites): Collect scheduled PK blood sample[7]		X	X	X	X	X	X	X	X		X		X		X		X	X	
Subject satisfaction with postsurgical pain control																		X	X
Part 1 only Question subject re: predefined treatment-emergent ORAEs																		X	
Physician satisfaction with return of sensory/motor function																		X	X
Record concomitant medications[8]	◄----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	---►
Record AEs (starting at randomization)[9]	◄----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	---►

Abbreviations: AE = adverse event; d = day; min = minutes; NRS-A = numeric rating scale with activity; NRS-R = numeric rating scale at rest; OBAS = overall benefit of analgesia score; OR = operating room; ORAEs = opioid-related adverse events; PCA = patient-controlled analgesia; PK = pharmacokinetic.

* Postsurgical efficacy assessments will be conducted at the time points specified *after the end of surgery*.

[1] Before study drug administration.

[2] Measure vital signs (heart rate and blood pressure) after subject has rested in supine position for at least 5 minutes.

[3] If the neurological assessment reveals a neurological event that the Investigator believes may be associated with high levels of systemic bupivacaine, an unscheduled PK blood sample should be collected at the time that the event is noted.

[4] Electrocardiogram testing should begin approximately 1 hour prior to study drug administration and continue through 72 hours after study drug administration.

[5] Sensory function will be assessed at baseline, when the subject wakes up after surgery (general surgery subjects only), and at 2, 4, 12, 24, 36, 48, 60, and 72 hours after the end of surgery, or until the subject's sensitivity to cold is demonstrated on two consecutive evaluations.

[6] Also record NRS pain intensity scores at first request for rescue pain medication.

[7] Collect blood samples for PK analysis from subjects at specific sites during Part 1 of the study at baseline, 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours *after the beginning of study drug administration*. Blood samples should be collected even if the subject is not yet in surgery or is still in surgery.

[8] Instruct subject to discontinue prohibited medications. Record date/time of all medications starting 3 days prior to surgery through 72 hours after surgery. Record medications administered for treatment of an AE through Day 30.

[9] If a cardiac or neurological event occurs during Part 1 or Part 2 of the study that the Investigator believes may be associated with high levels of systemic bupivacaine, an unscheduled PK blood sample should be collected at the time that the event is noted.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

4.1. List of Abbreviations

AE	Adverse event
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
ASA	American Society of Anesthesiologists
AUC	Area under the curve
$AUC_{0\text{-tlast}}$	The area under the plasma concentration-time curve from the time of administration to the time of the last quantifiable concentration calculated using the lin/log trapezoidal rule
$AUC_{0\text{-}\infty}$	The area under the plasma concentration-time curve from the time of administration extrapolated to infinity.
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	The maximum observed plasma concentration obtained directly from the experimental data without interpolation
CRF	Case Report Form
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numeric rating scale
NRS-A	Numeric rating scale with activity
NRS-R	Numeric rating scale at rest
NSAIDs	Non-steroidal anti-inflammatory drugs
OBAS	Overall benefit of analgesia score
OR	Operating room

PCA	Patient-controlled analgesia
PK	Pharmacokinetic
PO	Oral
QTcB	The heart rate-corrected QT interval using Bazett's formula
QTcF	The heart rate-corrected QT interval using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SNRI	Selective norepinepherine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
λ_z	The apparent terminal elimination rate constant
$t_{1/2el}$	The apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
TKA	Total knee arthroplasty
T_{max}	The time to attain C_{max}
US	United States (of America)
wWOCF	windowed Worst-Observation-Carried-Forward

4.2. Definition of Terms

Pharmacokinetic terms are defined in Section 12.4.

5. ETHICS

5.1. Institutional Review Board/Independent Ethics Committee

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

5.2. Ethical Conduct of the Study

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

5.3. Subject Information and Consent

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

The Investigator will explain to the subject that he/she is completely free to decline entry into the study and may withdraw from the study at any time, for any reason, without risking 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, sites, laboratories, and other service providers is available upon request to the IRB/ECs and regulatory agencies.

7. INTRODUCTION

7.1. Indication

Liposome bupivacaine was developed to extend pain relief with a single dose administration without the use of indwelling catheters and to decrease the requirement for supplemental opioid medications. It is indicated for use as an analgesic injected into the surgical site for postsurgical pain relief. This study will explore the safety, efficacy, and pharmacokinetic (PK) profile of liposome bupivacaine when administered via a femoral nerve block.

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

7.2. EXPAREL (bupivacaine liposome injectable suspension)

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

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

- Bupivacaine HCl solution, a well-characterized anesthetic/analgesic, with more than 35 years of use in the US.
- DepoFoam, a liposomal extended-release formulation contained in the marketed products DepoCyt® (1999) and DepoDur® (2004). The form of DepoFoam used in each of the three products – DepoCyt, DepoDur, and liposome bupivacaine – has a slightly different mixture of lipid components. However, unlike the other two products, EXPAREL employs a novel lipid excipient (dierucoylphosphatidylcholine [DEPC]) in its formulation.

7.3. Summary of Human Experience with Liposome Bupivacaine

Pacira has completed 21 clinical studies and 1 observational follow-up study to investigate liposome bupivacaine. Across these studies, over 1300 human subjects received liposome bupivacaine at doses ranging from 9 mg to 665 mg administered by various routes: local infiltration into the surgical wound, subcutaneous, perineural, and epidural. The product generally has been well tolerated and in active comparator studies reported adverse events (AEs) occurred at a similar rate as the corresponding bupivacaine HCl controls.

Two nerve block studies have been completed. SKY0402-002 was a Phase 1 dose escalation study conducted to evaluate the safety, pharmacodynamics, and pharmacokinetics of liposome bupivacaine. A total of 37 healthy subjects were administered liposome bupivacaine perineurally for unilateral ankle block in healthy male volunteers (24 subjects received liposome bupivacaine and 12 subjects received bupivacaine HCl). The incidence and types of adverse events experienced were similar across treatment groups. All AEs were mild or moderate in severity; those related to liposome bupivacaine were mild in severity. There were no serious adverse events (SAEs), deaths, or discontinuations due to adverse events.

SKY0402-C-203 was a Phase 2 nerve block study was performed in which three doses of liposome bupivacaine (155, 199, and 310 mg) were compared to bupivacaine HCl (125 mg) in a bunionectomy. A total of 38 patients received liposome bupivacaine. Liposome bupivacaine was well tolerated and several doses demonstrated statistically significant separation from bupivacaine HCl using multiple efficacy measures at multiple time points throughout the 72 hours; a PK curve also was defined.

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

The robust nature of the efficacy results in both pivotal studies (SKY0402-C-316 and SKY0402-C-317) was demonstrated across subgroups of patients with various prognostic features and across demographic subgroups.

Following the NDA submission of EXPAREL (liposome bupivacaine), numerous clinical studies were initiated in which liposome bupivacaine was administered via various routes of administration (including infiltration into the transversus abdominis plane [TAP] and intraoperative wound infiltration or instillation); final results are not available at this time.

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

8. OBJECTIVES

8.1. Primary Objectives

Part 1: The primary objectives of Part 1 are to (1) evaluate three dose levels of liposome bupivacaine versus placebo with respect to the magnitude and duration of the analgesic effect achieved following single dose injection femoral nerve block with liposome bupivacaine, and (2) select a single therapeutic dose of liposome bupivacaine from the three dose levels to be tested in Part 2.

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

8.2. Secondary Objectives

The secondary objectives are to evaluate additional efficacy parameters, characterize the PK profile of liposome bupivacaine when administered as a femoral nerve block, and further assess the safety profile of liposome bupivacaine.

9. STUDY DESIGN AND PLAN

9.1. Study Design

This is a Phase 2/3, multicenter, randomized, double-blind, parallel-group, placebo-controlled, dose-ranging study in subjects undergoing primary unilateral total knee arthroplasty (TKA) under general or spinal anesthesia. Note: Bupivacaine cannot be used as the spinal anesthetic.

On Day 1, eligible subjects will be randomized to receive a single dose of study drug administered within 2 hours prior to the surgical procedure as a femoral nerve block. Study drug administration will be performed in a blinded manner (see Section 11.5.1). At the conclusion of the block, a femoral nerve catheter is to be left in place and hep-locked (see "Postsurgical Rescue Medication" below). Additionally, a patient-controlled analgesia (PCA) pump will be established prior to the completion of the surgery. *The PCA pump will not be loaded at this time*. The use of fentanyl will be permitted during surgery. However, intraoperative administration of morphine or any other analgesics (including intrathecal opioids), local anesthetics, or anti-inflammatory agents is prohibited, unless needed to treat an AE.

All subjects will be required to remain in the study site for a minimum of 72 hours after the end of surgery for postsurgical assessments. The study staff will ensure adequate safety precautions are in place in order to prevent falls (e.g., use of support devices during ambulation, such as a knee immobilizer and walker/crutches) as needed.

Part 1

During Part 1 of the study, approximately 100 subjects (25 per treatment arm) will be randomized to receive a single dose injection femoral nerve block with either one of three doses of liposome bupivacaine (67, 133, or 266 mg) or placebo in 20 mL under ultrasound guidance. Preservative-free normal saline will be added to the 67 mg and 133 mg doses of study drug to achieve a volume of 20 mL.

After all subjects have completed the 72-hour assessments in Part 1, an analysis will be conducted in order to select a single therapeutic dose from the three liposome bupivacaine dose levels tested. An unblinded dose selection committee will review at least the results from the following assessments conducted during Part 1: (1) the area under the curve (AUC) of the numeric rating scale (NRS) at rest (NRS-R) pain intensity scores through 72 hours; (2) total postsurgical opioid consumption; (3) the time to first opioid rescue; and (4) safety data. Based on a clinical evaluation of the results the committee will determine the apparent efficacy and safety of each of the three liposome bupivacaine dose levels tested and will recommend a dose level for Part 2 of the study. Statistical significance will not be required in order to recommend a dose level for Part 2. The unblinded dose selection committee also will recommend whether the sample size for Part 2 should be increased.

Part 2

In Part 2 of the study, approximately 180 subjects (randomized 1:1, resulting in approximately 90 liposome bupivacaine subjects and 90 placebo subjects) will receive a single dose injection femoral nerve block with the selected dose of liposome bupivacaine (i.e., 67, 133, or 266 mg) or placebo in 20 mL under ultrasound guidance.

Postsurgical Rescue Medication

Subjects should only receive rescue medication upon request for pain control, as needed.

First Rescue Medication (IV Hydromorphone)

The first rescue medication will be intravenous (IV) hydromorphone 0.5 mg, which will be administered once via bolus only. At this time, the PCA should be loaded with opioid (morphine or hydromorphone only).

Second Rescue Medication (PCA and/or PO Opioid)

The second rescue medication will be an on-demand PCA-administered opioid (morphine or hydromorphone). The PCA pump will be programmed to deliver either on-demand morphine or on-demand hydromorphone boluses at a dose and lockout interval in accordance with the site's standard practice. A continuous infusion (background or basal rate) of morphine or hydromorphone is not permitted. If the subject's pain is excessive or pain control is inadequate, then the bolus dose may be adjusted according to local hospital practices; however, **adding a basal rate is prohibited**.

Once a subject is able to tolerate oral (PO) medication, PO immediate-release oxycodone may be administered (but not more than 10 mg every 4 hours).

Third Rescue Medication (Conventional Bupivacaine HCl)

If a subject's pain is inadequately controlled by opioids, a third rescue, a femoral nerve block, consisting of conventional bupivacaine HCl at a concentration of 0.125% (1.25 mg/mL) at a rate of 8 mL per hour for up to 12 hours may be administered via the previously placed femoral nerve catheter.

Subjects who do not receive adequate pain control with this regimen are to be withdrawn from the study and followed for AEs only. No other analgesic agents, including non-steroidal anti-inflammatory agents (NSAIDs), are allowed during the 72-hour observation period.

Postsurgical Assessments

Postsurgical assessments will include pain intensity scores using the 0-10 point NRS-R and NRS with activity (NRS-A) (where the prescribed activity is active knee flexion up to 45 degrees) (see Appendix 1); use of supplemental opioid pain medication; neurological assessment (see Appendix 2); cardiac assessment [i.e., ECG recordings]; sensory function assessment [i.e., cold test]; motor function assessment [i.e., 20-meter walk test]; vital signs; overall benefit of analgesia score (OBAS) questionnaire (see Appendix 3); subject satisfaction with postsurgical pain control (see Appendix 4); physician satisfaction with return of sensory/motor function (see Appendix 5); and an opioid-related AE questionnaire during Part 1 only (see Appendix 6). Adverse events will be recorded through Day 30. If a cardiac or neurological event occurs during Part 1 or Part 2 of the study that the Investigator believes may be associated with high levels of systemic bupivacaine, an unscheduled PK blood sample should be collected at the time that the event is noted.

Safety and efficacy assessments will be conducted at pre-specified time points *after the end of surgery* (defined as the time of last suture/staple). A follow-up visit will be scheduled for all subjects on Day 30.

Pharmacokinetic Assessments (Part 1 only)

Blood samples for PK analysis will be obtained from subjects at specific sites during Part 1 of the study at baseline, 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours *after the beginning of study drug administration*. Blood samples for PK analysis should be collected even if the subject is not yet in surgery or is still in surgery. Placebo samples will be collected to maintain the treatment double-blind but will not be analyzed. Samples from subjects receiving bupivacaine nerve block rescue will not be analyzed. (Note: At time points when the PK and NRS pain intensity assessments coincide, the NRS pain intensity assessments will be conducted before the blood draw.)

Unscheduled blood samples also may be collected during Part 1 or Part 2 of the study if a cardiac or neurological event occurs that the Investigator believes may be associated with high levels of systemic bupivacaine.

9.1.1. Duration of the Study and Subject Participation

Each subject's participation in this study could be up to 64 days (up to 30 days for the screening period and up to 34 days for post-dosing follow-up).

9.1.2. Study Stopping Rules

No formal stopping rules are planned for this study. If, however, Pacira, the Investigator, or officials from regulatory authorities discover conditions during the study that indicate that the study or study site should be terminated, this action may be taken after Pacira has consulted with appropriate regulatory authorities and notified the Investigator(s).

9.2. Discussion of Study Design

Liposome bupivacaine is approved for infiltration into a surgical wound. This multicenter, randomized, double-blind, parallel-group study is a comparison of the efficacy and safety of liposome bupivacaine to placebo when administered as a femoral nerve block in subjects undergoing unilateral TKA. The double blind study design is intended to avoid potential bias resulting from subject or Investigator knowledge of the assigned treatment.

Total knee arthroplasty is a frequently performed surgical procedure that causes postsurgical pain of considerable intensity and duration. Standard analgesia following TKA often includes IV and PO opioids postoperatively. Therefore, TKA was selected as an appropriate pain model for investigating a sustained-release formulation of bupivacaine, which has the potential to overcome the limitation reported in previous studies with regard to the duration of the analgesic effect obtained with commercially-available products.

During Part 1, subjects will receive a single dose femoral nerve block with one of three dose levels of liposome bupivacaine (67, 133, or 266 mg). An unblinded dose selection committee will review study data, determine the apparent efficacy and safety of each of the three liposome bupivacaine dose levels tested, and recommend a dose level to be tested during Part 2 of the study. In Part 2 of the study, subjects will receive a single dose injection femoral nerve block with the selected dose of liposome bupivacaine (i.e., 67, 133, or 266 mg) or placebo.

All subjects will receive an opioid (morphine, hydromorphone, and/or oxycodone) and conventional bupivacaine HCl, as needed, to control breakthrough postsurgical pain.

Neurological and cardiac assessments will be conducted to rule out bupivacaine toxicity related to high plasma exposure. Additionally, sensory and motor function assessments will be conducted in order to test for restoration of nerve function.

10. STUDY POPULATION

10.1. Inclusion Criteria

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

1. Male or female, ≥18 years of age.
2. Scheduled to undergo primary unilateral TKA under general or spinal anesthesia.
3. American Society of Anesthesiology (ASA) Physical Status 1, 2, or 3.
4. Able to demonstrate motor function by performing a 20-meter walk, unassisted with the optional use of a 4-legged walker, and sensory function by exhibiting sensitivity to cold.
5. Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments.

10.2. Exclusion Criteria

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

1. Currently pregnant, nursing, or planning to become pregnant during the study or within 1 month after study drug administration. Female subjects must be surgically sterile or at least 2 years menopausal, or using an acceptable method of birth control. If of child-bearing potential, must have a documented negative pregnancy test within 24 hours before surgery.
2. Planned concurrent surgical procedure (e.g., bilateral TKA).
3. Use of any of the following medications within the times specified before surgery: long-acting opioid medication, NSAIDs, or aspirin (except low-dose aspirin used for cardioprotection or acetaminophen) within 3 days, or any opioid medication within 24 hours.
4. Concurrent painful physical condition or concurrent surgery that may require analgesic treatment (such as an NSAID or opioid) in the postsurgical period for pain that is not strictly related to the surgical site administered study treatment, and which may confound the postsurgical assessments (e.g., significant pain from other joints including the non-index knee joint, chronic neuropathic pain, prior contralateral TKA, concurrent foot surgery).
5. Initiation of treatment with any of the following medications within 1 month of study drug administration or if the medication(s) are being given to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinepherine reuptake inhibitors (SNRIs), gabapentin, pregabalin (Lyrica®), or duloxetine (Cymbalta®).
6. Current use of systemic glucocorticosteroids within 1 month of enrollment in this study.
7. Body weight < 50 kilograms (110 pounds) or a body mass index ≥ 40 kg/m^2.
8. Contraindication to hydromorphone, oxycodone, or bupivacaine.

9. Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study.
10. Previous participation in a liposome bupivacaine study.
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. Failure to pass the urine drug screen.
13. Uncontrolled anxiety, schizophrenia, or other psychiatric disorder that, in the opinion of the Investigator, could interfere with study assessments or compliance.
14. Malignancy in the last 2 years, with the exception of non-metastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.
15. Current or historical evidence of any clinically significant disease or condition, especially cardiovascular or neurological conditions that, in the opinion of the Investigator, may increase the risk of surgery or complicate the subject's postsurgical course.
16. Significant medical conditions or laboratory results that, in the opinion of the Investigator, indicate an increased vulnerability to study drugs and procedures.
17. Subjects who are planned to receive Entereg® (alvimopan).
18. Subjects who will receive prophylactic antiemetics or planned postsurgical antiemetics given without regard to the subject's emesis needs.
19. Use of dexmedetomidine HCl (Precedex®) within 3 days of surgery.

10.3. Removal of Subjects from Therapy or Assessment

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

Subjects who withdraw from the study postsurgically should be followed for AEs . All AEs that occur through Day 30 after surgery must be recorded. If a subject who withdraws from the study has an ongoing AE, every effort must be made to follow such events until satisfactory resolution is obtained, or further follow-up is otherwise no longer warranted.

Safety assessments performed during the early termination visit should include the neurological examination, cold test, 20-meter walk test, and collection of a blood sample for PK analysis, if possible.

10.3.1. Withdrawal Secondary to Adverse Events

If a subject experiences an AE that renders him/her incapable of continuing with the remaining study assessments, then he/she will be discontinued from further participation in the study. A final evaluation should be performed so that the subject's study participation can be terminated in a safe and orderly manner (see Section 10.3).

10.3.2. Voluntary or Study Investigator Withdrawal

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

If a subject is discontinued by the Investigator or voluntarily withdraws from the study after receiving liposome bupivacaine, he/she should be followed for AEs (see Section 10.3). A final evaluation should be performed so that the subject can be terminated in a safe and orderly manner.

11. TREATMENTS

11.1. Treatment to be Administered

Study Drug

Subjects will receive a single dose injection femoral block with either one of three doses of liposome bupivacaine (67, 133, or 266 mg) or placebo (preservative-free normal saline) in 20 mL volume under ultrasound guidance according to the randomization schedule. Preservative-free normal saline will be added to the 67 mg and 133 mg doses of study drug to achieve a volume of 20 mL (i.e., 15 mL of saline will be added to the 67 mg dose [5 mL] of liposome bupivacaine and 10 mL of saline will be added to the 133 mg dose [10 mL]). Study drug administration will be performed by study personnel who are NOT involved with protocol-specific, postsurgical assessments.

Rescue Medication

Subjects should only receive rescue medication upon request, as needed.

The first rescue medication will consist of IV hydromorphone 0.5 mg, which will be administered once via bolus only. At this time, the PCA should be loaded with opioid (morphine or hydromorphone only).

The second rescue medication will consist of an on-demand PCA-administered opioid (morphine or hydromorphone). The PCA pump will be programmed to deliver either on-demand morphine or on-demand hydromorphone boluses at a dose and lockout interval consistent with the site's standard practice. A continuous infusion (background or basal rate) of morphine or hydromorphone is not permitted. If the subject's pain is excessive or pain control is inadequate, then the bolus dose may be adjusted according to local hospital practices; however, **adding a basal rate is prohibited**. Once the subject is tolerating PO medication, PO immediate-release oxycodone may be administered (but not more than 10 mg every 4 hours).

If a subject's pain is inadequately controlled by opioids, a third rescue, a femoral nerve block, consisting of conventional bupivacaine HCl at a concentration of 0.125% (1.25 mg/mL) at a rate of 8 mL per hour for up to 12 hours will be administered via the previously placed femoral nerve catheter.

No other analgesic agents, including NSAIDs, are allowed during the 72-hour observation period or until the subject is withdrawn from the study, whichever is sooner. Subjects who do not achieve adequate pain relief with this regimen will be withdrawn from the study and followed for AEs per Section 10.3.

11.1.1. Administration Technique

Study drug (liposome bupivacaine or placebo) will be administered under ultrasound guidance by the anesthesiologist into the femoral nerve as described below (adopted from Mariano 2009).

Patients will have their femoral nerve located by ultrasound guidance alone. The recommended method is as follows: With a linear array transducer in a sterile sleeve, the femoral nerve will be identified in a transverse (short-axis) view at the inguinal crease. In a transverse view, the

internal appearance of the peripheral nerve bundle is a mixture of hypoechoic neural tissue (fascicles) and hyperechoic connective tissue (perineurium and epineurium). Once the optimal image of the femoral nerve is obtained, a local anesthetic skin wheal will be raised lateral to the ultrasound transducer. A needle will be inserted through the skin wheal and directed medially in plane beneath the ultrasound transducer toward the femoral nerve. The study drug (20 mL) will be injected posterior to the femoral nerve *via* the needle. A flexible epidural-type catheter will then be placed through the length of the needle and advanced 5 cm beyond the needle tip. Once the catheter has been inserted, the needle itself will be withdrawn over the catheter. The catheter tip position will be assessed by injecting 1 mL of air via the catheter under ultrasound guidance with the appearance of hyperechoic air bubbles posterior to the femoral nerve confirming proper catheter placement (and replaced, if necessary). Because the in-plane ultrasound-guided needle placement technique effectively "tunnels" the catheter in a lateral-to-medial direction under the transducer, the catheter will not be tunneled further. The catheter will be secured with sterile liquid adhesive, a clear occlusive dressing, and an anchoring device to affix the catheter hub to the subject. After negative aspiration, 2 mL of normal saline will be injected *via* the catheter to help ensure future patency.

11.1.2. Study Drug Administration Considerations

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

Administration of additional local anesthetics including bupivacaine or lidocaine is prohibited except where specified for spinal anesthesia or rescue. Bupivacaine cannot be used as the spinal anesthetic. Liposome bupivacaine may not be administered to a subject if it has been held in a syringe for more than 4 hours after preparation. In order to prevent the study drug from settling, gently inverting and re-inverting the syringe several times prior to administration is recommended.

11.2. Identity of Investigational Product(s)

11.2.1. Description of Liposome Bupivacaine

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

11.2.2. Description of Reference Product

Placebo will consist of preservative-free normal saline for injection and will be supplied by the study sites. Subjects in the placebo group will receive 20 mL of placebo.

11.2.3. Description of Diluents

Preservative-free normal saline for injection will be added to the 67 mg (5 mL) and 133 mg (10 mL) doses of study drug to achieve a volume of 20 mL.

11.3. Method of Assigning Subjects to Treatment

11.3.1. Randomization Scheme

In Part 1 of the study, approximately 100 subjects (25 per treatment arm) will be randomized to receive a single dose injection femoral block with either one of three doses of liposome bupivacaine (67, 133, or 266 mg) or placebo.

In Part 2 of the study, approximately 180 subjects (randomized 1:1, resulting in approximately 90 liposome bupivacaine subjects and 90 placebo subjects) will be randomized to receive single dose injection femoral nerve block with the selected dose level (i.e., 67, 133, or 266 mg liposome bupivacaine) or placebo.

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

11.3.2. Randomization Procedures

Once a subject is identified as being qualified for the study per the eligibility criteria (see Section 10.1 and Section 10.2), and is at the study site for surgery, the research pharmacist or designee will contact the centralized randomization service to obtain a randomization assignment (4-digit random code identifier). The subject will be considered randomized into the study once the assignment is received.

11.3.3. Replacement of Subjects

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

11.4. Selection of Doses in the Study

During the clinical development of liposome bupivacaine, single doses ranging from 9 mg to 665 mg were safely administered via various routes. Pharmacokinetic studies have shown that because liposome bupivacaine releases bupivacaine gradually as the lipid structure breaks down, administration of liposome bupivacaine 266 mg results in a maximum plasma concentration equivalent to that seen with standard bupivacaine 100 mg. Based on this experience, a similar maximum total dose was deemed appropriate for this study.

During Part 1 of the current study, subjects will receive a single dose femoral nerve block with one of three dose levels of liposome bupivacaine (67, 133, or 266 mg) or placebo. During Part 2 of the study, subjects will receive a single dose injection femoral nerve block with the selected dose level of liposome bupivacaine (i.e., 67, 133, or 266 mg) or placebo.

11.5. Blinding

11.5.1. Blinding Procedures

Liposome bupivacaine and placebo are visually distinguishable; therefore, to maintain the double-blind study design, the Principal Investigator and any study personnel involved in protocol-specific postsurgical assessments will remained blinded to treatment assignment. Only unblinded study personnel who are NOT involved with protocol-specific, postsurgical assessments may prepare or administer the study drug. Staff members conducting study-specific, postsurgical assessments and the subjects will remain blinded to the assigned treatment throughout the study. If a subject experiences an SAE, Pacira will not automatically unblind the subject's treatment, unless it is necessary to manage treatment of the SAE. Expedited SAEs will be unblinded by Pacira for regulatory reporting purposes.

Unblinded randomization assignments will be provided via a randomization system. At each site, only the individual(s) who are identified in the randomization system to receive unblinded randomization assignments will be responsible for preparing study drug.

Site surveys suggest that study sites will vary in their standard (and feasible) procedures for preparing sterile study drug in a blinded fashion. Therefore, each site will be responsible for providing their written blinding procedures for study drug preparation, transportation, and administration that will ensure that the blind is maintained throughout each of these steps. This documentation will be made available to Pacira for review before the site enrolls a subject into the study. Assignment of blinded and unblinded responsibilities regarding the preparation of study drug should take into account that **liposome bupivacaine may not be held in a syringe for more than 4 hours after preparation for administration**.

The presurgical administration of study drug will be recorded using the minimal amount of information necessary to avoid unblinding staff who will be participating in blinded procedures.

No crossover will be permitted between the blinded and unblinded study site personnel during the study period. The assignment of site monitors will also be segregated. Blinded monitors will review case report forms (CRFs), clinic charts, and all other study-related documents that do not disclose the allocation of study treatment. Care should be taken in recording and review of operating room records to not record information in an unblinded fashion. Pharmacy or any other clinic records providing unblinded information (e.g., randomization, study drug preparation, study drug accountability, study drug administration) will be reviewed by specialized unblinded monitors who will notify Pacira of treatment noncompliance.

11.5.2. Unblinding Procedures

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

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

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

11.6. Prior and Concomitant Therapy and Medications

11.6.1. Prior and Concomitant Medications and Therapy

Permitted Prior Medications and Therapy

- Low-dose aspirin for cardioprotection.
- Acetaminophen use is permitted up to the time of surgery.

Restricted Prior Medications and Therapy

- Systemic glucocorticosteroids are not permitted within 1 month of enrollment into this study.
- Initiation of treatment with any of the following medications within 1 month of study drug administration or if the medication(s) are being given to control pain is not permitted: SSRIs, SNRIs, gabapentin, pregabalin (Lyrica), or duloxetine (Cymbalta).
- Long-acting opioid medications, NSAIDs, or aspirin (except for low-dose aspirin used for cardioprotection or acetaminophen) are not permitted within 3 days of study drug administration.
- Dexmedetomidine HCl (Precedex) use is not permitted within 3 days of surgery.
- No opioid medications are permitted within 24 hours of study drug administration.

Concomitant medications

All medications taken within 3 days of study drug administration and up to 72 hours after the end of surgery or until the subject is withdrawn from the study, whichever is sooner, will be recorded on the CRF. Any medications administered in association with AEs occurring during the study will be recorded through Day 30.

11.6.2. Permitted and Restricted Therapy or Medications During Surgery

Permitted

- Short and ultra-short acting opioids (e.g., fentanyl) will be allowed during surgery.

Restricted

- Bupivacaine cannot be used as the spinal anesthetic.
- No agents are to be admixed with liposome bupivacaine (e.g., epinephrine, dexamethasone, and clonidine).

- Lidocaine and other local anesthetics will not be permitted to be locally administered during the surgery because they are known to interact with liposome bupivacaine resulting in the displacement of bupivacaine and elevated plasma levels.
- Intrathecal opioids.
- The use of opioids other than fentanyl (e.g., morphine, hydromorphone HCl), acetaminophen, ketorolac, or other NSAIDs will not be permitted intraoperatively except for emergency use to treat an AE.
- Entereg (alvimopan) use is prohibited.
- Prophylactic antiemetics or planned postsurgical antiemetics given without regard to the subject's emesis needs is prohibited.

11.6.3. Permitted and Restricted Therapy or Medications After Surgery through 72 Hours After Surgery

Permitted

- Rescue medication use is permitted as described in Section 11.

Restricted

- No other analgesics are permitted within 72 hours after surgery.
- Entereg (alvimopan) use is prohibited.
- Prophylactic antiemetics or planned postsurgical antiemetics given without regard to the subject's emesis needs.
- Dexmedetomidine HCl (Precedex) use is prohibited.

For study purposes, it is important to standardize pain management modalities during the first 72 hours following study drug administration. Therefore, the study staff must adhere closely to the treatment options and requirements noted in the protocol. After 72 hours, the analgesic regimen may be adjusted for each subject individually, as deemed appropriate by the physician responsible for the postsurgical care.

All concomitant medication will be recorded through 72 hours after the end of surgery or until the subject is withdrawn from the study, whichever is sooner.

11.7. Treatment Compliance

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

11.8. Accountability of Study Drug

Any shipment of liposome bupivacaine 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 liposome bupivacaine 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 Assessments

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

- Pain intensity scores using the NRS-R at baseline (prior to the nerve block) and 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours, and at first request for rescue pain medication (Appendix 1).
- Pain intensity scores using the NRS-A (where the prescribed activity is actively flexing the involved knee up to 45 degrees) at baseline (prior to the nerve block) and 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours, and at first request for rescue pain medication (Appendix 1).
- Time of first opioid rescue.
- Opioid use.
- Conventional bupivacaine HCl use.
- Sensory function assessment (i.e., cold test) at baseline, when the subject wakes up after surgery (general surgery subjects only), and at 2, 4, 12, 24, 36, 48, 60, and 72 hours after surgery, or until the subject's sensitivity to cold is demonstrated on two consecutive evaluations.
- Overall benefit of analgesia score questionnaire at 24, 48, and 72 hours (Appendix 3).
- Subject satisfaction with postsurgical pain control at 72 hours and Day 30 using a 5-point Likert scale (Appendix 4).
- Predefined treatment-emergent opioid-related AEs at 72 hours following surgery during Part 1 only (Appendix 6).

12.2. Efficacy Endpoints

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

Primary Endpoint

The primary efficacy endpoint is the AUC of the NRS-R pain intensity scores through 72 hours.

Secondary Endpoints

The following secondary endpoints will be analyzed using a hierarchical testing procedure:

- Total postsurgical opioid consumption (in mg) through 72 hours.
- Time to first opioid rescue.

Tertiary Endpoints

- Total postsurgical opioid consumption (in mg) through 24, 36, 48, and 60 hours.
- Overall benefit of analgesia score questionnaire at 24, 48, and 72 hours.
- Subject satisfaction with postsurgical pain control at 72 hours and Day 30.
- The NRS-R and NRS-A pain intensity scores at each assessed time point.
- The AUC of the NRS-R pain intensity scores through 24, 36, 48, and 60 hours.
- The AUC of the NRS-A pain intensity scores through 24, 36, 48, 60, and 72 hours.
- The AUC of the NRS-R pain intensity scores from 24-48 and 48-72 hours.
- Proportion of subjects who are pain free (defined as an NRS pain intensity score of 0 or 1) at each assessed time point.
- Proportion of subjects who receive the following rescue medication(s):
  - Subjects who receive no rescue medications (i.e., opioid or conventional bupivacaine HCl).
  - Subjects who only receive IV hydromorphone bolus.
  - Subjects who receive IV hydromorphone bolus and a second opioid medication.
  - Subjects who receive IV hydromorphone bolus, a second opioid medication, and conventional bupivacaine HCl.
- Proportion of subjects at each time point with sensitivity to cold in one of the dermatomes.

12.3. Pharmacokinetic Measurements (Part 1 Only)

Blood samples for PK analysis will be obtained from subjects at specific sites during Part 1 of the study at baseline, 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours *after the beginning of study drug administration*. Blood samples for PK analysis should be collected even if the subject is not yet in surgery or is still in surgery. Placebo samples will be collected to maintain the treatment double-blind but will not be analyzed. Samples from subjects receiving bupivacaine nerve block rescue will not be analyzed. (Note: At time points when the PK and NRS pain intensity assessments coincide, the NRS pain intensity assessments will be conducted before the blood draw.)

12.4. Pharmacokinetic Endpoints

Pharmacokinetic parameters are to be estimated from the plasma bupivacaine concentration-time profiles by non-compartmental analysis and are to include the following:

$AUC_{0\text{-tlast}}$ The area under the plasma concentration-time curve from the time of administration to the time of the last quantifiable concentration calculated using the lin/log trapezoidal rule.

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

12.5. Safety Assessments

The following safety assessments will be conducted at the times specified:

- Adverse events from the time of randomization through Day 30.
- Vital signs (resting heart rate and blood pressure) at baseline, 30 minutes, 1 hour, and 2 hours after surgery.
- Neurological assessment at baseline, 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 60, and 72 hours after surgery (see Appendix 2).
- Cardiac assessment (i.e., ECG recordings) at baseline (beginning approximately 1 hour prior to study drug administration) through 72 hours after study drug administration. Electrocardiogram changes will be examined using the ECG data closest to the median T_{max} from each dose group.
- Motor function assessment (i.e., ability to perform a 20-meter walk, unassisted with the optional use of a 4-legged walker) at 24 hours, 72 hours, and on Day 30.
- Physician satisfaction with return of sensory/motor function at 72 hours and on Day 30 (see Appendix 5).

12.6. Safety Endpoints

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

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

- Proportion of subjects able to walk 20 meters, unassisted, at 24 hours, 72 hours, and on Day 30.
- Rating of physician satisfaction with return of sensory/motor function at 72 hours and Day 30.

12.7. Appropriateness of Measures

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

The neurological and cardiac safety assessments are based on the known signs and symptoms associated with systemic bupivacaine toxicity. The motor and sensory function assessments are standard tests to determine restoration of nerve function.

13. STUDY PROCEDURES

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

13.1. Instructions for Conducting Procedures and Measures

With the exception of the PK assessments (which will be conducted after the beginning of study drug administration), all assessments conducted after baseline will be timed from the end of surgery. Day 1 is defined as the day on which study drug is administered. The beginning of surgery is defined as the time of the first incision. The end of surgery is defined as the time of the last suture/staple. Postsurgical is defined as after the end of surgery.

Subjects will be hospitalized for at least 72 hours after surgery; therefore, postsurgical analgesia and collection of study data through the primary endpoint will take place under the supervision of study staff.

13.1.1. Pain Intensity Assessments

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

The subject's pain intensity will be assessed with activity (NRS-A). The prescribed activity is active knee flexion up to 45 degrees. The subject will respond to the following question, "*On a scale of 0 to 10, where 0 = no pain and 10 = worst possible pain, how much pain are you having right now?"* The subject's response will be recorded.

Note: At time points when the NRS pain intensity assessments coincide, the NRS-R will be conducted before the NRS-A. At time points when the NRS pain intensity assessment(s) and a PK assessment coincide, the NRS assessment will be conducted before the blood draw. Additionally, if ice or passive extenders are used, these must be stopped at least 15 minutes prior to the NRS pain intensity assessments. If subjects are in immobilizers, these must be removed at least 15 minutes prior to the NRS pain intensity assessments.

13.1.2. Overall Benefit of Analgesia Score Questionnaire

The OBAS questionnaire (Lehmann 2010) will be completed at 24, 48, and 72 hours (see Appendix 3).

13.1.3. Neurological Assessment

A neurological assessment will be conducted at baseline, 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 60, and 72 hours after surgery. The examination will include the subject's orientation. Additionally, the subject will be asked whether s/he is experiencing any numbness and tingling of the mouth and lips, a metallic taste, blurred vision, tremors, or twitching (see Appendix 2). If the neurological assessment reveals a neurological event that the

Investigator believes may be associated with high levels of systemic bupivacaine, an unscheduled PK blood sample should be collected at the time that the event is noted.

13.1.4. Cardiac Assessment (Electrocardiogram Recordings)

Digital 12-lead holter ECGs will be recorded using the Mortara Instrument Digital H12+™ ECG continuous recorder (Mortara Instrument, Inc., Milwaukee, Wisconsin), which will continuously record all 12 leads simultaneously from baseline through approximately 72 hours after drug administration. The ECG signal will be recorded on compact flash memory cards provided to the sites. The subject's unique identification number and demographic information will be recorded for each card. Without knowledge of subject treatment assignment, a central laboratory will generate a 10-second, 12-lead digital ECG at each time point specified in the protocol. If targeted ECG time points are artifactual and of poor quality, the central laboratory will capture analyzable 10-second ECGs as close as possible to the targeted time points.

Digital ECGs will be transmitted by the central laboratory and processed via its validated data management system, EXPERT. Interval duration measurements will first be obtained by trained analysts using the proprietary validated electronic caliper system applied on a computer screen utilizing the method of Global Median Beat. The Global Median Beat is created by an algorithm, where one representative beat for each of the 12 leads is selected and superimposed, creating a single superimposed (Global Median) beat. Trained analysts will then review for correct interval duration measurement (IDM) caliper placement and adjudicate the pre-placed algorithm calipers as necessary. A cardiologist will then verify the interval durations and perform the morphology analysis, noting any T-U wave complex that suggests an abnormal form compatible with an effect on cardiac repolarization.

On-screen measurements of the HR, PR, QRS, and QT interval durations will be performed and derived variables RR, QTcF, and QTcB will be calculated using the following formulae:

$QTcB = QT/\sqrt{RR}$

$QTcF = QT/\sqrt[3]{RR}$

$RR = 60/HR$

Each fiducial point (onset of P wave, onset of Q wave, offset of S wave, and offset of T wave) will be marked. The original ECG waveform and such annotations will be saved separately in XML format for independent review.

Electrocardiogram changes in RR, PR, QRS, QT, QTcF, and QTcB will be examined at the time closest to the median T_{max}.

13.1.5. Sensory Function Assessment (Cold Test)

For the sensory function assessment, the subject's sensitivity to cold in the innervated dermatomes (L2, L3) (see Appendix 7) will be assessed at baseline, when the subject wakes up after surgery (general surgery subjects only), and at 2, 4, 12, 24, 36, 48, 60, and 72 hours after surgery, or until the subject's sensitivity to cold has returned in two consecutive evaluations.

The subject's skin will be wiped with ice or an alcohol pad. The subject will then be asked, "Does this feel cold - yes or no?"

13.1.6. Motor Function Assessment (20-Meter Walk Test)

Each subject's ability to perform a 20-meter walk, unassisted with the optional use of a 4-legged walker, on a level surface will be assessed at baseline (during screening) and postsurgically at 24 hours, 72 hours, and on Day 30.

Subjects will be transported to the start of the course by wheelchair, assisted into a standing position, and instructed to walk from end-to-end at their own pace while attempting to cover 20 meters with or without using a four-leg walker. The following standardized limited encouragement from the staff should be offered: "You're doing well" or "Keep up the good work." The outcome of the test will be recorded as either "yes" (the subject was able to walk the full 20 meter distance) or "no" (the subject was unable to walk the full 20 meter distance).

13.1.7. Vital Signs

Vital signs (heart rate and blood pressure) will be assessed after the subject has rested in a supine position for at least 5 minutes and before the NRS assessments when the assessments coincide. The subject will remain in a supine position during the assessment.

13.1.8. Subject Satisfaction with Postsurgical Pain Control

The subject's satisfaction with postsurgical pain control will be assessed at 72 hours and Day 30 using the Likert Scale (see Appendix 4).

13.1.9. Physician Satisfaction with Sensory/Motor Function

The physician's satisfaction with return of sensory/motor function will be assessed at 72 hours and on Day 30 using a Likert scale (see Appendix 5).

13.1.10. Fall Prevention

The study staff must ensure adequate safety precautions are in place in order to prevent falls (e.g., use of a knee immobilizer and walker/crutches during ambulation, as needed). Additionally, the study staff must be educated regarding possible continuous peripheral nerve block-induced muscle weakness and necessary fall precautions.

13.2. Screening Procedures

- Explain study purpose and procedures.
- Obtain signed ICF.
- Assess eligibility.
- Record relevant medical/surgical history, demographics, and baseline characteristics.
- Measure vital signs (heart rate and blood pressure) after subject has rested for at least 5 minutes in the supine position.
- Record concomitant medications taken within 3 days prior to surgery.
- Test ability of subject to perform 20-meter walk, unassisted with the optional use of a 4-legged walker, per Section 13.1.6.

13.3. Baseline Procedures (Day -1 to Day 1)

- Confirm eligibility.
- Update relevant medical/surgical history.
- Perform urine pregnancy test for women of childbearing potential before study drug administration.
- Perform urine drug screen.
- Perform physical examination.
- Measure vital signs (heart rate and blood pressure) after subject has rested for at least 5 minutes in the supine visit.
- Record subject's baseline assessment of pain intensity using the NRS-R followed by the NRS-A (see Appendix 1).
- Perform neurological assessment (see Appendix 2).
- Start 12-lead digital ECG recording approximately 1 hour prior to study drug administration.
- Perform sensory function assessment (cold test).
- Part 1 only: Collect baseline blood sample for PK analysis (specific sites only).
- Record concomitant medications taken within 3 days prior to surgery.
- Randomize subject and prepare study drug (Day 1).
- Administer study drug according to the randomization schedule within 2 hours prior to the surgical procedure.
- Record start and stop time of study drug administration.
- At the conclusion of the block, place and hep-lock the femoral nerve catheter.
- Record AEs starting after subject randomization.

13.4. Intraoperative Procedures

- Install the PCA pump (unloaded) prior to the completion of the surgery.
- Record start and stop times of surgery.
- Record intraoperative opioids administered.
- Perform ECG recordings.
- Part 1 only: Collect blood samples for PK analysis (specific sites only) per Section 12.3. (Blood samples for PK analysis should be collected even if the subject is not yet in surgery or is still in surgery.)
- Record concomitant medications.
- Record AEs and any treatment(s) for the events.

- If a cardiac or neurological event occurs during Part 1 or Part 2 of the study that the Investigator believes may be associated with high levels of systemic bupivacaine, an unscheduled PK blood sample should be collected at the time that the event is noted.

13.5. Procedures After Surgery Through 72 Hours

Part 1 Only

- Question subject regarding the predefined treatment-emergent opioid-related AEs at 72 hours after surgery (see Appendix 6).
- Collect scheduled blood samples for PK analysis at specific sites only per Section 12.3.

Parts 1 and 2

- Administer rescue medication for breakthrough pain per Section 11.
- Load PCA pump with morphine or hydromorphone if IV hydromorphone 0.5 mg × 1 bolus is administered.
- Record date, time, and amount of all rescue medication administered (IV hydromorphone bolus, PCA opioid, oxycodone, and/or conventional bupivacaine HCl) through 72 hours after surgery.
- Record subject's assessment of pain intensity using the NRS-R followed by the NRS-A at the following time points: 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after surgery and at first request for rescue pain medication, if applicable (see Appendix 1).
- Perform neurological assessment at 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 60, and 72 hours after surgery per Section 13.1.3 (see Appendix 2).
- Perform cardiac assessment (i.e., 12-lead digital ECG recordings) through 72 hours after study drug administration.
- Perform sensory function assessment (i.e., cold test) when the subject wakes up after surgery (general anesthesia subjects only), and at 2, 4, 12, 24, 36, 48, 60, and 72 hours after surgery, or until the subject's sensitivity to cold has returned to the baseline level in two consecutive evaluations per Section 13.1.5.
- Perform motor function assessment (i.e., ability of subject to perform a 20-meter walk, unassisted with the optional use of a 4-legged walker) at 24 hours and 72 hours per Section 13.1.6.
- Measure vital signs (heart rate and blood pressure) after subject has rested for at least 5 minutes in the supine position at 30 minutes, 1 hour, and 2 hours after surgery.
- Complete OBAS questionnaire (see Appendix 3) at 24, 48, and 72 hours after surgery.
- Obtain overall rating of subject satisfaction with postsurgical pain control using the Likert scale at 72 hours after surgery (see Appendix 4).
- Record AEs and any treatment(s) for the events.

- If a cardiac or neurological event occurs during Part 1 or Part 2 of the study that the Investigator believes may be associated with high levels of systemic bupivacaine, an unscheduled PK blood sample should be collected at the time that the event is noted.
- Record concomitant medications.
- Assess physician's satisfaction with return of sensory/motor function using a Likert scale (see Appendix 5).

13.6. Additional Procedures at Withdrawal if Prior to 72 Hours

- Perform neurological assessment per Section 13.1.3 (see Appendix 2).
- Perform sensory function assessment (i.e., cold test) unless the subject's sensitivity to cold has returned to the baseline level in two consecutive evaluations per Section 13.1.5.
- Perform motor function assessment (i.e., ability of subject to perform a 20-meter walk, unassisted with the optional use of a 4-legged walker) per Section 13.1.6.
- Collect blood sample for PK analysis, if possible.

13.7. Postsurgical Visit (Day 30)

- Obtain overall rating of subject satisfaction with postsurgical pain control using the Likert scale (see Appendix 4).
- Test ability of subject to perform a 20-meter walk, unassisted with the optional use of a 4-legged walker, per Section 13.1.6.
- Assess physician's satisfaction with return of sensory/motor function using a Likert scale (see Appendix 5).
- Record AEs and any treatment(s) for the events.

14. ADVERSE EVENT REPORTING

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

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

14.1. Adverse Events

14.1.1. Definitions

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

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

An AE that occurs after randomization and before the start of the study drug administration is identified as a pretreatment AE (PTAE). An AE that occurs after the administration of the study treatment is considered a TEAE. All AEs must be recorded and reported accordingly, whether they appear causally related to the study drug or not. Adverse events will be followed until the outcome is known or until the end of the study.

Definition of Adverse Reaction: Any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

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

14.1.2. Recording Adverse Events

It is the responsibility of the Investigator to document all AEs (i.e., PTAEs and TEAEs) with an onset after the subject is randomized. For the purpose of this study, all AEs that occur through Day 30 after surgery must be recorded regardless of whether or not they are considered related to study drug. Whenever feasible, AE terms should be documented as medical diagnoses (highest possible level of integration); otherwise, the AEs should be reported separately as individual signs or symptoms. Only one AE per line should be recorded in the AE CRF; for example, an AE of nausea and vomiting should be listed as two separate events: the event of nausea and the event of vomiting. If a diagnosis is established after symptoms are recorded on the AE CRF, the diagnosis should be recorded and the symptoms collapsed (removed; i.e., lined through and initialed). Whenever possible, abnormal laboratory results should be reported as their clinical corollary (e.g., low potassium should be recorded as hypokalemia).

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

Any condition noted before the subject is randomized will be listed as Medical History and is considered a pre-existing condition. If a pre-existing condition changes (i.e., becomes more severe or more frequent), at any time after randomization, or after study drug administration, it is considered an AE. 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

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

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

14.1.4. Relationship of Adverse Events to Study Drug

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

Not Related:	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).

Related: There is reason to conclude that the drug caused the event (i.e**.,** ***there is a reasonable possibility*** based on evidence to suggest that the drug caused the event).

14.1.5. Outcome of Adverse Events

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

Recovered/Resolved: The event resolved and the subject recovered from the AE.

Recovered/Resolved with Sequelae: The initial event resolved, but has a continuing abnormal condition as a result of the AE.

Not Recovered/ Not Resolved: At the time of last assessment, the event was ongoing, with an undetermined outcome. Note: ongoing AEs are not to be considered resolved as a result of death.

Recovering/Resolving: At the time of last assessment, the event was decreasing in frequency, severity, etc., and a resolution was expected.

Fatal: The AE directly caused death.

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

14.1.6. Action Taken with Subject due to an Adverse Event

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

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

14.2. Serious Adverse Events

14.2.1. Definition of a Serious Adverse Event

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

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

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

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

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

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

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

14.2.2. Reporting Serious Adverse Events

Any SAE or death that occurs at any time after randomization through Day 30, whether or not related to study drug, must be reported by the Investigator or designee to Pacira Drug Safety or designee by telephone or fax within 24 hours of discovery. Telephone contact information for Pacira Drug Safety/designee can be found in the regulatory binder.

Investigators should not wait to receive additional information to fully document the event before notifying Pacira Drug Safety or designee of the SAE. The telephone or fax 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 subject-identifying information redacted prior to forwarding to Pacira Drug Safety or designee. In the event of a fatal or life-threatening SAE, any required follow-up must be provided to Pacira Drug Safety or designee immediately. The Investigator will follow all SAEs until resolved or the condition stabilizes and further follow-up is not warranted.

If the Investigator is made aware of any SAEs after Day 30, these should also be reported to Pacira Drug Safety or designee provided the SAE is considered related to study drug. 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. A separate SAP will be developed for the analysis of the ECG results.

15.1. Study Hypothesis

Part 1

The primary objectives of Part 1 are to (1) evaluate three dose levels of liposome bupivacaine versus placebo with respect to the magnitude and duration of the analgesic effect achieved following single dose injection femoral nerve block with liposome bupivacaine, and (2) select a single therapeutic dose of liposome bupivacaine from the three dose levels tested.

Part 2

The primary null hypothesis is:

> H_0: The means of the AUC of the NRS-R pain intensity scores through 72 hours are not different between the liposome bupivacaine and placebo groups.

The alternative hypothesis is:

> H_A: The mean AUC of the NRS-R pain intensity scores through 72 hours for the liposome bupivacaine group is less than for the placebo group.

15.2. Study Endpoints

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

15.3. Determination of Sample Size

Part 1

The sample size for Part 1 of the study was not based on formal statistical power calculations.

Part 2

A study population of approximately 180 subjects is planned with approximately 90 subjects in each treatment group (liposome bupivacaine and placebo). The sample size was estimated based on the results of a Phase 3 hemorrhoidectomy study of liposome bupivacaine versus placebo where the mean (standard deviation) AUC of the NRS-R pain intensity scores through 72 hours was 141 (101) and 202 (104) for the liposome bupivacaine and placebo groups, respectively. A two-group t-test with 0.05 two-sided significance level will have > 97% power to detect a difference in means of 61, assuming that the common standard deviation is 104, when the sample size in each group is 90.

After the data from Part 1 are evaluated, the sample size for Part 2 may be increased.

15.4. Analysis Populations

The following analysis sets are planned:

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

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

Pharmacokinetic: The PK analysis set will include all subjects in the safety analysis set who receive liposome bupivacaine, provide sufficient samples to allow for calculation of PK parameters required for analysis, and who do not receive conventional bupivacaine HCl postsurgically.

15.5. Handling Subject Dropouts and Discontinuations

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

Missing scores before the first non-missing score will be replaced by the median score at the missing time point from other subjects in the same treatment group. Missing scores after the last non-missing score will be replaced by the last non-missing score (last observation carried forward). Linear interpolation will be used to replace missing scores between two non-missing scores. Subjects who have no pain scores after surgery will have the missing scores replaced by the median score at the missing time point from other subjects in the same treatment group.

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

15.6. Statistical Analyses

15.6.1. Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group, separately for Part 1 and Part 2.

15.6.2. Study Compliance

The percentage of subjects in each analysis set and the percentage who fail to complete the study (as well as the reasons for discontinuation) will be displayed by treatment group, separately for Part 1 and Part 2.

15.6.3. Efficacy Analyses

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

Efficacy data for Part 1 and Part 2 will be analyzed separately.

15.6.3.1 Primary Efficacy Measure

The primary efficacy measure in this study is the AUC of the NRS-R pain intensity scores through 72 hours.

Handling of Subjects Requiring Rescue Medication

For AUC of the NRS-R and NRS-A pain intensity scores, prior to analysis the windowed Worst-Observation-Carried-Forward (wWOCF) imputation method will be applied. For subjects who take rescue pain medication, their pain intensity scores recorded within the window of controlled type of rescue medication (6 hours for oxycodone, 4 hours for morphine, and 2 hours for IV hydromorphone) will be replaced by the 'worst' observation. For subjects who require a rescue with conventional bupivacaine HCl, the window will be from the start of the bupivacaine infusion until the end of the infusion plus 12 hours. All pain scores within that window will be replaced by the 'worst' observation. The worst observation will be the highest score in the time interval from the end of surgery up to the time prior to taking their first rescue pain medication. Note that pain intensity scores in the window that are higher than the worst value prior to rescue pain medication will not be overwritten. If no pain intensity score is available prior to the first rescue pain medication, the worst observation from all available measurements will be used instead.

Part 1

For AUC of the NRS-R pain intensity scores through 72 hours, each dose of liposome bupivacaine will be compared to placebo using analysis of covariance (ANCOVA) with treatment as the main effect and the baseline NRS-R pain intensity score as the covariate. Based on the model, the difference between each dose of liposome bupivacaine and placebo will be estimated along with the 2-sided 95% confidence interval (CI).

Part 2

For AUC of the NRS-R pain intensity scores through 72 hours, liposome bupivacaine will be compared to placebo using ANCOVA with treatment as the main effect and the baseline NRS-R pain intensity score as the covariate. Based on the model, the difference between the treatment groups will be estimated along with the 2-sided 95% CI.

15.6.3.2 Secondary Efficacy Measures

The secondary efficacy measures for Part 2 of this study are:

- Total postsurgical opioid consumption through 72 hours
- Time to first opioid rescue.

These efficacy measures will be analyzed using a hierarchical fixed-sequence stepwise testing procedure. To protect the Type 1 error rate, the testing will be performed in a sequentially rejective fashion. First the total postsurgical opioid consumption through 72 hours will be tested. If the test of opioid consumption is significant at the two-sided 0.05 level then, and only then, the time to first opioid rescue will be tested. Each test will be declared positive at the two-sided 0.05 significance level.

For total postsurgical opioid consumption, opioid medications will be converted to a morphine equivalent amount. All opioids administered through72 hours will be included in the analysis. Prior to analysis, the natural logarithm transformation will be applied to the total amount. To test for significant differences between liposome bupivacaine and placebo an analysis of variance (ANOVA) with treatment as the main effect will be used. Based on the model, liposome bupivacaine will be compared to placebo and a two-sided 95% CI about the differences will be presented.

The time from end of surgery to the first use of an opioid rescue through 72 hours after surgery will be summarized with medians and Kaplan-Meier estimates. A log-rank test will be used to compare liposome bupivacaine to placebo.

15.6.3.3 Tertiary Efficacy Measures

Continuous Measures of Efficacy

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

For total postsurgical opioid consumption, opioid medications will be converted to a morphine equivalent amount. All opioids administered through the specified time period will be included in the analysis. Prior to analysis, the natural logarithm transformation will be applied to the total amount.

Part 1

At the end of the study, summary statistics for each measure will be shown at each time point by treatment group. No statistical tests will be performed.

Part 2

Summary statistics for each measure will be shown at each time point by treatment group. To test for significant differences between liposome bupivacaine and placebo with respect to continuous measures of efficacy, an ANOVA with treatment as the main effect or ANCOVA with treatment as the main effect and the baseline value as the covariate will be used. Based on the model, liposome bupivacaine will be compared to placebo and two-sided 95% CIs about the differences will be presented.

Categorical Measures of Efficacy

Part 1

At the end of the study, the proportion of subjects in each category will be calculated and summarized at each time point by treatment group. No statistical tests will be performed.

Part 2

The proportion of subjects in each category will be calculated and summarized at each time point by treatment group. A chi-square test or Cochran-Mantel-Haenszel test will be used to compare liposome bupivacaine to placebo.

15.6.4. Pharmacokinetic Analyses

Part 1

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

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

Descriptive statistics will be used to summarize the PK parameters.

Part 2

Not applicable.

15.6.5. Safety Analyses

All safety analyses will be based on actual treatment received.

15.6.5.1 Adverse Events

Adverse events from Part 1 and Part 2 will be shown separately and combined.

Adverse event verbatim terms will be mapped to preferred terms and related system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). All summaries of AEs will only include TEAEs. Events that start prior to the start of study drug administration will be identified in listings only. Incidence rates of TEAEs and the proportion of subject prematurely withdrawn from the study due to a TEAE will be shown for each treatment group. Incidence rates also will be displayed for each treatment group for study drug-related TEAEs and by severity. Incidence rates of SAEs also will be shown for each treatment group. All incidence rates will be categorized and displayed by system organ class and preferred term.

15.6.5.2 Vital Signs

Descriptive statistics for each vital sign for baseline and change from baseline at each time point will be summarized for each treatment group, for Part 1 and Part 2 separately and combined.

15.6.5.3 Proportion of Subjects Able to Walk 20 Meters, Unassisted

The proportion of subjects able to walk 20 meters, unassisted with the optional use of a four-legged walker, at 24 hours, 72 hours, and Day 30 will be summarized for each treatment group, for Part 1 and Part 2 separately and combined. For Part 2, the proportion in each of the liposome bupivacaine group will be compared to the placebo group using a chi-square test.

15.6.5.4 Rating of Physician's Satisfaction with Return of Sensory/Motor Function

The physician's satisfaction with return of sensory/motor function will be summarized for each treatment group, for Part 1 and Part 2 separately and combined. For Part 2, a Cochran-Mantel-Haenszel test will be used to compare liposome bupivacaine to placebo.

15.6.5.5 Neurological Assessments

The proportion of subjects who are oriented at each time point will be summarized for each treatment group, for Part 1 and Part 2 separately and combined. The proportion of subjects who have at least one of the neurologic events will be summarized for each treatment group, for Part 1 and Part 2 separately and combined.

15.7. Significance Testing

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

15.8. Interim Analyses

After all subjects have completed, or discontinued from, Part 1 of the study, an unblinded dose selection committee will review at least the results of the primary efficacy measure and the two secondary efficacy measures and safety data. The committee will determine the apparent efficacy and safety of each of the three liposome bupivacaine dose levels tested and will recommend a dose level for Part 2 of the study.

The committee also will run sample size estimates based on the results (mean differences and variances) of the primary efficacy measures and make a recommendation for Part 2 of the study. However, the sample size for Part 2 will not be fewer than 90 subjects per treatment arm.

16. REFERENCES

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EXPAREL Investigator's Brochure, Edition 15, 09 July 2012.

17. INVESTIGATOR AGREEMENT

Printed Name of Investigator: _____

Printed Title/Position: _____

Printed Institution Address: _____

_____

_____

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

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

_____ _____

Signature of Investigator Date

18. APPENDICES

Appendix 1: Subject's Reported Pain (Numeric Rating Scale)

Note: Subjects will be evaluated for pain using the NRS-R followed by the NRS-A (where the prescribed activity is active knee flexion up to 45 degrees) at baseline, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after surgery.

Pain Intensity Scale

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

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

Appendix 2: Neurological Assessment

A neurological assessment will be conducted at baseline, 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 60, and 72 hours after surgery.

The examination will include the subject's orientation.

- Is the subject oriented? □ Yes □ No □ Not Assessable

Additionally, the subject will be asked the following questions:

- Do you have numbness of the lips, the tongue, or around the mouth? □ Yes □ No
- Do you have a metallic taste in your mouth? □ Yes □ No
- Are you having problems with your hearing? □ Yes □ No
- Are you having problems with your vision? □ Yes □ No
- Are your muscles twitching? □ Yes □ No

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

If the neurological assessment reveals a neurological event that the Investigator believes may be associated with high levels of systemic bupivacaine, an unscheduled PK blood sample should be collected at the time that the event is noted.

Appendix 3: Overall Benefit of Analgesia Score Questionnaire

Note: The OBAS questionnaire will be completed at 24, 48, and 72 hours after surgery.

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

Appendix 4: Subject Satisfaction with Postsurgical Pain Control (Likert Scale)

Note: The subject's satisfaction with postsurgical pain control will be conducted at 72 hours after surgery and on Day 30.

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

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

Appendix 5: Physician's Satisfaction with Return of Sensory/Motor Function (Likert Scale)

Note: The physician's satisfaction with return of sensory/motor function will be assessed at 72 hours after surgery and on Day 30

Please circle the number below that best describes your overall satisfaction with the subject's return of sensory/motor function. (Circle one number only.)

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

Appendix 6: Opioid-Related Adverse Events Questionnaire

The opioid-related adverse events questionnaire will be completed at 72 hours after surgery during Part 1 only. The subject will be asked the questions below.

Since your operation, have you had:

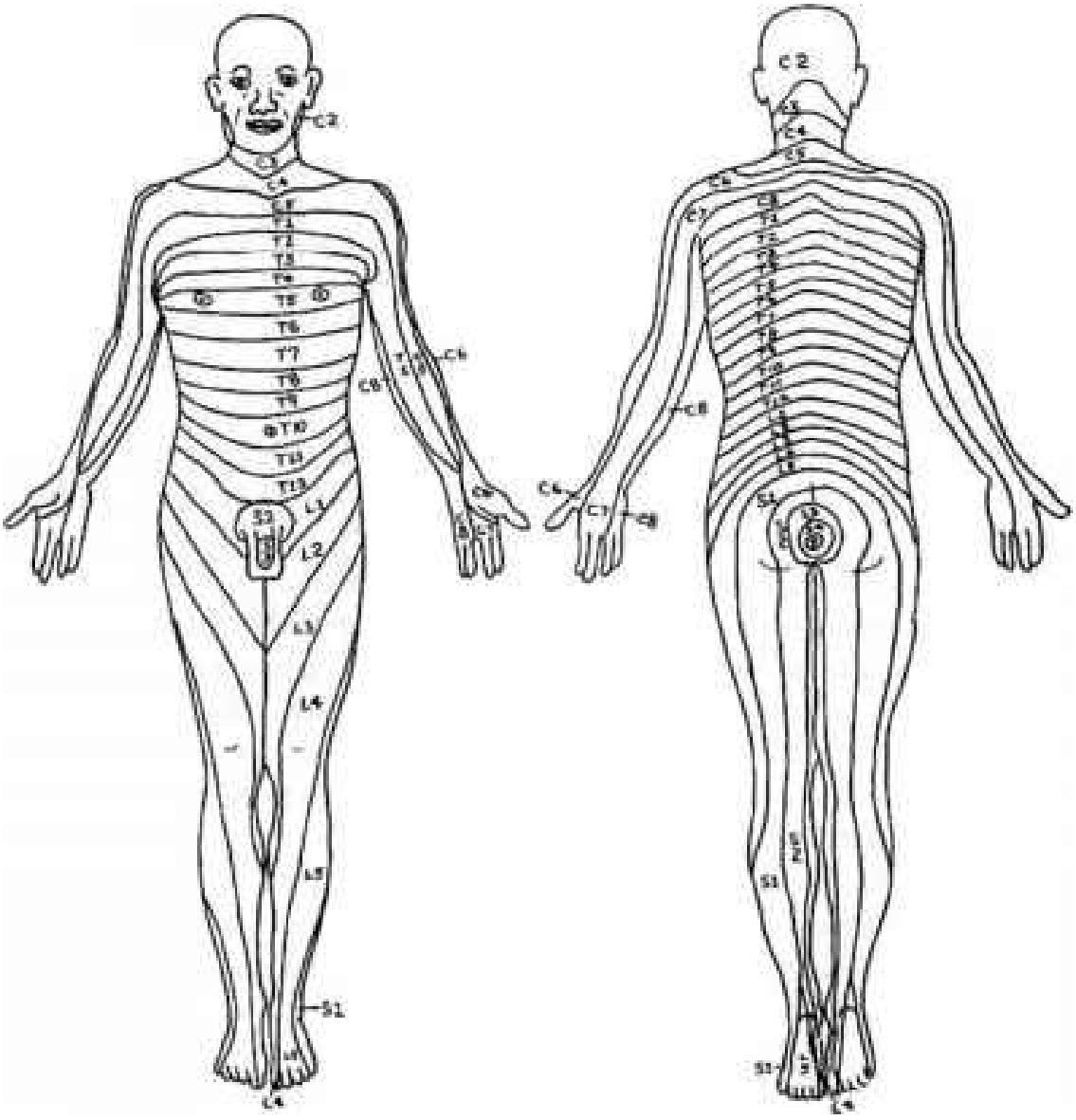
- Itching all over your body? ☐ Yes ☐ No
- Excessive tiredness? ☐ Yes ☐ No
- Difficulty breathing? ☐ Yes ☐ No
- Did you need a postsurgical bladder catheter? ☐ Yes ☐ No
- Vomiting? ☐ Yes ☐ No
- Need for medicine to prevent vomiting? ☐ Yes ☐ No
- Constipation? ☐ Yes ☐ No
- Confusion? ☐ Yes ☐ No
- Delirium? ☐ Yes ☐ No

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

Appendix 7: Dermatome Map

For the sensory function assessment, the subject's sensitivity in the innervated dermatomes (L2, L3) will be assessed at baseline, when the subject wakes up after surgery, and at 2, 4, 12, 24, 36, 48, 60, and 72 hours after surgery, or until the subject's sensitivity to cold has returned in two consecutive evaluations.

The subject's skin will be wiped with ice or an alcohol pad. The subject will then be asked, "Does this feel cold - yes or no?"



Site-Specific Addendum to Clinical Study Protocol Amendment 1

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Single Injection Femoral Nerve Block with Liposome Bupivacaine for Postsurgical Analgesia in Subjects Undergoing Total Knee Arthroplasty

Protocol No.:	402-C-323
EudraCT No.:	N/A
IND No.:	69,198
Study Phase:	2/3
Study Drug:	Liposome bupivacaine
Date:	14 January 2013
Study Site:	Site 001
Investigator:	Tim I. Melson, MD
Sponsor:	Pacira Pharmaceuticals, Inc. 10450 Science Center Drive San Diego, CA 92121 Tel: (858) 625-2424

SIGNATURE PAGE

Erol Onel, MD Executive Medical Director	14 January 2013 Date
Gary Patou, MD Chief Medical Officer	14 January 2013 Date
George Wagner Executive Director, Regulatory Affairs	14 January 2013 Date

Pharmacokinetic Assessments

Per protocol amendment 1, blood samples for pharmacokinetic (PK) analysis are to be collected from subjects at specific sites during Part 1 of the study at baseline, 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after the beginning of study drug administration.

Per this protocol addendum, additional blood draws for PK analysis may be collected from a subset of up to 20 subjects across two or more WIRB sites at 84, 96, 120, 144, 168 hours after the beginning of study drug administration, and on Day 10. The exact timing of the extra blood draws may be modified based on a review of the data by an unblinded statistician and pharmacokineticist. After a subject has been discharged from the hospital, the blood samples may be collected on an outpatient basis at the site or by a home healthcare agency designated by the study staff.

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.

_____ _____

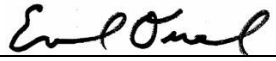
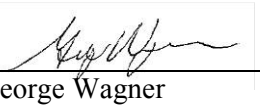
Signature of Investigator Date

Site-Specific Addendum to Clinical Study Protocol Amendment 1

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Single Injection Femoral Nerve Block with Liposome Bupivacaine for Postsurgical Analgesia in Subjects Undergoing Total Knee Arthroplasty

Protocol No.:	402-C-323
EudraCT No.:	N/A
IND No.:	69,198
Study Phase:	2/3
Study Drug:	Liposome bupivacaine
Date:	14 January 2013
Study Site:	Site 005
Investigator:	Harold S. Minkowitz, MD
Sponsor:	Pacira Pharmaceuticals, Inc. 10450 Science Center Drive San Diego, CA 92121 Tel: (858) 625-2424

SIGNATURE PAGE

	14 January 2013
Erol Onel, MD Executive Medical Director	Date
	14 January 2013
Gary Patou, MD Chief Medical Officer	Date
	14 January 2013
George Wagner Executive Director, Regulatory Affairs	Date

Pharmacokinetic Assessments

Per protocol amendment 1, blood samples for pharmacokinetic (PK) analysis are to be collected from subjects at specific sites during Part 1 of the study at baseline, 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after the beginning of study drug administration.

Per this protocol addendum, additional blood draws for PK analysis may be collected from a subset of up to 20 subjects across two or more WIRB sites at 84, 96, 120, 144, 168 hours after the beginning of study drug administration, and on Day 10. The exact timing of the extra blood draws may be modified based on a review of the data by an unblinded statistician and pharmacokineticist. After a subject has been discharged from the hospital, the blood samples may be collected on an outpatient basis at the site or by a home healthcare agency designated by the study staff.

INVESTIGATOR AGREEMENT

Printed Name of Investigator: _____

Printed Title/Position: _____

Printed Institution Address: _____

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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