Pacira Pharmaceuticals, Inc.
EXPAREL

Document:	Clinical Study Protocol
Official Title:	A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Assess the Efficacy and Safety of Intercostal Nerve Block with Liposome Bupivacaine in Subjects Undergoing Posterolateral Thoracotomy
NCT Number:	NCT01802411
Document Date:	September 23, 2012

Clinical Study Protocol Amendment 1

A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Assess the Efficacy and Safety of Intercostal Nerve Block with Liposome Bupivacaine in Subjects Undergoing Posterolateral Thoracotomy

Protocol No.:	402-C-322
EudraCT No.:	2012-003275-19
IND No.:	69,198
Study Phase:	3
Study Drug:	Liposome bupivacaine
Date:	23 September 2012 (Amendment 1) 08 August 2012 (original)
Study Sites:	Up to 30 sites in the United States and Europe
Sponsor:	Pacira Pharmaceuticals, Inc. 10450 Science Center Drive San Diego, CA 92121 Tel: (858) 625-2424

SUMMARY OF CHANGES

The changes made to the original study protocol are as follows:

General

Minor clarifications were made throughout the protocol.

Section 2 (Synopsis)

- Methodology:
  - The dosage guidance for the second rescue medication was revised for both the US and European sites.
  - The time frame of the cardiac assessment (ECG recording) was changed *from*: "The cardiac assessment (i.e., ECG recordings) will be recorded at baseline (approximately 1 hour prior to surgery) and during the first 72 hours after surgery" *to*: "The cardiac assessment (i.e., ECG recordings) will be started at baseline (approximately 1 hour prior to surgery) and continue for a total of 72 hours."
  - The end of the AE/SAE reporting time frame was clarified *from*: "Day 30" *to:* "until the Day 30 follow-up contact."
- Eligibility Criteria:
  - Inclusion criterion #5 was changed *from:* "Able to demonstrate sensory function by exhibiting sensitivity in each of the dermatomes in which study drug will be administered" *to:* "Able to demonstrate sensory function by exhibiting sensitivity to cold anywhere within the dermatomes supplied by any of the nerves to which study drug will be administered."
  - Exclusion criterion #3: "acetaminophen/paracetamol" was deleted.
- Reference Product:
  - For consistency, "preservative-free sodium chloride" was changed to "preservative-free normal saline."
- Efficacy Endpoints:
  - The sensitivity to cold endpoint was changed *from*: "Proportion of subjects at each time point with sensitivity to cold in one of the dermatomes" *to*: "Proportion of subjects at each time point with sensitivity to cold anywhere within the dermatomes supplied by any of the nerves to which study drug was administered."
- Safety Assessments:
  - The time frame of the cardiac assessment (ECG recording) was changed as stated above.

- The ECG assessment was changed from: "Electrocardiogram changes will be examined using the ECG data closest to the median T_{max}" *to*: "Electrocardiogram changes will be examined using the ECG data closest to the T_{max}."

Section 4 (List of Abbreviations)

"HR," "QTcB," and "QTcF" were added to the List of Abbreviations.

Table 1 (Time and Events Schedule of Study Procedures)

The time window for the 72-hour time point assessments was changed *from*: ±2 hours *to*: ±4 hours.

Sections 9, 10, 11, 12, 13, and 14

The changes made in the Synopsis (listed above) were made to Sections 9 though 14.

Section 11.5.1 (Blinding Procedures)

The blinding procedures were clarified.

Section 11.6.1 (Prior and Concomitant Medications and Therapy)

Acetaminophen/paracetamol was deleted.

Section 11.8 (Accountability of Study Drug)

Text was revised.

Section 13.1.3 (Neurological Assessment)

Text pertaining to the assessment of the subject's orientation was added.

Section 13.1.4 – Cardiac Assessment (Electrocardiogram Recordings)

The cardiac assessment procedures were revised.

Section 13.5 – Procedures After Surgery Through 72 Hours

- The second bullet under "US sites" was deleted due to redundancy.
- For consistency, the bullet pertaining to the sensory function assessment was changed *from*: "..or until the subject's sensitivity to cold has returned to the baseline level in two consecutive evaluations..." *to* "... or until the subject's sensitivity to cold has returned in two consecutive evaluations."

Section 15.6.3.3 – Tertiary Efficacy Measures

Under the subheading Categorical Measures of Efficacy, text was changed *from*: "A chi-square test or Cochran-Mantel-Haenszel test will be used to compare liposome bupivacaine to placebo" *to*: "A chi-square test or Wilcoxon Rank Sum test will be used to compare liposome bupivacaine to placebo."

Section 15.6.5.4 – Rating of Physician's Satisfaction with Wound Healing

Text was changed *from*: "To test for significant differences between liposome bupivacaine and placebo, an ANOVA with treatment as the main effect will be used" *to*: "To test for significant differences between liposome bupivacaine and placebo, a Wilcoxon Rank Sum test with treatment as the main effect will be used."

Section 16 – References

The date of the Investigator's Brochure was changed to match the date of the recently updated IB.

Appendix 2 (Neurological Assessment)

The following sentence was added: "If the subject is not oriented, record as an AE."

Appendix 5 (Physician's Satisfaction with Wound Healing)

The scale used for the wound healing assessment was changed from an 11-point NRS to a 5-point Likert scale.

Appendix 7 (Dermatome Map)

The text was revised to match the changes stated above.

SIGNATURE PAGE

Erol Onel, MD Executive Medical Director	25 September 2012 Date
Gary Patou, MD Chief Medical Officer	25 September 2012 Date
Patricia Mills, RN Sr. Director, Drug Safety and Pharmacovigilance	26 September 2012 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 1.3%, 13.3 mg/mL		

Title of Study: A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Assess the Efficacy and Safety of Intercostal Nerve Block with Liposome Bupivacaine in Subjects Undergoing Posterolateral Thoracotomy

Principal Investigators: To be determined.

Study Center(s): Up to 30 sites in the United States and Europe.

Publications (Reference): None.

Objectives:

Primary Objective:

The primary objective is to evaluate the efficacy of intercostal nerve block using liposome bupivacaine compared with placebo in subjects undergoing posterolateral thoracotomy.

Secondary Objectives:

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

Methodology:

This is a Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled study conducted to investigate the efficacy and safety of liposome bupivacaine (total of 266 mg in 20 mL) divided into three equal doses in three syringes of approximately 88 mg in 6.6 mL volume per nerve and administered to each of three nerve segments (index nerve, nerve above, and nerve below) compared with saline placebo nerve block.

After completing screening procedures, eligible subjects undergoing posterolateral thoracotomy will be randomized 1:1 to receive either liposome bupivacaine or placebo. Study drug will be administered in a blinded manner after the posterolateral thoracotomy is completed (i.e., just prior to the surgical site closure). The use of opioids (other than fentanyl), acetaminophen/paracetamol, ketorolac or other non-steroidal anti-inflammatory drugs (NSAIDs), and local anesthetics other than the study drug will not be permitted intraoperatively, except for emergency use to treat an AE.

At all US sites only, subjects will have a patient-controlled analgesia (PCA) pump established prior to the completion of the surgery. *The PCA pump will not be loaded at this time*. All subjects will be required to remain in the study site for a minimum of 72 hours following surgery for postsurgical assessments.

Postsurgical Rescue Medication

Rescue medication should only be provided upon subject request, as needed.

First Rescue Medication

The first rescue medication will be intravenous (IV) fentanyl 100 mcg, which will be administered once via bolus only. At this time, the PCA pump should be loaded with opioid (morphine or hydromorphone only) for subjects at the US sites only.

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Postsurgical Rescue Medication (Cont.)

Second Rescue Medication

For the US sites only, the second rescue medication will be PCA-administered opioid (morphine or hydromorphone). The PCA pump will be programmed to deliver either of the following recommended doses: (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. A continuous infusion (background or basal rate) of morphine is not permitted. The recommended bolus doses may be adjusted according to local hospital practices; however, **adding a basal rate is prohibited**.

For the European sites only, the second rescue medication will be intramuscular (IM) administered opioid (morphine) up to10 mg every 4 hours.

At all sites, once a subject is tolerating oral (PO) medication, PO immediate-release oxycodone may be administered (but not more than 10 mg every 4 hours).

Subjects who do not achieve adequate pain relief with this regimen will be withdrawn from the study and followed for safety only.

Postsurgical Assessments

Subjects will be evaluated for pain intensity using the numeric rating scale at rest (NRS-R) at baseline and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours following surgery, at first request for rescue pain medication, and on Day 12 (see Appendix 1). Subjects also will be evaluated for pain intensity with activity (defined as pain intensity with cough) using the NRS with activity (NRS-A) at baseline and 24, 48, and 72 hours following surgery and on Day 12 (see Appendix 1). Note: At time points when the pain intensity assessments coincide, the NRS-R will be conducted before the NRS-A. Additionally, if chest tube removal or a PK blood draw coincides with pain intensity assessment(s), the pain intensity assessment(s) must be conducted before the other procedures.

Neurological assessments 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 (see Appendix 2). The cardiac assessment (i.e., ECG recordings) will be started at baseline (approximately 1 hour prior to surgery) and continue for a total of 72 hours. The sensory function assessment (i.e., cold test) will be conducted 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 (see Appendix 7).

The overall benefit of analgesia score (OBAS) questionnaire will be completed at 24, 48, and 72 hours following surgery (see Appendix 3). The subject's overall satisfaction with postsurgical pain control will be assessed at 72 hours following surgery, on Day 12, and on Day 30 using a 5-point Likert scale (see Appendix 4). A wound healing assessment will be performed on Day 12 (see Appendix 5). Predefined, treatment-emergent opioid-related AEs will be assessed at 72 hours after surgery (see Appendix 6). Adverse events will be recorded through the Day 30 follow-up contact. If a cardiac or neurological event occurs during 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.

Pharmacokinetic Assessments: Blood samples for PK analysis will be obtained from subjects at specific sites at baseline, 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after the end of surgery. Placebo samples will be collected to maintain the treatment double-blind but 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.)

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

Number of Subjects (Planned):

A total of 180 subjects are planned for enrollment into this study in a 1:1 randomization, resulting in approximately 90 subjects in the 266 mg liposome bupivacaine group and 90 subjects in the placebo group.

Eligibility Criteria:

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 a thoracotomy of at least 3 inches (7.6 cm) of intercostal incisional length or requiring insertion of an inter-rib spreader/retractor for a primary thoracic non-infectious indication under general anesthesia.
3. American Society of Anesthesiologists (ASA) Physical Status 1 - 3.
4. Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments.
5. Able to demonstrate sensory function by exhibiting sensitivity to cold anywhere within the dermatomes supplied by any of the nerves to which study drug will be administered.

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, 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. Any planned pleurodesis as part of the surgical procedure.
3. Use of any of the following medications within the times specified before surgery: long-acting opioid medication, NSAID, or aspirin (except for low-dose aspirin used for cardioprotection) within 3 days and any opioid medication within 24 hours.
4. Use of selective serotonin reuptake inhibitors (SSRIs), gabapentin, pregabalin (Lyrica®), or duloxetine (Cymbalta®) within 3 days of surgery.
5. 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 surgery, and which may confound the postsurgical assessments (e.g., cancer pain, chronic neuropathic pain, concurrent abdominal surgery).
6. Current use of systemic glucocorticosteroids within 1 month of enrollment.
7. Body weight < 50 kilograms (110 pounds) or a body mass index ≥ 35 kg/m^2.
8. Contraindication to any of the pain-control agents planned for surgical or postsurgical use (i.e., fentanyl, morphine, 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.

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Exclusion Criteria (Cont.)

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. Uncontrolled anxiety, schizophrenia, or other psychiatric disorder that, in the opinion of the Investigator, could interfere with study assessments or compliance.
13. 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 or interfere with the determination of pain intensity related solely to the surgery.
14. Significant medical conditions (including widely disseminated metastatic disease) or laboratory results that, in the opinion of the Investigator, indicate an increased vulnerability to study drugs and procedures.
15. Subjects who are planned to receive Entereg® (alvimopan).
16. Subjects who will receive prophylactic antiemetics or planned postsurgical antiemetics given without regard to the subject's emesis needs.

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

Name: Liposome bupivacaine

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

Dosage: Single total administration of 266 mg (approximately 88 mg to each of three nerve segments) of 6.6 mL volume each for a total of 20 mL.

Lot Number: To be determined.

Mode of Administration: Nerve block (intercostal).

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

Name: Placebo (normal saline for injection).

Dosage: Single total administration of 266 mg (approximately 88 mg to each of three nerve segments) of 6.6 mL volume each for a total of 20 mL.

Lot Number: To be determined.

Mode of Administration: Nerve block (intercostal).

Duration of Subject Participation in Study: Each subject's participation in this study may be up to 64 days (up to 30 days for screening and 34 days for post-dosing follow-up).

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 and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours following surgery, at first request for rescue pain medication, and on Day 12.
- Pain intensity scores using the NRS-A (where the prescribed activity is cough) at baseline and 24, 48, and 72 hours following surgery, and on Day 12.
- Time of first opioid rescue.
- Opioid use.

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Efficacy Assessments (Cont.)

- Sensory function assessment (i.e., cold test) 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.
- Overall benefit of analgesia score questionnaire at 24, 48, and 72 hours.
- Subject's satisfaction with postsurgical pain control at 72 hours, Day 12, and Day 30 using a 5-point Likert scale.
- Predefined treatment-emergent opioid-related AEs at 72 hours following surgery.

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 area under the curve (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, Day 12, 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-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 medication.
  - Subjects who only receive IV fentanyl as a rescue medication.
  - Subjects who receive IV fentanyl and a second opioid medication.
- Incidence of predefined treatment-emergent opioid-related AEs (diffuse pruritus, overt respiratory depression, urinary retention as measured by need for postsurgical bladder catheterization, constipation, sedation, confusion, delirium, vomiting, or need for antiemetic medication) at 72 hours.
- Proportion of subjects at each time point with sensitivity to cold anywhere within the dermatomes supplied by any of the nerves to which study drug was administered.

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Pharmacokinetic Endpoints:

Pharmacokinetic parameters will be estimated from the 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 end of surgery). 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 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 (λz).
- The apparent terminal elimination half-life ($t_{1/2\ el}$).

Safety Assessments:

The following safety assessments will be conducted:

- Adverse events from the time of randomization through the Day 30 follow-up contact.
- Vital signs (resting heart rate and blood pressure) at screening, baseline, and 1, 12, 24, 48, and 72 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) started at baseline (approximately 1 hour prior to surgery) and continued for a total of 72 hours. Electrocardiogram changes will be examined using the ECG data closest to the T_{max}.
- Physician's satisfaction with wound healing on Day 12.

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 SAEs through the Day 30 follow-up contact.
- 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 $T_{max.}$
- Rating of physician's satisfaction with wound healing on Day 12.

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Statistical Methods:

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

Descriptive summaries will be provided by treatment group. Liposome bupivacaine will be compared with 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 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, the time to first opioid rescue will be tested. The result will be declared statistically significant at the 0.05 significance level.

Safety data will be summarized by treatment group.

Table 1. Time and Events Schedule of Study Procedures

	Screen Visit	Day -1 to Day 1	Day 1	15min	30min	1h	2h	4h	8h	12h	18h	24h	30h	36h	42h	48h	60h	72h	Day 12	Day 30[10]
Time Window	**Within 30 days**			**±5 min**	**±5 min**	**± 15 min**	**± 30 min**	**± 30 min**	**± 30 min**	**± 30 min**	**± 1h**	**± 1h**	**± 2h**	**± 2h**	**±2h**	**±2h**	**±2h**	**±4h**	**±4 days**	**±4 days**
Obtain signed informed consent form	X																			
Assess/confirm eligibility	X	X																		
Medical/surgical history	X	X																		
Demographics and baseline characteristics	X																			
Urine pregnancy test (for women of childbearing potential)[1]		X																		
Physical examination including height and weight		X																		
Vital signs[2]	X	X				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	X		
Perform cardiac assessment (ECG recordings)[4]		X	←	-	-	-	-	-	-	-	-	-	-	-	-	→				
Perform sensory function assessment (cold test)[5]		X					X	X		X		X		X		X	X	X		
Randomize subject and prepare study drug		X																		
Administer study drug; record start and stop time			X																	
Record start and stop time of surgery			X																	
Record location of chest tube			X																	
Record intraoperative opioids administered and doses			X																	
For US sites, install **unloaded** PCA pump (prior to the completion of the surgery)			X																	
Conduct NRS-R pain intensity assessment[6]		X				X	X	X	X	X		X		X		X	X	X	X	
Conduct NRS-A pain intensity assessment		X										X				X		X	X	
Record times and amounts of rescue medication administered			←	-	-	-	-	-	-	-	-	-	-	-	-	→				
Specific sites only: Collect blood sample for PK analysis[7]		X		X	X	X	X	X	X	X		X		X		X	X	X		
Record time of chest tube removal				←	-	-	-	-	-	-	-	-	-	-	-	-	-	→		
Record time subject is moved into and out of the ICU			←	-	-	-	-	-	-	-	-	-	-	-	-	-	-	→		
Complete OBAS questionnaire												X				X		X		
Subject satisfaction with pain control (Likert scale)																		X	X	X
Question subject re: predefined treatment-emergent ORAEs																		X		
Physician satisfaction with wound healing																			X	
Record concomitant medications[8]	←	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	→		
Record AEs (starting at randomization)[9]		←	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	→

AE = adverse event; ECG = electrocardiogram; h = hour; ICU = Intensive Care Unit; NRS-A = numeric rating scale with activity; NRS-R = numeric rating scale at rest; OBAS = overall benefit of analgesia score; ORAEs = opioid-related AEs; PCA = patient-controlled analgesia; PK = pharmacokinetic.

[1] Before study drug administration.
[2] Measure heart rate and blood pressure after subject has rested for at least 5 minutes in the supine position.
[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 will be started at baseline (approximately 1 hour prior to surgery) and continue for a total of 72 hours.
[5] Sensory function 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 the end of surgery, or until the subject's sensitivity to cold has returned in two consecutive evaluations.
[6] Also record NRS-R at first request for rescue pain medication.
[7] Collect blood samples for PK analysis at baseline, 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after the end of 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 the Day 30 follow-up contact.
[9] If a cardiac or neurological event occurs during 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.
[10] Day 30 assessments will be conducted via a telephone call.

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LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

4.1. List of Abbreviations

AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
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
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IM	Intramuscular
IRB	Institutional Review Board
IV	Intravenous
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

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
PTAE	Pre-treatment adverse event
SAE	Serious adverse event
SAP	Statistical analysis plan
λ_z	The apparent terminal elimination rate constant
$t_{1/2el}$	The apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
T_{max}	The time to attain C_{max}
US	United States
wWOCF	windowed Worst-Observation-Carried-Forward

4.2. Definition of Terms

Pharmacokinetic (PK) terms are defined in Section 12.4.

5. ETHICS

5.1. Institutional Review Board/Independent Ethics Committee

Prior to enrolling 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 his/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 PK profile of liposome bupivacaine when administered via a new route – intercostal nerve block.

Intercostal nerve blocks provide excellent analgesia for chest and upper abdominal surgery including thoracotomy. As with many other regional techniques, the advantages of ICNBs include superior analgesia, improved pulmonary mechanics, and opioid-sparing effects such as reduced central nervous system depression and avoidance of urinary retention. However, supplemental systemic analgesia is always necessary (Ho AMH 2012).

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 EXPAREL to have a similar onset of action to standard bupivacaine.

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

- Bupivacaine HCl solution, a well-characterized anesthetic/analgesic, with more than 35 years of 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 EXPAREL – 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 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 (bupivacaine liposome injectable suspension), 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 EXPAREL (liposome bupivacaine) in the setting of wound infiltration.

8. OBJECTIVES

8.1. Primary Objective

The primary objective is to evaluate the efficacy of intercostal nerve block using liposome bupivacaine compared with placebo in subjects undergoing posterolateral thoracotomy.

8.2. Secondary Objectives

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

9. OVERALL STUDY DESIGN AND PLAN

9.1. Study Design

This is a Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled study conducted to investigate the efficacy and safety of liposome bupivacaine (total of 266 mg in 20 mL) divided into three equal doses in three syringes of approximately 88 mg in 6.6 mL volume per nerve and administered to each of three nerve segments (index nerve, nerve above, and nerve below) compared with saline placebo nerve block.

After completing screening procedures, eligible subjects undergoing posterolateral thoracotomy will be randomized 1:1 to receive either liposome bupivacaine or placebo. Study drug will be administered after the posterolateral thoracotomy is completed (i.e., just prior to the surgical site closure). Study drug administration will be performed in a blinded manner (see Section 11.5.1). The use of opioids (other than fentanyl), acetaminophen/paracetamol, ketorolac, or other non-steroidal anti-inflammatory drugs (NSAIDs), and local anesthetics other than the study drug will not be permitted intraoperatively except for emergency use to treat an AE. At all US sites only, subjects will have a patient-controlled analgesia (PCA) pump established prior to the completion of the surgery. *The PCA pump will not be loaded at this time*. All subjects will be required to remain in the study site for a minimum of 72 hours following surgery for postsurgical assessments.

Postsurgical Rescue Medication

Rescue medication should only be provided upon subject request, as needed.

First Rescue Medication

The first rescue medication will be intravenous (IV) fentanyl 100 mcg, which will be administered once via bolus only. At this time, the PCA pump should be loaded with opioid (morphine or hydromorphone only) for subjects at the US sites only.

Second Rescue Medication

For the US sites only, the second rescue medication will be PCA-administered opioid (morphine or hydromorphone). The PCA pump will be programmed to deliver either of the following recommended doses: (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. A continuous infusion (background or basal rate) of morphine is not permitted. The recommended bolus doses may be adjusted according to local hospital practice; however, **adding a basal rate is prohibited**.

For the European sites only, the second rescue medication will be intramuscular (IM) administered opioid (morphine) up to 10 mg every 4 hours.

At all sites, once a subject is tolerating oral (PO) medication, PO immediate-release oxycodone may be administered, as needed (but not more than 10 mg every 4 hours).

Subjects who do not achieve adequate pain relief with this regimen will be withdrawn from the study and followed for safety only.

Postsurgical Assessments

Subjects will be evaluated for pain using the numeric rating scale at rest (NRS-R) at baseline and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours following surgery, at first request for rescue pain medication, and on Day 12 (see Appendix 1). Subjects also will be evaluated for pain with activity (defined as pain intensity with cough) using the NRS with activity [NRS-A] at baseline and 24, 48, and 72 hours following surgery and on Day 12 (see Appendix 1). (Note: At time points when the NRS pain intensity assessments coincide, the NRS-R will be conducted before the NRS-A.) Additionally, if chest tube removal or a PK blood draw coincides with pain intensity assessment(s), the pain intensity assessment(s) must be conducted before the other procedures.

Neurological assessments 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 (see Appendix 2). The cardiac assessment (i.e., ECG recordings) will be started at baseline (approximately 1 hour prior to surgery) and continue for a total of 72 hours. The sensory function assessment (i.e., cold test) will be conducted 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 (see Appendix 7).

The overall benefit of analgesia score (OBAS) questionnaire will be completed at 24, 48, and 72 hours following surgery (see Appendix 3). The subject's overall satisfaction with postsurgical pain control will be assessed 72 hours following surgery, on Day 12, and on Day 30 using a 5-point Likert scale (see Appendix 4). A wound healing assessment will be performed by the physician on Day 12 (see Appendix 5). Predefined, treatment-emergent opioid-related AEs will be assessed at 72 hours following surgery (see Appendix 6). Adverse events will be recorded through the Day 30 follow-up contact. If a cardiac or neurological event occurs during 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.

Pharmacokinetic Assessments

Blood samples for PK analysis will be obtained from subjects at specific sites at baseline, 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after the end of surgery. Placebo samples will be collected to maintain the treatment double-blind but 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 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

No more than 30 days should pass between signing of the ICF and performance of the surgery. Therefore, each subject may participate in the study for a maximum of 64 days.

9.1.2. Study Stopping Rules

No formal stopping rules are planned for this study. If, however, Pacira, the Investigator, or officials from regulatory authorities discover conditions during the study that indicate that the

study or study site should be terminated, this action may be taken after Pacira has consulted with appropriate regulatory authorities and notified the Investigator(s).

9.2. Discussion of Study Design

Liposome bupivacaine is approved for infiltration into a surgical wound. This Phase 3, multicenter, randomized, double-blind, parallel-group study is a comparison of the efficacy and safety of liposome bupivacaine to placebo when administered as an intercostal nerve block in subjects undergoing posterolateral thoracotomy. The study is double blind, which is intended to avoid potential bias resulting from subject or Investigator knowledge of the assigned treatment.

This study will explore the safety and efficacy of liposome bupivacaine when administered via a new route – intercostal nerve block. Posterolateral thoracotomy model was selected as patients experience moderate to severe postsurgical pain that typically lasts for 2-3 days.

All subjects may receive opioids, as needed, to control breakthrough postsurgical pain as defined in Section 11.6.3.

Neurological and cardiac assessments will be conducted to rule out bupivacaine toxicity related to high plasma exposure. Additionally, sensory 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 a thoracotomy of at least 3 inches (7.6 cm) of intercostal incisional length or requiring insertion of an inter-rib spreader/retractor for a primary thoracic non-infectious indication under general anesthesia.
3. American Society of Anesthesiologists (ASA) Physical Status 1 - 3.
4. Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments.
5. Able to demonstrate sensory function by exhibiting sensitivity to cold anywhere within the dermatomes supplied by any of the nerves to which study drug will be administered.

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, 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. Any planned pleurodesis as part of the surgical procedure.
3. Use of any of the following medications within the times specified prior to surgery: Long-acting opioid medication, NSAID, or aspirin (except for low-dose aspirin used for cardioprotection) within 3 days and any opioid medication within 24 hours.
4. Use of selective serotonin reuptake inhibitors (SSRIs), gabapentin, pregabalin (Lyrica®), or duloxetine (Cymbalta®) within 3 days of surgery.
5. 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 surgery, and which may confound the postsurgical assessments (e.g., cancer pain, chronic neuropathic pain, concurrent abdominal surgery).
6. Current use of systemic glucocorticosteroids within 1 month of enrollment.
7. Body weight < 50 kilograms (110 pounds) or a body mass index ≥ 35 kg/m^2.
8. Contraindication to any of the pain-control agents planned for surgical or postsurgical use (i.e., fentanyl, morphine, 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. Uncontrolled anxiety, schizophrenia, or other psychiatric disorder that, in the opinion of the Investigator, could interfere with study assessments or compliance.
13. 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 or interfere with the determination of pain intensity related solely to the surgery.
14. Significant medical conditions (including widely disseminated metastatic disease) or laboratory results that, in the opinion of the Investigator, indicate an increased vulnerability to study drugs and procedures.
15. Subjects who are planned to receive Entereg® (alvimopan).
16. Subjects who will receive prophylactic antiemetics or planned postsurgical antiemetics given without regard to the subject's emesis needs.

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 after receiving study drug should be followed for safety through Day 30. If a subject who withdraws from the study has an ongoing AE, every effort must be made to follow such events until satisfactory resolution is obtained, or further follow-up is otherwise no longer warranted.

10.3.1. Withdrawal Secondary to Adverse Events

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

10.3.2. Voluntary or Study Investigator Withdrawal

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

If a subject is discontinued by the Investigator or voluntarily withdraws from the study after receiving liposome bupivacaine, he/she should be followed for safety through Day 30. 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

Liposome bupivacaine (total of 266 mg in 20 mL) or placebo (preservative-free normal saline) will be divided into three equal doses in three syringes of approximately 88 mg in 6.6 mL volume per nerve and administered to each of three nerve segments (index nerve, nerve above, and nerve below) according to the randomization schedule. Study drug administration will be performed in a blinded manner utilizing syringes masked by finger cots.

Rescue Medication

Rescue medication should only be provided upon subject request.

First Rescue Medication

The first rescue medication will consist of IV fentanyl 100 mcg, which will be administered once via bolus only. At this time, the PCA pump should be loaded with opioid (morphine or hydromorphone only) for subjects at the US sites only.

Second Rescue Medication

For the US sites only, the second rescue medication will be PCA-administered opioid (morphine or hydromorphone). The PCA pump will be programmed to deliver either of the following recommended doses: (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. A continuous infusion (background or basal rate) of morphine is not permitted. The recommended bolus doses may be adjusted according to local hospital practices; however, **adding a basal rate is prohibited**.

For the European sites only, the second rescue medication will be IM-administered opioid (morphine) up to10 mg every 4 hours.

For all sites, once the subject is tolerating PO medication, PO immediate-release oxycodone may be administered, as needed (but not more than 10 mg every 4 hours).

Subjects who do not achieve adequate pain relief with this regimen will be withdrawn from the study and followed for safety only.

11.1.1. Administration Technique

Immediately prior to closure, study drug (liposome bupivacaine or placebo) will be administered under direct visualization by the surgeon into the index nerve as well as the nerve immediately above and immediately below using the surgeon's normal and usual technique. The volume to be administered is approximately 6.6 mL to each nerve, for a total of 20 mL.

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. 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 syringes 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.

11.3. Method of Assigning Subjects to Treatment

11.3.1. Randomization Scheme

Subjects will be centrally randomized to receive 266 mg liposome bupivacaine or placebo (normal saline for injection) in a 1:1 ratio. The randomization code will be generated by a centralized randomization system, which will also be used to communicate subject randomizations to study sites. All randomized subjects will have both a unique subject identifier and a unique random code identifier. No subject or random code identifiers are to be reused once assigned. The randomization will be stratified by region (US and Europe).

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 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 total dose was deemed appropriate for this study.

11.5. Blinding

11.5.1. Blinding Procedures

Liposome bupivacaine and placebo are visually distinguishable; therefore, to maintain the double-blind study design, only unblinded study personnel who are NOT involved with protocol-specific, postsurgical assessments may prepare the study drug. Staff members conducting study-specific, postsurgical assessments and the subjects will remain blinded to the assigned treatment throughout the study. If a subject experiences 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 and transportation to the operating room. 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**.

Once the study drug is prepared in syringes as a sterile preparation, it will be placed under a sterile drape on a sterile tray for use when needed in the operating room. The individuals preparing study drug will not be allowed to perform any of the postsurgical assessments or reveal the assigned study treatment to any other members of the study team at any time. Syringes containing study drug and covered by finger cots will need to be gently inverted several times to re-suspend any settling of the study drug that may have occurred prior to administration.

The administration of study drug will be recorded in the operating room charts 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 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

Prior medications

Long-acting opioid medications, NSAIDs, or aspirin (except for low-dose aspirin used for cardioprotection) are not permitted within 3 days of study drug administration. 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 will be recorded on the CRF. Any medications administered in association with AEs occurring during the study will be recorded through the Day 30 follow-up contact.

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

- No agents are to be admixed with liposome bupivacaine (e.g., epinephrine, dexamethasone, or clonidine).
- The use of opioids other than fentanyl (e.g., morphine, hydromorphone HCl), acetaminophen/paracetamol, ketorolac or other NSAIDs, and local anesthetics other than the study drug will not be permitted intraoperatively except for emergency use to treat an AE.
- 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.
- Entereg (alvimopan) use is prohibited.

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

Permitted

- Rescue medication use is permitted as described in Section 11.1.

Restricted

- No other analgesics are permitted during the first 72 hours following study drug administration.
- Local anesthetics.
- Entereg (alvimopan) use is prohibited.
- Prophylactic antiemetics or planned postsurgical antiemetics given without regard to the subject's emesis needs.

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 subject's postsurgical care.

All concomitant medication will be recorded through 72 hours after the end of surgery.

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 a study drug transmittal and receipt form to assist the unblinded pharmacist or designee in maintaining current and accurate inventory records. At a minimum, the unblinded pharmacist 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 unblinded pharmacist or designee must retain vials containing used, unused, or expired liposome bupivacaine for return or destruction, as instructed by Pacira, following confirmation of study drug accountability data by an unblinded monitor. A record of drug return or destruction will be maintained in the pharmacy binder and a copy provided to Pacira. Inventory records must be readily available for inspection by the unblinded 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 on the Delegation of Authority and Accountability Log will have the ability to access, prepare, and administer the study 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 and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours following surgery, at first request for rescue pain medication, and on Day 12 (Appendix 1).
- Pain intensity scores using the NRS-A (where the prescribed activity is cough) at baseline and 24, 48, and 72 hours following surgery, and on Day 12 (Appendix 1).
- Time of first opioid rescue.
- Opioid use.
- Sensory function assessment (i.e., cold test) 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 (Appendix 7).
- Overall benefit of analgesia score questionnaire at 24, 48, and 72 hours (see Appendix 3).
- Subject's satisfaction with postsurgical pain control at 72 hours, on Day 12, and on Day 30 using a 5-point Likert scale (Appendix 4).
- Predefined treatment-emergent opioid-related AEs at 72 hours following surgery (see 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, Day 12, 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-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 medication.
  - Subjects who only receive IV fentanyl as a rescue medication.
  - Subjects who receive IV fentanyl and a second opioid medication.
- Incidence of predefined treatment-emergent opioid-related AEs (diffuse pruritus, overt respiratory depression, urinary retention as measured by need for postsurgical bladder catheterization, constipation, sedation, confusion, delirium, vomiting, or need for antiemetic medication) at 72 hours.
- Proportion of subjects at each time point with sensitivity to cold anywhere within the dermatomes supplied by any of the nerves to which study drug was administered.

12.3. Pharmacokinetic Measurements

Blood samples for PK analysis will be obtained from subjects at specific sites at baseline, 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after the end of surgery. Placebo samples will be collected to maintain the treatment double-blind but 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.
$AUC_{0\text{-}\infty}$	The area under the plasma concentration-time curve from the time of administration extrapolated to infinity. The residual area from the time of the last quantifiable concentration (C_{tlast}) to infinity is to be calculated using the approximation: $AUC_{t\text{-}\infty} = Ct_{last}/ \lambda_z$.
C_{max}	The maximum observed plasma concentration obtained directly from the experimental data without interpolation.
T_{max}	The time to 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:

- Adverse events from the time of randomization through the Day 30 follow-up contact.
- Vital signs (resting heart rate and blood pressure) at screening, baseline, and 1, 12, 24, 48, and 72 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) started at baseline (approximately 1 hour prior to surgery) and continued for a total of 72 hours. Electrocardiogram changes will be examined using the ECG data closest to the T_{max}.
- Physician's satisfaction with wound healing on Day 12 (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 treatment-emergent adverse events (TEAEs) and SAEs through the Day 30 follow-up contact.
- 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 T_{max}.
- Rating of physician's satisfaction with wound healing on Day 12.

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 sensory function assessment is a standard test 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

All assessments conducted after baseline will be timed from 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 will take place under the supervision of site study staff.

13.1.1. Numeric Rating Scale Pain Intensity Assessments

Pain intensity will be assessed using the NRS-R and 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), where the prescribed activity will consist of a cough. 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. Additionally, if chest tube removal or a PK blood draw coincides with an NRS pain intensity assessment(s), the NRS pain intensity assessment(s) must be conducted before the other procedures. If a blood draw and pain intensity assessment coincide, the pain intensity assessment will be conducted first.

13.1.2. Overall Benefit of Analgesia Score Questionnaire

The OBAS questionnaire (Lehmann 2010) will be completed at 24, 48 and 72 hours after surgery (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 of the mouth, tongue, or lips; a metallic taste; problems with hearing; problems with vision; or muscle twitching (see Appendix 2). For assessing the subject's orientation, the assessor should take into account what their normal expectation would be for a person at this time postsurgically. For example, if the subject is able to be woken up and is still slightly disoriented but in accordance with what would be expected for that time after surgery, then the

answer would be "Yes". If the subject is responding abnormally, then this would be marked "No" and it would be recorded as an AE. If the subject answers "Yes" to any of the additional questions on this assessment, the event will 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.

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 (approximately 1 hour prior to surgery) and continue for 72 hours. 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 flash card. Without knowledge of subject treatment assignment, the 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 heart rate (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 T_{max}.

13.1.5. Sensory Function Assessment (Cold Test)

For the sensory function assessment, the subject's sensitivity to cold anywhere within the dermatomes supplied by any of the nerves to which study drug is administered 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 (see Appendix 7).

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. Vital Signs

Vital signs (heart rate and blood pressure) will be measured at screening, baseline, and 1, 12, 24, 48, and 72 hours after surgery. Vital signs will be taken after the subject has rested in a supine position for at least 5 minutes and before the NRS pain intensity assessment(s) when the assessments coincide. The subject will remain in a supine position during the assessment.

13.1.7. Subject's Satisfaction with Postsurgical Pain Control

The subject's satisfaction with postsurgical pain control will be assessed at 72 hours, Day 12, and Day 30 using the Likert Scale (see Appendix 4).

13.1.8. Physician's Satisfaction with Wound Healing

The physician's satisfaction with wound healing will be assessed on Day 12 (see Appendix 5).

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.

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.
- 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 (Appendix 1).
- Perform neurological assessment (see Appendix 2).
- Start the 12-lead digital ECG recording approximately 1 hour prior to surgery.
- Perform sensory function assessment (i.e., cold test) (see Appendix 7).
- 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).
- Record AEs and any treatment(s) for the events starting after randomization.

13.4. Intraoperative Procedures

- Divide study drug into three syringes containing equal doses of approximately 88 mg in 6.6 mL volume per nerve.
- Administer study drug to each of three nerve segments (index nerve, nerve above, and nerve below) after the surgical procedure is completed according to the randomization schedule.
- For the US sites, install unloaded PCA pump prior to the completion of the surgery.
- Record start and stop times of surgery.
- Record start and stop time of study drug administration.
- Record location of chest tube.
- Record intraoperative opioids administered.
- Record concomitant medications.
- Record AEs and any treatment(s) for the events.
- If a cardiac or neurological event occurs 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

- Administer first rescue medication for breakthrough pain (IV fentanyl 100 mcg) via bolus only, if needed.
- Record date and time of IV fentanyl administration.
- Record date(s) and time(s) of second rescue medication administration
  - US sites only
    - Load PCA pump with morphine or hydromorphone immediately after IV fentanyl is administered. Program PCA pump dosing per Section 11.1

  - Once a subject is tolerating PO medication, administer PO immediate-release oxycodone, as needed, but not more than 10 mg every 4 hours.
  - Record date, time, and amount of all rescue medication administered through 72 hours after surgery.
- <u>European sites only</u>
  - Administer second rescue medication (IM-administered morphine), as needed, per Section 11.1.
  - Once a subject is tolerating PO medication, PO immediate-release oxycodone may be administered, as needed, but not more than 10 mg every 4 hours.
  - Record date, time, and amount of all rescue medication administered through 72 hours after surgery.

- Record all other concomitant medications.
- Measure vital signs (heart rate and blood pressure) after subject has rested for at least 5 minutes in the supine position at the following time points: 1, 12, 24, 48, and 72 hours after surgery.
- Record subject's assessment of pain intensity using the NRS-R at the following time points: 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after surgery and at first request for rescue pain medication, if appropriate (see Appendix 1).
- Record subject's assessment of pain intensity using the NRS-A at the following time points: 24, 48, and 72 hours after surgery (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).
- Continue the cardiac assessment (i.e., 12-lead digital ECG recordings) for a total of 72 hours.
- Perform sensory function assessment (i.e., cold test) 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 (see Appendix 7).
- Collect scheduled blood samples for PK analysis (specific sites only) at 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after the end of surgery per Section 12.3.
- Complete the OBAS questionnaire at 24, 48, and 72 hours after surgery (see Appendix 3).
- Obtain overall rating of subject satisfaction with postsurgical pain control using the Likert scale at 72 hours after surgery (see Appendix 4).
- Record date and time of chest tube removal.
- Record date and time subject is moved into and out of the Intensive Care Unit (ICU).
- Record AEs and any treatment(s) for the events.

- If a cardiac or neurological event occurs 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.
- Question subject regarding the predefined treatment-emergent opioid-related AEs at 72 hours after surgery (see Appendix 6).

13.6. Postsurgical Study Visit Procedures (Day 12)

- Record subject's assessment of pain intensity using the NRS-R and NRS-A (see Appendix 1).
- Obtain overall rating of subject satisfaction with postsurgical pain control using the Likert scale (see Appendix 4).
- Assess physician satisfaction with wound healing (see Appendix 5).
- Record AEs and any treatment(s) for the events.

13.7. Day 30 Follow-Up Contact

- Obtain overall rating of subject satisfaction with postsurgical pain control using the Likert scale (see Appendix 4).
- 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 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 with an onset after the subject is randomized (i.e., PTAEs and AEs). For the purpose of this study, all AEs that occur through the Day 30 follow-up contact 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 the Day 30 follow-up contact, 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 SAE after the Day 30 follow-up contact, the SAE 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 ECG results.

15.1. Study Hypothesis

The primary null hypothesis is:

> $H_{0:}$ The means of the AUC of 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

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 wound infiltration 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.

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 receive study drug in all three nerves 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 and who provide sufficient samples to allow for calculation of the PK parameters required for analysis.

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.

15.6.2. Study Compliance

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

15.6.3. Efficacy Analyses

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

15.6.3.1 Primary Efficacy Measure

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

For the AUC of the NRS-R pain intensity scores through 72 hours, 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 the treatment groups will be estimated along with the 2-sided 95% confidence intervals (CI).

Handling of Subjects Requiring Rescue Medication

For the AUC of the NRS-R 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 NRS-R pain intensity scores recorded within the window of controlled type of rescue medication (6 hours for IV fentanyl or oxycodone, 4 hours for morphine, and 2 hours for IV hydromorphone) will be replaced by the 'worst' observation. The worst observation will be the highest score in the time interval from the end of surgery up to the time prior to taking their first rescue pain medication. Note that NRS-R pain intensity scores in the window that are higher than the worst value prior to rescue pain medication will not be

overwritten. If no NRS-R pain intensity score is available prior to the first rescue pain medication, the worst observation from all available measurements will be used instead.

15.6.3.2 Secondary Efficacy Measures

The secondary efficacy measures in 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 through 72 hours will be included in the analysis. Prior to analysis, the natural logarithm transformation will be applied to the total amount. To test for a significant difference 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 difference 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 the 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 72 hours will be included in the analysis. Prior to analysis, the natural logarithm transformation will be applied to the total amount.

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 with placebo and two-sided 95% CIs about the differences will be presented.

Categorical Measures of Efficacy

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

15.6.4. Pharmacokinetic Analyses

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

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

Descriptive statistics will be used to summarize the PK parameters.

15.6.5. Safety Analyses

All safety analyses will be based on actual treatment received.

15.6.5.1 Adverse Events

Adverse event verbatim terms will be mapped to preferred terms and related system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). 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 will also be displayed for each treatment group for study drug-related TEAEs and by severity. Incidence rates of SAEs will also be shown for each treatment group. All incidence rates will be categorized and displayed by system organ class and preferred term.

15.6.5.2 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.

15.6.5.3 Neurological Assessments

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

15.6.5.4 Rating of Physician's Satisfaction with Wound Healing

The physician's satisfaction with wound healing will be summarized for each treatment group. To test for significant differences between liposome bupivacaine and placebo, a Wilcoxon Rank Sum test with treatment as the main effect will be used. Based on the model, liposome bupivacaine will be compared with placebo and the two-sided 95% CI about the difference will be presented.

15.7. Significance Testing

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

15.8. Interim Analyses

An interim analysis is not planned.

16. REFERENCES

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17. INVESTIGATOR AGREEMENT

Printed Name of Investigator: _____

Printed Title/Position: _____

Printed Institution Address: _____

_____

_____

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

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

_____ _____

Signature of Investigator Date

18. APPENDICES

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

Subjects will be evaluated for pain intensity using the NRS-R at baseline and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours following surgery, at the first request for rescue medication, and on Day 12.

Subjects will be evaluated for pain intensity using the NRS-A (where the prescribed activity is cough) at baseline, and 24, 48, and 72 hours following surgery and on Day 12.

At time points when the pain intensity assessments coincide, the NRS-R will be conducted before the NRS-A. Additionally, if chest tube removal or a PK blood draw coincides with the pain intensity assessment(s), the pain intensity assessment(s) must be conducted before the other procedures.

Pain Intensity Assessment (Numeric Rating 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 are you having right now? (Circle one number only.)

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

Appendix 2: 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

If the subject is not oriented, record as an AE.

Additionally, the subject will be asked the following questions:

- Do you have numbness of the lips, the tongue, or around the mouth? □ Yes □ No
- Do you have a metallic taste in your mouth? □ Yes □ No
- Are you having problems with your hearing? □ 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 additional 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 24, 48, and 72 hours following surgery.

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

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

Note: The subject's satisfaction with postsurgical pain control will be conducted 72 hours after surgery, on Day 12, 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 Wound Healing

Note: The physician's satisfaction with wound healing will be conducted on Day 12.

Please circle the number below that best describes your satisfaction with the subject's wound healing after surgery. (Circle one number only.)

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

Appendix 6: Treatment-Emergent Opioid-Related Adverse Events Questionnaire

The treatment-emergent opioid-related AE questionnaire will be completed at 72 hours after surgery. 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 to cold within the dermatomes supplied by any of the nerves to which study drug was administered 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?"