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STATISTICAL ANALYSIS PLAN

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

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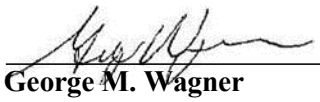
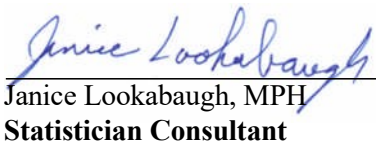
 **George M. Wagner** **Executive Director, Regulatory Affairs and Pharmacovigilance**	09 December 2013 Date
 Janice Lookabaugh, MPH **Statistician Consultant**	09 December 2013 Date

SUMMARY OF CHANGES

The changes made to the statistical analysis plan are as follows:

- Minor formatting and spelling corrections were made throughout.
- In Section 7.1.2 and Section 7.6.2.2 a note was added to clarify how combination opioids would be used in the imputation of NRS pain intensity scores.
- The table in Section 7.1.2 and in Section 7.6.2.2 had additional medications added to be consistent with what has been recorded in the clinical database.
- In Section 7.6.2.1 one sensitivity analysis of the primary efficacy variable was added.
- In Section 7.6.2.2 a clarification was added for how to calculate total dose of fentanyl when administered transdermally.
- In Section 7.6.2.3 a plot for cold sensitivity was added.
- In Section 7.7.2 an analysis of unbound bupivacaine was added.
- In Section 7.8.4 the description of transfusions was changed from intraoperatively or postsurgically to after study drug administration.
- Tables and listings were added or changed to be consistent with the above changes.

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ASA	American Society of Anesthesiologists
ATC	Anatomic therapeutic chemical
AUC	Area under the curve
$AUC_{(0\text{-}inf)}$	Area under the plasma concentration versus time curve from time 0 extrapolated to infinity after drug administration
$AUC_{(0\text{-}last)}$	Area under the plasma concentration versus time curve from time 0 to the last collection time after drug administration
BLOQ	Below the limit of quantification
CI	Confidence interval
C_{max}	The maximum observed plasma concentration obtained directly from the experimental data without interpolation
%CV	Coefficient of variation
CRF	Case report form
CSR	Clinical study report
eCRF	Electronic case report form
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IV	Intravenous
λz	Apparent terminal elimination rate constant

LOCF	Last observation carried forward
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numeric rating scale
NRS-A	Numeric rating scale with activity
NRS-R	Numeric rating scale at rest
OBAS	Overall benefit of analgesia score
ORAE	Opioid-related adverse event
PCA	Patient-controlled analgesia
PK	Pharmacokinetic
PO	Oral
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
TKA	Total knee arthroplasty
T_{max}	Time to maximum concentration
$t_{½}$	Half-life calculated from the apparent terminal elimination rate
WHO-DD	World Health Organization Drug Dictionary
wWOCF	Windowed worst observation carried forward

2. INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analysis and reporting of the clinical study 402-C-323 titled "A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Single Injection Femoral Nerve Block with Liposome Bupivacaine for Postsurgical Analgesia in Subjects Undergoing Total Knee Arthroplasty".

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials [1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association [2] and the Royal Statistical Society [3], for statistical practice.

The purposes of this SAP are to:

- Outline the types of analyses and presentations of data that will form the basis for drawing conclusions to the study objectives and hypotheses outlined in the protocol.
- Explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices for Good Statistical Practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR.

The following documents were reviewed in preparation of this SAP:

- Protocol 402-C-323 Amendment 2 issued on 19 April 2013.
- Case report forms (CRFs) for Protocol 402-C-323.
- ICH Guidance on Statistical Principles for Clinical Trials (E9).

The reader of this SAP is encouraged to also read the clinical study protocol and other identified documents for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

A separate SAP will be written for the analysis of electrocardiogram (ECG) data.

3. STUDY OBJECTIVES

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

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

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

4. STUDY OVERVIEW

This is a Phase 2/3, multicenter, randomized, double-blind, parallel-group, placebo-controlled, dose-ranging study in subjects undergoing primary unilateral total knee arthroplasty (TKA) under general or spinal anesthesia.

On Day 1, eligible subjects will be randomized to receive a single dose of study drug administered within 2 hours prior to the surgical procedure as a femoral nerve block.

All subjects will be required to remain in the study site for a minimum of 72 hours after the end of surgery for postsurgical assessments.

Part 1

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

After all subjects have completed the 72-hour assessments in Part 1, an analysis will be conducted in order to select a single therapeutic dose from the three liposome bupivacaine dose levels tested. The dose selected was 266 mg.

Part 2

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

Postsurgical Rescue Medication

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

First Rescue Medication (IV Hydromorphone)

The first rescue medication will be intravenous (IV) hydromorphone 0.5 mg, which will be administered once via bolus only.

Second Rescue Medication (PCA and/or PO Opioid)

The second rescue medication will be a patient-controlled analgesia (PCA) pump administered opioid (morphine or hydromorphone). The PCA pump will be programmed to deliver either: (1) on-demand morphine or (2) on-demand hydromorphone boluses at a dose and lockout interval in accordance with the site's standard practice. If a subject's pain is excessive or pain control is inadequate, then the bolus dose may be adjusted according to local hospital practices.

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

Third Rescue Medication (Conventional Bupivacaine HCl)

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

Postsurgical Assessments

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

Safety and efficacy assessments will be conducted at pre-specified time points after the end of surgery. A follow-up visit will be scheduled for all subjects on Day 30.

See Table 1 in the protocol for the times of each of the assessments.

Pharmacokinetic Assessments (Part 1 only)

Blood samples for PK analysis will be obtained from subjects at specific sites during Part 1 of the study at baseline, 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 24, 36, 48, 60, an 72 hours after the beginning of study drug administration.

At two sites, there was an addendum to the protocol that allowed for additional blood draws for PK analysis from up to 20 subjects at 84, 96, 120, 144, 168 hours after study drug administration, and on Day 10.

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

5. DEFINITIONS

The terms study site and center are used interchangeably.

Time 0 is defined as the start time of study drug administration for the PK analyses, and as the end time of surgery for the efficacy analyses.

Study day: Day 1 is defined as the day study drug is administered. Positive study days will be measured forward in time from Day 1, with Day 2 being the calendar day immediately following the day study drug is administered. Day -1 is the calendar day immediately preceding the day study drug is administered and negative study days will be measured backward from Day -1.

Study visits and time points will be determined from the scheduled times as reported on the electronic CRFs (eCRFs) for the summarization and analysis of data that are shown by time point, unless otherwise specified.

6. ANALYSIS SETS

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

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

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

7. STATISTICAL METHODS OF ANALYSIS

7.1. General Principles

Descriptive statistics (the number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum) will be used to summarize continuous variables. Means and medians will be presented to one more decimal place than the recorded data. Standard deviations will be presented to two more decimal places than the recorded data. Minimum and maximum values will be presented using the same number of decimal places as the recorded data. Percentages will be presented to one decimal place.

In addition, for PK parameters, geometric means and between-subject coefficient of variations (%CV) will be presented.

Frequency distributions (number [n] and percentage of subjects [%]) will be used to summarize categorical or qualitative variables. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment groups, unless otherwise specified.

All statistical tests will be performed against a two-sided alternative hypothesis with a significance level of 5% ($\alpha = 0.05$), and all confidence intervals (CIs) calculated will be two-sided 95% CIs. All tests will be declared to be statistically significant if the calculated p-value is ≤ 0.05 unless specified otherwise. Tests for binomial proportions will be conducted (1) using a normal approximation whenever each classification cell for each group to be compared contains expected cell counts of 5 or more subjects, or (2) using an exact method whenever any one classification cell for any one group to be compared contains expected cell counts of fewer than 5 subjects.

All analyses will be performed using SAS® Software version 9.2 or later.

Pharmacokinetic parameters will be derived using noncompartmental methods with WinNonlin® Professional Version 5.2 or later (Pharsight Corp., Cary, North Carolina).

For the listings, subjects will be listed under their randomized treatment, regardless of actual treatment received. Subjects who are randomized but do not receive study drug will be included in the listings with the treatment group identified as “Liposome bupivacaine xx mg, Not Treated” or “Placebo, Not Treated”, depending on their randomized treatment.

7.1.1. Calculation of AUC of NRS

Area under the curve (AUC) will be calculated using the trapezoidal method with the actual NRS pain intensity scores reported by the subject. Missing values will be imputed as described in Section 7.1.3. The time points “Baseline” and “First Rescue” will not be included in the calculation of AUC. However, “First Rescue” might be used for imputation purposes as described in Section 7.1.2. Time 0 NRS score will be set to a score of 0. Actual times, not scheduled times, when available will be used in the calculations. Linear interpolation will be used to calculate the pain intensity score at the end of an interval. For 72 hours, as an example, if the actual time is prior to 72 hours post-dose then the actual time

and the reported score will be used. In addition, the reported score will be carried forward to 72 hours. If the actual time is after 72 hours then linear interpolation between the 60-hour and 72-hour scores will be used to calculate the score at 72 hours and the time will be set to 72. The linear interpolation will be performed after missing pain scores are imputed as discussed is Section 7.1.2.

7.1.2. Imputation of NRS Pain Intensity Scores

For calculation of AUC of NRS pain intensity scores, the windowed worst observation carried forward (wWOCF) and last observation carried forward (LOCF) imputation procedure will be used as follows:

a) Windowed worst observation carried forward for rescue medications

For subjects who take a rescue medication, their NRS scores recorded within the window of controlled type of rescue medication (see the table below for the windows for the planned rescue medications) will be replaced by the 'worst' observation. The worst observation will be the highest score in the time interval from Time 0 to up to the time prior to taking the first rescue medication. The NRS score at the first rescue will be included in this calculation. Note that NRS scores in the window that are higher than the worst value prior to rescue medication will not be overwritten. If no NRS score is available prior to the first rescue the worst observation from all available NRS scores will be used instead.

Medication	Route	Window Used to Impute NRS
Oxycodone	PO	6 hours
Oxycontin (MS Contin)	PO	6 hours
Morphine	IV	4 hours
Hydromorphone (Dilaudid)	IV	2 hours
Hydromorphone (Dilaudid)	PO	4 hours
Fentanyl	IV	6 hours
Fentanyl	Transdermal	Start of administration until the end of the administration plus 6 hours
Hydrocodone	PO	6 hours
Bupivacaine HCl	Perineural	12 hours
Bupivacaine HCl	Infusion	Start of the infusion until the end of the infusion plus 12 hours

Ropivacaine		Start of the infusion until the end of the infusion plus 12 hours
Meperidine	IV	4 hours
Ultram	PO	6 hours

IV = intravenous; PO = oral.
If unplanned rescue medications are given then the window will be determined post-hoc prior to breaking the blind. If a combination opioid is given then the window will be determined by the opioid part of the medication. Opioids given postsurgically with an indication like 'anesthesia maintenance' will not be included for imputation purposes.

b) Missing scores before the first non-missing score will be replaced by the median score at the missing time point from the other subjects in the same treatment group.

c) Missing scores after the last non-missing score will be replaced by the LOCF.

d) Missing scores between two non-missing scores will not be replaced (i.e., linear interpolation will be used).

Subjects who have no pain intensity scores recorded after surgery will have the missing scores replaced by the median score at each time point from all subjects in the same treatment group.

7.1.3. Handling Missing Values

Surgery Date or Time

It is expected that all necessary information on surgery (start and stop date and time) and postsurgery rescue medication (start dates and times, doses, frequency) will be complete. Any such information that is missing and cannot be obtained through query resolution may be imputed, on a case-by-case basis, in a conservative manner that minimizes bias. For example, if pain medication taken on Day 1 has no time of administration recorded, the imputed time will be the end of surgery.

PCA Pump Interval Data

For some subjects, individual doses from the PCA pump were not collected. For some subjects the individual doses were not collected for the whole 72 hours and for some it was not collected for parts of the 72 hours. For these data the intervals during which medication was delivered via the PCA pump are known. So what was entered in the database was the medication, the start date and time of the interval, the stop date and time of the interval, and the total dose received.

For these cases, for purposes of imputing pain scores using the wWOCF imputation, it will be assumed that a dose was given at the beginning of the interval, a dose was given at the end of the interval, and a dose was given in the middle of the interval.

For these cases, for purposes of calculating the total postsurgical opioid consumption through the various time intervals, it will be assumed that the total dose was given at the beginning of the interval.

Rescue Pain Medication

For calculation of the total rescue pain medication usage (morphine equivalent) by time point, if a subject is discontinued early (e.g., dies, withdraws consent, is withdrawn from the study, or is lost to follow-up) before the end of the time interval (e.g., 24 hours after study drug administration), his or her total rescue pain medication usage through the time interval will be a projected amount. For example, if a subject discontinues early at 6 hours after surgery, the projected amounts through 24 hours will be actual amount + average amount (actual amount/6 hours) multiplied by the number of hours remaining in the time interval (24-6).

Adverse Event or Concomitant Medications Dates or Times

For AEs or concomitant medications with missing or partially missing start/stop date/time, the following imputation rules will be applied:

For partial start date/time:

- If the year is unknown, then the date will not be imputed and will be assigned a missing value.
- If the month is unknown, then:
  - i) If the year matches the year of the dose of study drug date, then the month and day of the dose of study drug date will be imputed.
  - ii) Otherwise, 'January' will be assigned.
- If the day is unknown, then:
  - i) If the month and year match the month and year of the dose of study drug date, then the day of the dose of study drug date will be imputed.
  - ii) Otherwise, '01' will be assigned.
- If the time is unknown, then:
  - i) If the date (day, month, and year) match the date of the dose of study drug date, then the time of the dose of study drug time will be imputed.
  - ii) Otherwise, "00' will be assigned.

For partial stop date/time:

- If the year is unknown, then the date will not be imputed and will be assigned a missing value.
- If the month is unknown, then 'December' will be assigned.
- If the day is unknown, then the last day of the month will be assigned.
- If the time is unknown, then the last time of the day will be assigned.

If the above rules for stop dates result in an illogical date with regards to the dates the subject is in the study, then the stop date will be replaced with the subject's date of completion/ withdrawal. Further, should the above rules not result in the most conservative date, then the imputed value may be replaced by a date that will lead to a more conservative analysis. Should this situation arise, specific details will be provided in the derived dataset specification documentation or documented in the derived analysis data set program using comments.

AE Severity or Relationship to Study Drug

If severity of an AE is not reported, then for tables of AEs by severity, the event will be classified as 'Severe'. If relationship to study drug is not reported for an AE, then for tables of study-drug related AEs, the event will be classified as related.

Time to Event Time

For calculating time to an event when only the hour, and not the minutes, are reported for the time of the event, then the minutes will be set to zero.

7.1.4. Multiplicity Adjustments

Part 1

The purpose of Part 1 of the study is to select a dose for use in Part 2. Therefore, no alpha-level adjustments for multiple comparisons between the three doses and placebo will be made.

Part 2

Since no multiple comparisons of the primary efficacy variable will be made, no alpha-adjustments will be made.

Also, since there is only one primary efficacy variable and all other efficacy variables are considered secondary, no alpha-adjustments for the primary response variable will be made.

There are two secondary efficacy variables that will be analyzed using a hierarchical fixed-sequence stepwise testing procedure (See Section 7.6.1). The two secondary efficacy variables will only be analyzed if the prmary efficacy variable is statistically significant at the two-sided 0.05 significance level. 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.

7.1.5. By-Center Analyses

Up to 40 sites/centers will enroll subjects in this study. The primary efficacy results will be summarized by site but site will not be included in any models.

7.2. Subject Disposition

The number and percentage of subjects who are in each analysis set, who completed the study, and who discontinued early from the study, along with reasons for early withdrawal, will be summarized by treatment group and for all subjects, separately for Part 1 and Part 2. In addition, the same summary will be produced by site for Part 2.

7.3. Description of Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group and for all subjects, separately for Part 1 and Part 2 for the safety analysis set and efficacy analysis set. The variables to be included in the summary are age, gender, ethnicity, race, American Society of Anesthesiologists (ASA) physical status class, height (cm), and weight (kg).

Conversions between units for height and weight will use the following formulas:

Weight (kg) = weight (lb) / 2.2046226

Height (cm) = height (in) / 2.54.

7.4. Prior and Concomitant Medication

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) and will be classified according to the default anatomical therapeutic chemical (ATC) classification system code and preferred term.

Prior medications are defined as medications with a stop date/time prior to study drug administration. Concomitant medications are defined as medications taken after the start of study drug administration (i.e., started prior to the start of study drug administration and continued after or started after the start of study drug administration).

Prior and concomitant medications will be summarized using n (%) of subjects by treatment group and for all subjects and by ATC class and preferred term separately for Part 1 and Part 2 for the safety analysis set. Subjects may have more than one medication per ATC category and preferred term. At each level of subject summarization, a subject will be counted once if he/she reports one or more medications at that level.

The tables of concomitant medications will not include rescue pain medications.

7.5. Measurements of Treatment Compliance

Study drug administration will be summarized by treatment group, separately for Part 1 and Part 2 for the safety analysis set. The variables to be included are duration of injection and volume of study drug administered. Surgery will be summarized by treatment group, separately for Part 1 and Part 2 for the efficacy analysis set. The variables to be included in the summary are length of surgery (end time minus start time, in minutes), type of anesthesia, and incision length.

7.6. Efficacy Analysis

All summaries of the efficacy variables will use the efficacy analysis set, which will be based on randomized treatment, and will be summarized separately for Part 1 and Part 2.

7.6.1. Efficacy Variables

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

Secondary efficacy variables are:

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

Tertiary efficacy variables are (the order of these variables has been changed from the order in the protocol to reflect how they will be discussed in the CSR):

- The NRS-R and NRS-A pain intensity scores at each assessed time point.
- The AUC of the NRS-R pain intensity scores through 24, 36, 48, and 60 hours.

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

7.6.2. Methods of Analysis

7.6.2.1 Primary Efficacy Variable

The primary efficacy variable is the AUC of the NRS-R pain intensity scores through 72 hours using the wWOCF + LOCF imputation method described in Section 7.1.2.

Each dose of liposome bupivacaine (Part 1) and the one dose of liposome bupivacaine (Part 2) 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 least squares (LS) means, LS mean difference between the two treatment groups, 95% CI for the LS mean difference(s) between liposome bupivacaine and placebo, and p-value will be reported.

For Part 2, descriptive statistics of the primary efficacy variable will also be shown by site.

Sensitivity Analyses of the Primary Efficacy Variable

For Part 2 a sensitivity analysis will be performed.

The sensitivity analysis will exclude subjects who had interval data for opioid consumption.

7.6.2.2 Secondary Efficacy Variables

The secondary efficacy variables for this study are:

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

For total postsurgical opioid consumption, opioid medications will be converted to a morphine equivalent amount (see the table below). The converted amounts will be totaled for each subject and used in the analysis. When fentanyl is given transdermally the total amount, prior to conversion, will be calculated as the start date/time of administration until the end date/time of administration or end date/time of 72 hours after surgery, whichever is sooner, multiplied by the dose. Projected amounts, for subjects who discontinue early, will be calculated as described in Section 7.1.3.

Medication	Unit	Route	Conversion (Multiplication) Factor
Oxycodone	mg	PO	0.5
Oxycontin	mg	PO	0.5
Morphine	mg	IV	1
Hydromorphone (Dilaudid)	mg	IV	6.7
Hydromorphone (Dilaudid)	mg	PO	1.3
Fentanyl	mcg	IV	0.1
Fentanyl	mcg	Transdermal	0.5
Hydrocodone	mg	PO	0.33

IV = intravenous; PO = oral.
If unplanned rescue medications are administered, then the conversion factor will be determined post-hoc prior to breaking the blind. If a combination opioid is administered then the opioid portion of the medication will be converted and included in the calculations. Opioids given postsurgically with an indication like 'anesthesia maintenance' will not be included in the calculation of total opioids.

Prior to analysis, the natural logarithm transformation will be applied to the total amount. When total amount of opioids used is 0, the result will be changed to the lesser of 1 or 0.5 of the smallest total amount observed in the study prior to being transformed with the natural logarithm. To test for significant differences between each liposome bupivacaine dose and placebo (Part 1) and between the one liposome bupivacaine dose and placebo (Part 2), an analysis of variance (ANOVA) with treatment as the main effect will be used. Based on the

model, the LS means, LS mean difference between the two treatment groups, 95% CI for the LS mean difference(s) between liposome bupivacaine and placebo, and p-value will be reported.

For the analysis of time to first opioid rescue, time to first opioid rescue will be computed in hours as the date/time of the first opioid rescue minus the date/time of the end of surgery. If a subject is not administered an opioid, the time to first administration will be censored at 72 hours after surgery or at the time of last follow-up, whichever is earliest. Time of last follow-up will be defined as the later of (1) the last pain assessment, (2) the start time of the last rescue or concomitant medication, or (3) the start time of the last AE.

Time to first opioid rescue will be analyzed by the Kaplan-Meier method. The n (%) of subjects administered an opioid as well as the n (%) of censored observations will be presented for each treatment group. In addition, Kaplan-Meier estimates in terms of the median and its 95% CI, and the 25^{th} and 75^{th} percentiles will be presented for each treatment. Log-rank tests will be used to compare each dose of liposome bupivacaine (Part 1) and the one dose of liposome bupivacaine (Part 2) to placebo.

For Part 2, the 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.

7.6.2.3 Tertiary Efficacy Variables

For Part 1, no statistical tests will be performed on any of the tertiary efficacy variables. Only descriptive statistics will be shown for each treatment.

For Part 2, the following describes the statistical analyses to be performed.

NRS-R, NRS-A, and AUC of Pain Intensity Scores

For the tertiary efficacy variables NRS-R, NRS-A, and the AUCs of the NRS-R and NRS-A pain intensity scores, the same analyses as those for the primary efficacy variable will be performed, except that the baseline NRS-A score will be used as the covariate for all variables using the NRS-A.

Proportion of Subjects Who are Pain Free

Pain free is defined as an NRS-R pain intensity score of 0 or 1. The number and percentage of subjects who are pain free will be summarized by treatment group for each time point. A chi-square test will be used to compare liposome bupivacaine to placebo.

Total Postsurgical Opioid Consumption Through 24, 36, 48, and 60 Hours

For the tertiary efficacy variables total opioid consumption through each of the time periods, the same analysis as that for the secondary efficacy variable of total opioid consumption through 72 hours will be performed.

Subjects Who Receive Rescue Medication

The category of 'Subjects who receive no rescue medication' is defined as subjects who report not taking any medication on the four Rescue Medication eCRFs.

The category of 'Subjects who only receive the IV hydromorphone bolus' is defined as subjects who report taking IV hydromorphone (or other opioid medications) on the First Rescue Medication eCRF and report not taking a medication on either of the Second Rescue Medication eCRFs or on the Third Rescue Medication eCRF.

The category of 'Subjects who receive the IV hydromorphone bolus and a second opioid medication' is defined as subjects who report taking IV hydromorphone (or other opioid medication) on the First Rescue Medication eCRF and who report taking a medication on either of the Second Rescue Medication eCRFs and report not taking a medication on the Third Rescue Medication eCRF.

The category of 'Subjects who receive the IV hydromorphone bolus, a second opioid medication, and conventional bupivacaine HCl' is defined as subjects who report taking IV hydromorphone (or other opioid medication) on the First Rescue Medication eCRF, who report taking a medication on either or both of the Second Rescue Medication eCRFs, and bupivacaine HCl on the Third Rescue Medication eCRF.

The number and percentage of subjects who are in each of the above categories will be summarized by treatment group. A chi-square test will be used to compare liposome bupivacaine to placebo for each of the categories.

Overall Benefit of Analgesia Score Questionnaire

The OBAS is calculated as follows:

1. Add all of the scores of questions one to six.
2. To this number, add four.
3. Subtract the score of question seven from this number.

Summary statistics will be provided by treatment group at each time point. A Wilcoxon Rank Sum test will be used to compare liposome bupivacaine to placebo.

Subject Satisfaction with Postsurgical Pain Control

Subjects will rate their satisfaction with postsurgical pain control as Extremely dissatisfied, Dissatisfied, Neither satisfied nor dissatisfied, Satisfied, or Extremely satisfied at 72 hours and on Day 30. The categories will be summarized by treatment group at each time point. A Wilcoxon Rank Sum test will be used to compare liposome bupivacaine to placebo.

Time to Sensitivity to Cold

Once a subject reports sensitivity to cold on two consecutive evaluations the subject will no longer be tested. The time to sensitivity to cold will be defined as the time of the first of two consecutive evaluations when the subject reports sensitivity to cold. Time to sensitivity to cold will be calculated from the end of surgery. If a subject never reports sensitivity to cold or never reports sensitivity to cold on two consecutive evaluations then the time will be

censored at 72 hours after the end of surgery or at the time of the last follow-up, whichever is earliest. Time of last follow-up will be defined as the later of (1) the last pain assessment, (2) the start time of the last rescue or concomitant medication, or (3) the start time of the last AE.

Time to sensitivity to cold will be analyzed by the Kaplan-Meier method. The n (%) of subjects with sensitivity to cold as well as the n (%) of censored observations will be presented for each treatment group. In addition, Kaplan-Meier estimates in terms of the median and its 95% CI, and the 25^{th} and 75^{th} percentiles will be presented for each treatment group. For Part 2, a log-rank test will be used to compare liposome bupivacaine to placebo.

A plot of the responses to cold sensitivity will be produced for Part 1 and Part 2 separately. The x-axis will show the scheduled hours post-op. The y-axis will be the subject number. An 'X' will be plotted for responses of 'Yes' and an 'O' will be plotted for responses of 'No'.

Figures should be created by site and treatment, combining sites with few subjects, in order to show about 20 subjects per figure.

Incidence of Predefined Treatment-Emergent Opioid-Related AEs

The determination of whether a subject had a treatment-emergent ORAE will be based solely on responses on the Predefined Treatment-Emergent ORAEs eCRF. This was collected in Part 1 only The number and percentage of subjects who have at least one ORAE will be summarized by treatment group. A chi-square test will be used to compare liposome bupivacaine to placebo.

The number and percentage of subjects who have each of the ORAEs will also be summarized by treatment group, although no statistical tests will be performed.

7.7. Pharmacokinetic Analyses

7.7.1. Pharmacokinetic Parameter Calculation Methods

Part 1

Pharmacokinetic parameters will be calculated by noncompartmental analysis method from concentration-time data using WinNonlin Professional (Version 5.2 or later) following these guidelines:

- Actual sampling times relative to study drug administration will be used for all calculations of the PK parameters. If there is any doubt as to the actual time a sample was taken, then the scheduled time will be used. Descriptive statistics will be used to summarize the PK parameters.
- There will be no imputation of missing data.

For the calculation of AUCs from PK concentrations, concentration below the limit of quantification (BLOQ) will be handled as follows:

- Pre-dose values will be set to zero.
- All remaining BLOQ values will be set to missing.

Pharmacokinetic parameters will be estimated according to the following guidelines:

- The maximum observed plasma concentration (C_{max}) will be obtained directly from the concentration-time data.
- Time to maximum concentration (T_{max}) is the time at which C_{max} is observed.
- The apparent terminal elimination rate constant (λ_Z) will be estimated at terminal phase by linear regression after log-transformation of the concentrations:
  - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression.
  - A minimum number of three data points in the terminal phase will be used in calculating λ_z with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope) and including C_{last}, t_{last}.
  - The adjusted correlation coefficient (R^2 adjusted) in general should be greater than 0.90. Any value less than 0.90 may be used at the pharmacokineticist's best knowledge and judgment.
  - An appropriate number of decimal places should be used for λ_z to enable the reported value of half-life ($t_{½}$) to be calculated.
- Half-life ($t_{1/2}$) will be calculated as $\ln 2/\lambda_Z$.
- AUC will be calculated as follows:
  - The linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.
  - $AUC_{(0\text{-}t)} = \int_0^t C(t)dt$.
  - $AUC_{(0\text{-}inf)} = \int_0^t C(t)dt + \int_t^\infty C(t)dt = AUC_{(0\text{-}t)} + C_t/\lambda_z$.
  - $C_{(t)}$ is last observed quantifiable concentration.

7.7.2. Pharmacokinetic Concentrations and Variables

The analysis of the PK data will be based on the PK analysis set.

Bupivacaine plasma concentrations will be listed by treatment group, subject, nominal time, and actual time. Concentrations that are BLOQ will be indicated by BLOQ in this listing.

Plasma concentrations will be summarized by treatment at each time point. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: n, geometric mean, arithmetic mean, SD, %CV, minimum, median, and maximum.

Pharmacokinetic parameters will be summarized by treatment. Descriptive statistics for calculated PK parameters will include: n, arithmetic mean, SD, %CV, geometric mean, median, minimum and maximum values. Geometric mean will not be presented for T_{max}. Values of %AUC extrapolated > 20% will be flagged in the listings.

Individual plasma concentration versus actual times will be plotted by treatment in linear and semi-logarithmic scale.

At the 15 minute time point, unbound bupivacaine will be evaluated. The percentage of unbound over the total (unbound/total*100) will be summarized for subjects who have both values.

7.8. Safety Analyses.

All summaries of the safety data will use the safety analysis set.

7.8.1. Adverse Events

All AEs will be coded and summarized by system organ class (SOC) and preferred term based on the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

An AE will be considered treatment-emergent if the onset is any time on or after study drug administration through Day 30.

Only treatment-emergent AEs (TEAEs) that were not solicited from the Neurological Assessment or from the Opioid-Related Adverse Event Questionnaire will be summarized in the tables. All other AEs, those that occur after randomization but prior to study drug administration, AEs that occur after Day 30, or AEs that were solicited from the Neurological Assessment or from the Opioid-Related Adverse Event Questionnaire will appear in listings only.

Tables of AEs will show Part 1 and Part 2 data separately and combined.

Treatment-emergent AEs will be summarized [n (%)] and grouped by SOC and preferred term for each treatment group and for all subjects. If a subject experiences more than one episode of a particular TEAE, the subject will be counted only once for that event at each level of summarization (overall, by SOC, and by preferred term).

Similarly, TEAEs will be summarized in terms of maximum severity (‘Mild’, ‘Moderate’, and ‘Severe’), study drug related TEAEs, and serious AEs.

7.8.2. Laboratory Parameters

Not applicable.

7.8.3. Vital Signs

Descriptive summaries of actual value and changes from Baseline will be calculated for systolic blood pressure, diastolic blood pressure, and heart rate. These summaries will be presented by treatment group at each time point for Part 1 and Part 2 separately and combined.

7.8.4. Other Safety Parameters

Neurological Assessments

The proportion of subjects who are oriented will be summarized by treatment group at each time point, for Part 1 and Part 2 separately and combined. Subjects who were ‘not assessable’

will not be included in the calculation of the proportion. The proportion of subjects who have at least one of the neurological events and the proportion of subjects who have each of the neurologic events will be summarized by treatment group, for Part 1 and Part 2 separately and combined.

20-Meter Walk Test

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

Physician's Satisfaction with Return of Sensory/Motor Function

The physician will rate his/her satisfaction with return of sensory/motor function as Extremely dissatisfied, Dissatisfied, Neither satisfied nor dissatisfied, Satisfied, or Extremely satisfied at 72 hours and on Day 30. The categories will be summarized by treatment group at each time point for Part 1 and Part 2 separately and combined. For Part 2, a Wilcoxon Rank Sum test will be used to compare liposome bupivacaine to placebo.

Transfusions

The proportion of subjects who had a transfusion (after study drug administration) will be summarized by treatment group for Part 1 and Part 2 separately and combined. To determine if a subject had a transfusion a review of the concomitant medications will be done. Medications such as Packed Red Blood Cells will indicate that a subject had a transfusion.

7.9. Interim Analysis

After all subjects have completed the 72-hour assessments, or discontinued prior to the 72-hour assessment from Part 1 of the study, an analysis will be conducted in order to select a single therapeutic dose from the three liposome bupivacaine dose levels tested. The committee will determine the apparent efficacy and safety of each of the three liposome bupivacaine dose levels tested and will recommend a dose level for Part 2 of the study. In order to make their assessment, the following tables will be produced by an unblinded statistician:

Table #	Table Title
14.1.1-1	Subject Disposition (All Subjects)
14.1.2.1-1	Demographic and Baseline Characteristics (Safety Analysis Set)
14.2.2.1-1	AUC of NRS-R Pain Intensity Scores Through 72 Hours wWOCF + LOCF Imputation for the Pain Scores (Efficacy Analysis Set)
14.2.2.2-1	Total Postoperative Consumption (mg) of Opioid Rescue Pain Medication Through 72 Hours (Efficacy Analysis Set)
14.2.2.3.2-1	Time to First Opioid Rescue (Efficacy Analysis Set)
14.3.1.2-1	Incidence of Treatment-Emergent Adverse Events (Safety Analysis Set)
14.3.4-1	20-Meter Walk Test (Safety Analysis Set)

In addition, blood plasma samples for PK analysis will be sent to a laboratory for analysis from approximately 100 subjects. The samples from those subjects who received liposome bupivacaine and who did not receive conventional bupivacaine HCl postsurgically will be assayed. The liposome bupivacaine concentrations will be sent to the unblinded statistician. The unblinded statistician will determine the C_{max} for each of these subjects. The maximum C_{max} will be provided to Pacira. Depending on the maximum C_{max}, Pacira will determine if ECG data at T_{max} need to be provided to the committee.

8. SAMPLE SIZE CALCULATIONS

Part 1

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

Part 2

A study population of approximately 180 subjects is planned with approximately 90 subjects in each treatment group (liposome bupivacaine and placebo). The sample size was estimated based on the results of a Phase 3 hemorrhoidectomy study of liposome bupivacaine versus placebo where the mean (SD) 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 SD is 104, when the sample size in each group is 90.

After the data from Part 1 are evaluated, the sample size for Part 2 may be increased. The evaluation of the data did not indicate that the sample size should be increased.

9. REFERENCES

1. US Federal Register. International Conference on Harmonisation; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. 16 September 1998.
2. American Statistical Association. Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, 07 August 1999. http://www.amstat.org/profession/ethicalstatistics.html
3. Royal Statistical Society. The Royal Statistical Society: Code of Conduct, August 1993. http://www.rss.org.uk/about/conduct.html.

10. LAYOUT OF TABLES, LISTINGS, AND FIGURES

The following are planned summary tables for Protocol 402-C-323. Tables will be numbered according to the nomenclature used to support the CSR. The final table numbering may be different from the SAP. No amendment will be made for changes in table numbering. All headers, titles, footnotes, and footers specified in the table templates will be displayed in the produced output unless otherwise specified. Notes to programmers will not be included in the tables. There will be a footnote in all tables that includes the program name, SAS version number, and the date that the output was produced.

Study Part 1 Planned Tables

Table Number	Table Title
14.1.1-1	Subject Disposition Study Part 1 (All Randomized Subjects)
14.1.2.1-1	Demographic and Baseline Characteristics Study Part 1 (Safety Analysis Set)
14.1.2.2-1	Demographic and Baseline Characteristics Study Part 1 (Efficacy Analysis Set)
14.1.3.1-1	Prior Medications Study Part 1 (Safety Analysis Set)
14.1.3.2-1	Concomitant Medications Study Part 1 (Safety Analysis Set)
14.2.1.1-1	Study Drug Administration Study Part 1 (Safety Analysis Set)
14.2.1.2-1	Surgery Study Part 1 (Efficacy Analysis Set)
14.2.2.1-1	AUC of NRS-R Pain Intensity Scores Through 72 Hours wWOCF + LOCF Imputation for the Pain Scores Study Part 1 (Efficacy Analysis Set)
14.2.2.2-1	Total Postoperative Consumption (mg) of Opioid Rescue Pain Medication Through 72 Hours Study Part 1 (Efficacy Analysis Set)
14.2.2.3-1	Time to First Opioid Rescue Study Part 1 (Efficacy Analysis Set)

Study Part 1 Planned Tables Continued

Table Number	Table Title
14.2.2.4-1	NRS-R Pain Intensity Scores Study Part 1 (Efficacy Analysis Set)
14.2.2.5-1	NRS-A Pain Intensity Scores Study Part 1 (Efficacy Analysis Set)
14.2.2.6-1	AUC of NRS-R Pain Intensity Scores Through 24, 36, 48, and 60 Hours wWOCF + LOCF Imputation for the Pain Scores Study Part 1 (Efficacy Analysis Set)
14.2.2.7-1	AUC of NRS-A Pain Intensity Scores Through 24, 36, 48, 60, and 72 Hours wWOCF + LOCF Imputation for the Pain Scores Study Part 1 (Efficacy Analysis Set)
14.2.2.8-1	AUC of NRS-R Pain Intensity Scores 24-48 and 48-72 Hours wWOCF + LOCF Imputation for the Pain Scores Study Part 1 (Efficacy Analysis Set)
14.2.2.9-1	Percentage of Subjects who are Pain Free at Each Time Point Study Part 1 (Efficacy Analysis Set)
14.2.2.10-1	Total Postoperative Consumption (mg) of Opioid Rescue Pain Medication Through 24, 36, 48, and 60 Hours Study Part 1 (Efficacy Analysis Set)
14.2.2.11-1	Subjects who Received Rescue Medication Through 72 Hours Study Part 1 (Efficacy Analysis Set)
14.2.2.12-1	Overall Benefit of Analgesia Score Questionnaire (Total Scores) Study Part 1 (Efficacy Analysis Set)
14.2.2.13-1	Subject Satisfaction with Postsurgical Pain Control Study Part 1 (Efficacy Analysis Set)
14.2.2.14-1	Time to Sensitivity to Cold Study Part 1 (Efficacy Analysis Set)

Study Part 1 Planned Tables Continued

Table Number	Table Title
14.2.2.15-1	Incidence of Predefined Treatment-Emergent Opioid-Related Adverse Events Study Part 1 (Efficacy Analysis Set)
14.2.3.1-1	Bupivacaine Plasma Concentrations (ng/mL) Study Part 1 (PK Analysis Set)
14.2.3.2-1	Bupivacaine Plasma Pharmacokinetic Parameters Study Part 1 (PK Analysis Set)
14.2.3.3-1	Percentage of Unbound Bupivacaine Plasma Concentrations (ng/mL) Study Part 1 (PK Analysis Set)
14.3.1.1-1	Overview of Treatment-Emergent Adverse Events Study Part 1 (Safety Analysis Set)
14.3.1.2-1	Incidence of Treatment-Emergent Adverse Events Study Part 1 (Safety Analysis Set)
14.3.1.3-1	Incidence of Study Drug Related Treatment-Emergent Adverse Events Study Part 1 (Safety Analysis Set)
14.3.1.4-1	Incidence of Treatment-Emergent Adverse Events by Severity (Part 1 of 2) Study Part 1 (Safety Analysis Set)
14.3.1.4-1	Incidence of Treatment-Emergent Adverse Events by Severity (Part 2 of 2) Study Part 1 (Safety Analysis Set)
14.3.1.5-1	Incidence of Serious Treatment-Emergent Adverse Events Study Part 1 (Safety Analysis Set)
14.3.2.1-1	Vital Signs Study Part 1 (Safety Analysis Set)
14.3.2.2-1	Vital Signs Change from Baseline Study Part 1 (Safety Analysis Set)
14.3.3-1	Neurological Assessment Study Part 1 (Safety Analysis Set)

Study Part 1 Planned Tables Continued

Table Number	Table Title
14.3.4-1	20-Meter Walk Test Study Part 1 (Safety Analysis Set)
14.3.5-1	Physician Satisfaction with Return of Sensory/Motor Function Study Part 1 (Safety Analysis Set)
14.3.6-1	Incidence of Transfusions Study Part 1 (Safety Analysis Set)

Study Part 1 Planned Figure

Figure Number	Table Title
1-1	Sensitivity to Cold Study Part 1 (Efficacy Analysis Set)

Study Part 2 Planned Tables

Table Number	Table Title
14.1.1.1-2	Subject Disposition Study Part 2 (All Randomized Subjects)
14.1.1.2-2	Subject Disposition by Site Study Part 2 (All Randomized Subjects)
14.1.2.1-2	Demographic and Baseline Characteristics Study Part 2 (Safety Analysis Set)
14.1.2.2-2	Demographic and Baseline Characteristics Study Part 2 (Efficacy Analysis Set)
14.1.3.1-2	Prior Medications Study Part 2 (Safety Analysis Set)
14.1.3.2-2	Concomitant Medications Study Part 2 (Safety Analysis Set)
14.2.1.1-2	Study Drug Administration Study Part 2 (Safety Analysis Set)
14.2.1.2-2	Surgery Study Part 2 (Efficacy Analysis Set)
14.2.2.1.1-2	AUC of NRS-R Pain Intensity Scores Through 72 Hours wWOCF + LOCF Imputation for the Pain Scores Study Part 2 (Efficacy Analysis Set)
14.2.2.1.2-2	AUC of NRS-R Pain Intensity Scores Through 72 Hours by Site wWOCF + LOCF Imputation for the Pain Scores Study Part 2 (Efficacy Analysis Set)

Study Part 2 Planned Tables Continued

Table Number	Table Title
14.2.2.1.3-2	AUC of NRS-R Pain Intensity Scores Through 72 Hours wWOCF + LOCF Imputation for the Pain Scores Excluding Subjects with PCA Interval Data Study Part 2 (Efficacy Analysis Set)
14.2.2.2-2	Total Postoperative Consumption (mg) of Opioid Rescue Pain Medication Through 72 Hours Study Part 2 (Efficacy Analysis Set)
14.2.2.3.2-2	Time to First Opioid Rescue Study Part 2 (Efficacy Analysis Set)
14.2.2.4-2	NRS-R Pain Intensity Scores Study Part 2 (Efficacy Analysis Set)
14.2.2.5-2	NRS-A Pain Intensity Scores Study Part 2 (Efficacy Analysis Set)
14.2.2.6-2	AUC of NRS-R Pain Intensity Scores Through 24, 36, 48, and 60 Hours wWOCF + LOCF Imputation for the Pain Scores Study Part 2 (Efficacy Analysis Set)
14.2.2.7-2	AUC of NRS-A Pain Intensity Scores Through 24, 36, 48, 60, and 72 Hours wWOCF + LOCF Imputation for the Pain Scores Study Part 2 (Efficacy Analysis Set)
14.2.2.8-2	AUC of NRS-R Pain Intensity Scores 24-48 and 48-72 Hours wWOCF + LOCF Imputation for the Pain Scores Study Part 2 (Efficacy Analysis Set)
14.2.2.9-2	Percentage of Subjects who are Pain Free at Each Time Point Study Part 2 (Efficacy Analysis Set)
14.2.2.10-2	Total Postoperative Consumption (mg) of Opioid Rescue Pain Medication Through 24, 36, 48, and 60 Hours Study Part 2 (Efficacy Analysis Set)

Study Part 2 Planned Tables Continued

Table Number	Table Title
14.2.2.11-2	Subjects who Received Rescue Medication Through 72 Hours Study Part 2 (Efficacy Analysis Set)
14.2.2.12-2	Overall Benefit of Analgesia Score Questionnaire (Total Scores) Study Part 2 (Efficacy Analysis Set)
14.2.2.13-2	Subject Satisfaction with Postsurgical Pain Control Study Part 2 (Efficacy Analysis Set)
14.2.2.14-2	Time to Sensitivity to Cold Study Part 2 (Efficacy Analysis Set)
14.3.1.1-2	Overview of Treatment-Emergent Adverse Events Study Part 2 (Safety Analysis Set)
14.3.1.2-2	Incidence of Treatment-Emergent Adverse Events Study Part 2 (Safety Analysis Set)
14.3.1.3-2	Incidence of Study Drug Related Treatment-Emergent Adverse Events Study Part 2 (Safety Analysis Set)
14.3.1.4-2	Incidence of Treatment-Emergent Adverse Events by Severity (Part 1 of 2) Study Part 2 (Safety Analysis Set)
14.3.1.4-2	Incidence of Treatment-Emergent Adverse Events by Severity (Part 2 of 2) Study Part 2 (Safety Analysis Set)
14.3.1.5-2	Incidence of Serious Treatment-Emergent Adverse Events Study Part 2 (Safety Analysis Set)
14.3.2.1-2	Vital Signs Study Part 2 (Safety Analysis Set)

Study Part 2 Planned Tables Continued

Table Number	Table Title
14.3.2.2-2	Vital Signs Change from Baseline Study Part 2 (Safety Analysis Set)
14.3.3-2	Neurological Assessment Study Part 2 (Safety Analysis Set)
14.3.4-2	20-Meter Walk Test Study Part 2 (Safety Analysis Set)
14.3.5-2	Physician Satisfaction with Return of Sensory/Motor Function Study Part 2 (Safety Analysis Set)
14.3.6-2	Incidence of Transfusions Study Part 2 (Safety Analysis Set)

Study Part 2 Planned Figure

Figure Number	Table Title
1-2	Sensitivity to Cold Study Part 2 (Efficacy Analysis Set)

Planned Listings

Listing Number	Listing Title
16.1.1	Eligibility
16.1.2	Unblinding
16.1.3	Subject Populations and Discontinuations
16.1.4	Hospital Discharge
16.2	Demographics
16.3.1	Medical History
16.3.2	Physical Examination
16.3.3	Electrocardiogram Recording (Holter Monitoring)
16.3.4	Prior and Concomitant Medications (Except for Rescue Pain Medications)
16.3.5	Transfusions Post Study Drug Administration
16.4.1	Study Drug Exposure
16.4.2	Surgery
16.5.1.1	Pain Intensity Scores at Rest and with Activity
16.5.1.2	AUC of NRS-R and NRS-A Pain Intensity Scores wWOCF + LOCF Imputation for the Pain Scores
16.5.2.1	Postoperative Consumption of Opioid Rescue Pain Medication
16.5.2.2	Postoperative Consumption of Rescue Pain Medication via PCA Pump (Interval Data)
16.5.2.3	Postoperative Consumption of Conventional Bupivacaine HCl Rescue Pain Medication
16.5.3	Overall Benefit of Analgesia Score Questionnaire
16.5.4	Subject Satisfaction with Postsurgical Pain Control
16.5.5	Sensitivity to Cold
16.5.6	Predefined Treatment-Emergent Opioid-Related Adverse Events at 72 Hours (Study Part 1)
16.6.1	Scheduled Bupivacaine Plasma Concentrations (Study Part 1)
16.6.2	Bupivacaine Plasma Pharmacokinetic Parameters (Study Part 1)
16.6.3	Unscheduled Bupivacaine Plasma Concentrations
16.7.1.1	Adverse Events (Part 1 of 2)
16.7.1.2	Adverse Events (Part 2 of 2)
16.7.1.3	Serious Adverse Events (Part 1 of 2)
16.7.1.4	Serious Adverse Events (Part 2 of 2)
16.7.1.5	Deaths
16.8	Height, Weight, and Vital Signs
16.9	Neurological Assessment
16.10	20-Meter Walk Test
16.11	Physician Satisfaction with Return of Sensory/Motor Function

STUDY PART 1 TABLES

Pacira Pharmaceuticals, Inc.
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Table 14.1.1-1 (Page x of Y)
Subject Disposition
Study Part 1
(All Randomized Subjects)

	LB 67 mg (N=XX) n (%)	LB 133 mg (N=XX) n (%)	LB 266 mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
Safety Analysis Set [1]	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Efficacy Analysis Set [2]	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
PK Analysis Set [3]	00 (00.0)	00 (00.0)	00 (00.0)	NA	00 (00.0)
Subjects Who Completed the Study	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Subjects Who Terminated Early	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Reason for Early Termination					
Subject Death	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Adverse Event	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Lack of Efficacy	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Lost to Follow-up	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Withdrawal by Subject	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Other	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine.
[1] The safety analysis set includes all subjects who received study drug.
[2] The efficacy analysis set includes all subjects in the safety analysis set who underwent the planned surgery.
[3] The PK analysis set includes all subjects in the safety analysis set who received liposome bupivacaine, provided sufficient samples to allow for calculation of PK parameters required for analysis, and who did not receive conventional bupivacaine HCl postsurgically.

Reference: Listing 16.1.3.

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Table 14.1.2.1-1 (Page x of Y)
Demographic and Baseline Characteristics
Study Part 1
(Safety Analysis Set)

	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)	All Subjects (N=XX)
Age (years)					
n	00	00	00	00	00
Mean	00.0	00.0	00.0	00.0	00.0
SD	00.00	00.00	00.00	00.00	00.00
Median	00	00	00	00	00
Minimum, Maximum	00, 00	00, 00	00, 00	00, 00	00, 00
Age Category					
<65	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
>=65	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Gender					
Male	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Female	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Ethnic Group					
Hispanic or Latino	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Not Hispanic or Latino	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Race [1]					
American Indian/Alaskan Native	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Asian	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Black or African American	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Native Hawaiian/Other Pacific Islander	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
White	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Other					

LB = liposome bupivacaine.
[1] Subjects may be counted in more than one category.
Reference: Listings 16.2 and 16.8.

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Table 14.1.2.1-1 (Page x of Y)
Demographic and Baseline Characteristics
Study Part 1
(Safety Analysis Set)

	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)	All Subjects (N=XX)
ASA Class					
1	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
2	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
3	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Height (cm)					
n	00	00	00	00	00
Mean	00.0	00.0	00.0	00.0	00.0
SD	00.00	00.00	00.00	00.00	00.00
Median	00	00	00	00	00
Minimum, Maximum	00, 00	00, 00	00, 00	00, 00	00, 00
Weight (kg)					
n	00	00	00	00	00
Mean	00.0	00.0	00.0	00.0	00.0
SD	00.00	00.00	00.00	00.00	00.00
Median	00	00	00	00	00
Minimum, Maximum	00, 00	00, 00	00, 00	00, 00	00, 00

ASA = American Society of Anesthesiologists; LB = liposome bupivacaine.
[1] Subjects may be counted in more than one category.

Reference: Listings 16.2 and 16.8.

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Table 14.1.2.2-1 (Page x of Y)
Demographic and Baseline Characteristics
Study Part 1
(Efficacy Analysis Set)

	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)	All Subjects (N=XX)
Age (years)					
n	00	00	00	00	00
Mean	00.0	00.0	00.0	00.0	00.0
SD	00.00	00.00	00.00	00.00	00.00
Median	00	00	00	00	00
Minimum, Maximum	00, 00	00, 00	00, 00	00, 00	00, 00
Age Category					
<65	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
>=65	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Gender					
Male	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Female	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Ethnic Group					
Hispanic or Latino	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Not Hispanic or Latino	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Race [1]					
American Indian/Alaskan Native	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Asian	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Black or African American	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Native Hawaiian/Other Pacific Islander	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
White	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Other					

LB = liposome bupivacaine.
[1] Subjects may be counted in more than one category.
Reference: Listings 16.2 and 16.8.

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Table 14.1.2.2-1 (Page x of Y)
Demographic and Baseline Characteristics
Study Part 1
(Efficacy Analysis Set)

	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)	All Subjects (N=XX)
ASA Class					
1	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
2	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
3	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Height (cm)					
n	00	00	00	00	00
Mean	00.0	00.0	00.0	00.0	00.0
SD	00.00	00.00	00.00	00.00	00.00
Median	00	00	00	00	00
Minimum, Maximum	00, 00	00, 00	00, 00	00, 00	00, 00
Weight (kg)					
n	00	00	00	00	00
Mean	00.0	00.0	00.0	00.0	00.0
SD	00.00	00.00	00.00	00.00	00.00
Median	00	00	00	00	00
Minimum, Maximum	00, 00	00, 00	00, 00	00, 00	00, 00

ASA = American Society of Anesthesiologists; LB = liposome bupivacaine.
[1] Subjects may be counted in more than one category.
Reference: Listings 16.2 and 16.8.

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Table 14.1.3.1-1 (Page x of Y)
Prior Medications
Study Part 1
(Safety Analysis Set)

ATC Class WHO-DD Preferred Term	LB 67 mg (N=XX) n (%)	LB 133 mg (N=XX) n (%)	LB 266 mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
Any Prior Medication	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
ATC Class 1	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 1	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 2	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
….					
ATC Class 2	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 3	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 4	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)

ATC = Anatomical Therapeutic Chemical classification system; LB = liposome bupivacaine; WHO-DD = World Health Organization Drug Dictionary.
Note: Prior medications are defined as medication with a stop date/time prior to study drug administration.
At each level of summation (overall, ATC class, and preferred term), subjects are only counted once.

Reference: Listing 16.3.4.

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Table 14.1.3.2-1 (Page x of Y)
Concomitant Medications
Study Part 1
(Safety Analysis Set)

ATC Class WHO-DD Preferred Term	LB 67 mg (N=XX) n (%)	LB 133 mg (N=XX) n (%)	LB 266 mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
Any Prior Medication	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
ATC Class 1	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 1	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 2	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
….					
ATC Class 2	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 3	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 4	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)

ATC = Anatomical Therapeutic Chemical classification system; LB = liposome bupivacaine; WHO-DD = World Health Organization Drug Dictionary.
Note: Concomitant medications are defined as medications (other than rescue pain medication) taken on or after the start of study drug administration. This table does not include rescue pain medications.
At each level of summation (overall, ATC class, and preferred term), subjects are only counted once.

Reference: Listing 16.3.4.1.

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Table 14.2.1.1-1 (Page x of Y)
Study Drug Administration
Study Part 1
(Safety Analysis Set)

	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)
Duration of Injection (min)				
n	00	00	00	00
Mean	00.0	00.0	00.0	00.0
SD	00.00	00.00	00.00	00.00
Median	00	00	00	00
Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
Volume of Study Drug Administered (mL)				
n	00	00	00	00
Mean	00.0	00.0	00.0	00.0
SD	00.00	00.00	00.00	00.00
Median	00	00	00	00
Minimum, Maximum	00, 00	00, 00	00, 00	00, 00

LB = liposome bupivacaine.

Reference: Listing 16.4.1.

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Table 14.2.1.2-1 (Page x of Y)
Surgery
Study Part 1
(Efficacy Analysis Set)

	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)
Duration of Surgery (min)				
n	00	00	00	00
Mean	00.0	00.0	00.0	00.0
SD	00.00	00.00	00.00	00.00
Median	00	00	00	00
Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
Type of Anesthesia				
General	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Spinal	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Other	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Incision Length (cm)				
n	00	00	00	00
Mean	00.00	00.00	00.00	00.00
SD	00.000	00.000	00.000	00.000
Median	00.00	00.00	00.00	00.00
Minimum, Maximum	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0

LB = liposome bupivacaine.

Reference: Listing 16.4.2.

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Table 14.2.2.1-1 (Page x of Y)
AUC of NRS-R Pain Intensity Scores Through 72 Hours
wWOCF + LOCF Imputation for the Pain Scores
Study Part 1
(Efficacy Analysis Set)

Statistics	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)
n	00	00	00	00
Mean	000.0	000.0	000.0	000.0
SD	00.00	00.00	00.00	00.00
Median	0000	0000	0000	0000
Minimum, Maximum	000, 000	000, 000	000, 000	000, 000
LSM (Standard Error) [1]	00.0 (00.00)	00.0 (00.00)	00.0 (00.00)	00.0 (00.00)
LSM Difference (Standard Error) [2]	00.0 (00.00)	00.0 (00.00)	00.0 (00.00)	
95% CI for Difference [2]	00.0, 00.0	00.0, 00.0	00.0, 00.0	
P-value [2]	0.0000	0.0000	0.0000	

AUC = area under the curve calculated using the trapezoidal method; CI = confidence interval; LB = liposome bupivacaine; LSM = least squares mean; NRS-R = numeric rating scale at rest.
Scores are based on a numeric rating scale where 0 = no pain and 10 = worst possible pain.
wWOCF + LOCF = imputation using the worst observation prior to the use of rescue medication within a medication window and last-observation-carried-forward for missing values.
[1] From an analysis of covariance with treatment as the main effect and the baseline NRS-R pain intensity score as the covariate.
[2] Difference from placebo.

Reference: Listings 16.5.1.1 and 16.5.1.2.

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Table 14.2.2.2-1 (Page x of Y)
Total Postoperative Consumption (mg) of Opioid Rescue Pain Medication Through 72 Hours
Study Part 1
(Efficacy Analysis Set)

Statistics	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)
n	00	00	00	00
Mean	00.00	00.00	00.00	00.00
SD	00.000	00.000	00.000	00.000
Median	00.00	00.00	00.00	00.00
Minimum, Maximum	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0
Geometric LSM [1]	00.00	00.00	00.00	00.00
Geometric LSM Ratio [2]	00.00	00.00	00.00	
95% CI for Ratio [2]	00.00, 00.00	00.00, 00.00	00.00, 00.00	
P-value [2]	0.0000	0.0000	0.0000	

CI = confidence interval; LB = liposome bupivacaine; LSM = least squares mean,
If the total amount of opioid used was 0 mg, the value was set to the lesser of 1 mg or one half of the smallest total amount observed in the study prior to being transformed into the natural logarithm.
[1] From an analysis of variance with treatment as the main effect on natural log transformed opioid amount.
Results are presented in the original, non-transformed scale.
[2] Geometric LSM ratio is the anti-log LSM difference (LB/placebo).

Reference: Listing 16.5.2.1.

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Table 14.2.2.3-1 (Page x of Y)
Time to First Opioid Rescue
Study Part 1
(Efficacy Analysis Set)

	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)
Subjects Administered an Opioid Rescue [n (%)]	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Censored Observations [n (%)]	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Quartiles (hours) [1]				
First Quartile (25% Administered an Opioid)	000	000	000	000
Median (50% Administered an Opioid)	000	000	000	000
Third Quartile (75% Administered an Opioid)	000	000	000	000
Minimum, Maximum	00, 00*	00, 00*	00, 00*	00, 00*
95% CI of Median	(000, 000)	(000, 000)	(000, 000)	(000, 000)
P-value from Log-Rank Test	0.0000	0.0000	0.0000	0.0000

* indicates a censored observation.
CI = confidence interval; LB = liposome bupivacaine,
[1] Estimates from a Kaplan-Meier Analysis.

Reference: Listing 16.5.2.1.

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Table 14.2.2.4-1 (Page x of Y)
NRS-R Pain Intensity Scores
Study Part 1
(Efficacy Analysis Set)

Time Point	Statistics	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)
Baseline	n	00	00	00	00
	Mean	00.0	00.0	00.0	00.0
	SD	00.00	00.00	00.00	00.00
	Median	00.0	00.0	00.0	00.0
	Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	95% CI about the Mean	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0
First Request	n	00	00	00	00
	Mean	00.0	00.0	00.0	00.0
	SD	00.00	00.00	00.00	00.00
	Median	00.0	00.0	00.0	00.0
	Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	95% CI about the Mean	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0
2 Hours	n	00	00	00	00
	Mean	00.0	00.0	00.0	00.0
	SD	00.00	00.00	00.00	00.00
	Median	00.0	00.0	00.0	00.0
	Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	95% CI about the Mean	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0
Etc.					

CI = confidence interval; LB = liposome bupivacaine; NRS-R = numeric rating scale at rest.
Pain scores are based on a numeric rating scale where 0 = no pain and 10 = worst possible pain.

Reference: Listing 16.5.1.1.

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Table 14.2.2.5-1 (Page x of Y)
NRS-A Pain Intensity Scores
Study Part 1
(Efficacy Analysis Set)

Time Point	Statistics	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)
Baseline	N	00	00	00	00
	Mean	00.0	00.0	00.0	00.0
	SD	00.00	00.00	00.00	00.00
	Median	00.0	00.0	00.0	00.0
	Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	95% CI about the Mean	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0
First Request	N	00	00	00	00
	Mean	00.0	00.0	00.0	00.0
	SD	00.00	00.00	00.00	00.00
	Median	00.0	00.0	00.0	00.0
	Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	95% CI about the Mean	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0
2 Hours	N	00	00	00	00
	Mean	00.0	00.0	00.0	00.0
	SD	00.00	00.00	00.00	00.00
	Median	00.0	00.0	00.0	00.0
	Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	95% CI about the Mean	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0
Etc.					

CI = confidence interval; LB = liposome bupivacaine; NRS-A = numeric rating scale with activity.
Pain scores are based on a numeric rating scale where 0 = no pain and 10 = worst possible pain.

Reference: Listing 16.5.1.1.

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Table 14.2.2.6-1 (Page x of Y)
AUC of NRS-R Pain Intensity Scores Through 24, 36, 48, and 60 Hours
wWOCF + LOCF Imputation for the Pain Scores
Study Part 1
(Efficacy Analysis Set)

Time Point	Statistics	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)
24 Hours	n	00	00	00	00
	Mean	00.0	00.0	00.0	00.0
	SD	00.00	00.00	00.00	00.00
	Median	00.0	00.0	00.0	00.0
	Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	95% CI about the Mean	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0
36 Hours	n	00	00	00	00
	Mean	00.0	00.0	00.0	00.0
	SD	00.00	00.00	00.00	00.00
	Median	00.0	00.0	00.0	00.0
	Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	95% CI about the Mean	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0
48 Hours	n	00	00	00	00
	Mean	00.0	00.0	00.0	00.0
	SD	00.00	00.00	00.00	00.00
	Median	00.0	00.0	00.0	00.0
	Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	95% CI about the Mean	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0
Etc.					

AUC = area under the curve calculated using the trapezoidal method; CI = confidence interval; LB = liposome bupivacaine; NRS-R = numeric rating scale at rest.
Pain scores are based on a numeric rating scale where 0 = no pain and 10 = worst possible pain.
wWOCF + LOCF = imputation using the worst observation prior to the use of rescue medication within a medication window and last-observation-carried-forward for missing values.
Reference: Listings 16.5.1.1 and 16.5.1.2.

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Table 14.2.2.7-1 (Page x of Y)
AUC of NRS-A Pain Intensity Scores Through 24, 36, 48, 60, and 72 Hours
wWOCF + LOCF Imputation for the Pain Scores
Study Part 1
(Efficacy Analysis Set)

Time Point	Statistics	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)
24 Hours	n	00	00	00	00
	Mean	00.0	00.0	00.0	00.0
	SD	00.00	00.00	00.00	00.00
	Median	00.0	00.0	00.0	00.0
	Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	95% CI about the Mean	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0
36 Hours	n	00	00	00	00
	Mean	00.0	00.0	00.0	00.0
	SD	00.00	00.00	00.00	00.00
	Median	00.0	00.0	00.0	00.0
	Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	95% CI about the Mean	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0
48 Hours	n	00	00	00	00
	Mean	00.0	00.0	00.0	00.0
	SD	00.00	00.00	00.00	00.00
	Median	00.0	00.0	00.0	00.0
	Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	95% CI about the Mean	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0
Etc.					

AUC = area under the curve calculated using the trapezoidal method; CI = confidence interval; LB = liposome bupivacaine; NRS-A = numeric rating scale with activity.
Pain scores are based on a numeric rating scale where 0 = no pain and 10 = worst possible pain.
wWOCF + LOCF = imputation using the worst observation prior to the use of rescue medication within a medication window and last-observation-carried-forward for missing values.
Reference: Listings16.5.1.1 and 16.5.1.2 .

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Table 14.2.2.8-1 (Page x of Y)
AUC of NRS-R Pain Intensity Scores 24-48 and 48-72 Hours
wWOCF + LOCF Imputation for the Pain Scores
Study Part 1
(Efficacy Analysis Set)

Time Point	Statistics	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)
24-48 Hours	n	00	00	00	00
	Mean	00.0	00.0	00.0	00.0
	SD	00.00	00.00	00.00	00.00
	Median	00.0	00.0	00.0	00.0
	Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	95% CI about the Mean	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0
48-72 Hours	n	00	00	00	00
	Mean	00.0	00.0	00.0	00.0
	SD	00.00	00.00	00.00	00.00
	Median	00.0	00.0	00.0	00.0
	Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	95% CI about the Mean	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0

AUC = area under the curve calculated using the trapezoidal method; CI = confidence interval; LB = liposome bupivacaine; NRS-R = numeric rating scale at rest.
Pain scores are based on a numeric rating scale where 0 = no pain and 10 = worst possible pain.
wWOCF + LOCF = imputation using the worst observation prior to the use of rescue medication within a medication window and last-observation-carried-forward for missing values.

Reference: Listings16.5.1.1 and 16.5.1.2.

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Table 14.2.2.9-1 (Page x of Y)
Percentage of Subjects who are Pain Free at Each Time Point
Study Part 1
(Efficacy Analysis Set)

Time Point	LB 67 mg (N=XX) n/ N (%)	LB 133 mg (N=XX) n/ N (%)	LB 266 mg (N=XX) n/ N (%)	Placebo (N=XX) n/ N (%)
2 Hours	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
4 Hours	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
8 Hours	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
12 Hours	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
24 Hours	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
36 Hours	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
Etc				

LB = liposome bupivacaine. n/N = Number of subjects with a pain score of 0 or 1 / Number of subjects with a pain score at the time point.
Pain Free is defined as an NRS-R pain intensity score of 0 or 1.

Reference: Listing 16.5.1.1.

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Table 14.2.2.10-1 (Page x of Y)
Total Postoperative Consumption (mg) of Opioid Rescue Pain Medication Through 24, 36, 48, and 60 Hours
Study Part 1
(Efficacy Analysis Set)

Time Point	Statistics	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)
24 Hours	n	00	00	00	00
	Mean	00.00	00.00	00.00	00.00
	SD	00.000	00.000	00.000	00.000
	Median	00.00	00.00	00.00	00.00
	Minimum, Maximum	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0
36 Hours	n	00	00	00	00
	Mean	00.00	00.00	00.00	00.00
	SD	00.000	00.000	00.000	00.000
	Median	00.00	00.00	00.00	00.00
	Minimum, Maximum	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0
Etc.					

LB = liposome bupivacaine.

Reference: Listing 16.5.2.1.

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Table 14.2.2.11-1 (Page x of Y)
Subjects Who Received Rescue Medication Through 72 Hours
Study Part 1
(Efficacy Analysis Set)

	LB 67 mg (N=XX) n (%)	LB 133 mg (N=XX) n (%)	LB 266 mg (N=XX) n (%)	Placebo (N=XX) n (%)
Received No Rescue Medication	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Received Only the First Rescue	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Received the First Rescue and a Second Opioid Rescue	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Received all Three Rescues	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine.

Reference: Listings 16.5.2.1 and 16.5.2.2.

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Table 14.2.2.12-1 (Page x of Y)
Overall Benefit of Analgesia Score Questionnaire (Total Scores)
Study Part 1
(Efficacy Analysis Set)

Time Point	Statistics	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)
24 Hours	n	00	00	00	00
	Mean	00.0	00.0	00.0	00.0
	SD	00.00	00.00	00.00	00.00
	Median	00.0	00.0	00.0	00.0
	Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	95% CI about the Mean	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0
48 Hours	n	00	00	00	00
	Mean	00.0	00.0	00.0	00.0
	SD	00.00	00.00	00.00	00.00
	Median	00.0	00.0	00.0	00.0
	Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	95% CI about the Mean	00.0, 00.0	00.0, 00.0	00.0, 00.0	00.0, 00.0
Etc.					

CI = confidence interval; LB = liposome bupivacaine.
Note: The lower the score, the better the overall analgesic treatment.

Reference: Listing 16.5.3.

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Table 14.2.2.13-1 (Page x of Y)
Subject Satisfaction with Postsurgical Pain Control
Study Part 1
(Efficacy Analysis Set)

Time Point	Assessment	LB 67 mg (N=XX) n/N (%)	LB 133 mg (N=XX) n/N (%)	LB 266 mg (N=XX) n/N (%)	Placebo (N=XX) n/N (%)
72 Hours	Extremely Dissatisfied (1)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Dissatisfied (2)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Neither Satisfied or Dissatisfied (3)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Satisfied (4)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Extremely Satisfied (5)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
Day 30	Extremely Dissatisfied (1)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Dissatisfied (2)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Neither Satisfied or Dissatisfied (3)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Satisfied (4)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Extremely Satisfied (5)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)

LB = liposome bupivacaine. n/N = Number of subjects with a subject satisfaction score of 1, 2, 3, 4, or 5 / Number of subjects with a subject satisfaction score at the time point.
Note: Percentages are based on number of subjects with a score at the time point.

Reference: Listing 16.5.4.

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Table 14.2.2.14-1 (Page x of Y)
Time to Sensitivity to Cold
Study Part 1
(Efficacy Analysis Set)

	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)
Subjects with Sensitivity to Cold [n (%)]	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Censored Observations [n (%)]	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Quartiles (hours) [1]				
First Quartile (25% with Sensitivity to Cold)	000	000	000	000
Median (50% with Sensitivity to Cold)	000	000	000	000
Third Quartile (75% with Sensitivity to Cold)	000	000	000	000
Minimum, Maximum	00, 00*	00, 00*	00, 00*	00, 00*
95% CI of Median	(000, 000)	(000, 000)	(000, 000)	(000, 000)

* indicates a censored observation.
CI = confidence interval; LB = liposome bupivacaine,
[1] Estimates from a Kaplan-Meier Analysis.

Reference: Listing 16.5.5.

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Table 14.2.2.15-1 (Page x of Y)
Incidence of Predefined Treatment-Emergent Opioid-Related Adverse Events
Study Part 1
(Efficacy Analysis Set)

	LB 67 mg (N=XX) n (%)	LB 133 mg (N=XX) n (%)	LB 266 mg (N=XX) n (%)	Placebo (N=XX) n (%)
Subjects with at Least One Event	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Diffuse Pruritus	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Overt Respiratory Depression	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Urinary Retention [1]	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Constipation	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Sedation	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Confusion	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Delirium	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Vomiting	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Need for Antiemetic Medication	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine.
[1] Urinary retention was measured by need for postsurgical bladder catheterization.

Reference: Listing 16.5.6.

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Table 14.2.3.1-1 (Page x of Y)
Bupivacaine Plasma Concentrations (ng/mL)
Study Part 1
(PK Analysis Set)

Time Point	Statistics	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)
Baseline	n	00	00	00
	Mean	000.00	000.00	000.00
	SD	0.000	0.000	0.000
	%CV	000.00	000.00	000.00
	Median	0.00	0.00	0.00
	Minimum, Maximum	00.0, 00.0	00.0, 00.0	00.0, 00.0
15 Minutes	n	00	00	00
	Mean	000.00	000.00	000.00
	SD	0.000	0.000	0.000
	%CV	000.00	000.00	000.00
	Median	0.00	0.00	0.00
	Minimum, Maximum	00.0, 00.0	00.0, 00.0	00.0, 00.0
30 Minutes	n	00	00	00
	Mean	000.00	000.00	000.00
	SD	0.000	0.000	0.000
	%CV	000.00	000.00	000.00
	Median	0.00	0.00	0.00
	Minimum, Maximum	00.0, 00.0	00.0, 00.0	00.0, 00.0
Etc.				

LB = liposome bupivacaine.

Reference: Listing 16.6.1.

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Table 14.2.3.2-1 (Page x of Y)
Bupivacaine Plasma Pharmacokinetic Parameters
Study Part 1
(PK Analysis Set)

Parameter	Statistics	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)
Cmax (ng/mL)	n	00	00	00
	Mean	000.00 0	000.00 0	000.00 0
	SD	0.0000	0.0000	0.0000
	%CV	000.00	000.00	000.00
	Geometric Mean	00.0	00.0	00.0
	Median	0.000	0.000	0.000
	Minimum, Maximum	00.00, 00.00	00.00, 00.00	00.00, 00.00
Tmax (hours)	n	00	00	00
	Mean	000.00 0	000.00 0	000.00 0
	SD	0.0000	0.0000	0.0000
	%CV	000.00	000.00	000.00
	Geometric Mean	00.0	00.0	00.0
	Median	0.000	0.000	0.000
	Minimum, Maximum	00.00, 00.00	00.00, 00.00	00.00, 00.00
AUC0-last (h*ng/mL)	n	00	00	00
	Mean	000.00 0	000.00 0	000.00 0
	SD	0.0000	0.0000	0.0000
	%CV	000.00	000.00	000.00
	Geometric Mean	00.0	00.0	00.0
	Median	0.000	0.000	0.000
	Minimum, Maximum	00.00, 00.00	00.00, 00.00	00.00, 00.00
Etc.				

LB = liposome bupivacaine.
Reference: Listing 16.6.2.

Programmer Note: The other parameters should be AUC0-inf (h*ng/mL), and half-life (t1/2) (hours).

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Table 14.2.3.3-1 (Page x of Y)
Percentage of Unbound Bupivacaine Plasma Concentrations (ng/mL)
Study Part 1
(PK Analysis Set)

Time Point	Statistics	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)
15 Minutes	n	00	00	00
	Mean	000.00	000.00	000.00
	SD	0.000	0.000	0.000
	Median	0.00	0.00	0.00
	Minimum, Maximum	00.0, 00.0	00.0, 00.0	00.0, 00.0

LB = liposome bupivacaine.

Reference: Listing 16.6.1.

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Table 14.3.1.1-1 (Page x of Y)
Overview of Treatment-Emergent Adverse Events
Study Part 1
(Safety Analysis Set)

	LB 67 mg (N=XX) n (%)	LB 133 mg (N=XX) n (%)	LB 266 mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
Subjects with at Least One TEAE	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Maximum Severity: Mild	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Maximum Severity: Moderate	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Maximum Severity: Severe	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
At Least One TEAE Related to Study Drug	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
At Least One Serious TEAE	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Subjects Discontinued Because of a TEAE	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Deaths on Study	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine, TEAE = treatment-emergent adverse event.

Reference: Listings 16.7.1.1 and 16.7.1.2.

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Table 14.3.1.2-1 (Page x of Y)
Incidence of Treatment-Emergent Adverse Events
Study Part 1
(Safety Analysis Set)

System Organ Class Preferred Term	LB 67 mg (N=XX) n (%)	LB 133 mg (N=XX) n (%)	LB 266 mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
Subjects with at Least One TEAE	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
System Organ Class 1	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 1	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 2	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
….					
System Organ Class 2	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 3	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 4	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine, TEAE = treatment-emergent adverse event.
At each level of summation (overall, system organ class, preferred term), subjects are only counted once.

Reference: Listings 16.7.1.1 and 16.7.1.2..

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Table 14.3.1.3-1 (Page x of Y)
Incidence of Study Drug Related Treatment-Emergent Adverse Events
Study Part 1
(Safety Analysis Set)

System Organ Class Preferred Term	LB 67 mg (N=XX) n (%)	LB 133 mg (N=XX) n (%)	LB 266 mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
Subjects with at Least One TEAE	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
System Organ Class 1	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
….					
System Organ Class 2	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 3	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 4	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine, TEAE = treatment-emergent adverse event.
At each level of summation (overall, system organ class, preferred term), subjects are only counted once.

Reference: Listings 16.7.1.1 and 16.7.1.2..

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Table 14.3.1.4-1 (Page x of Y)
Incidence of Treatment-Emergent Adverse Events by Severity (Part 1 of 2)
Study Part 1
(Safety Analysis Set)

System Organ Class Preferred Term	LB 67 mg (N = XX) Mild n (%)	 Moderate n (%)	 Severe n (%)	LB 133 mg (N = XX) Mild n (%)	 Moderate n (%)	 Severe n (%)
Subjects with at Least One TEAE	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
System Organ Class 1	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Preferred Term 1	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Preferred Term 2	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
…						
System Organ Class 2	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Preferred Term 3	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Preferred Term 4	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
…						

LB = liposome bupivacaine, TEAE = treatment-emergent adverse event.
At each level of summation (overall, system organ class, preferred term), subjects are only counted once using the highest severity.

Reference: Listings 16.7.1.1 and 16.7.1.2..

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Table 14.3.1.4-1 (Page x of Y)
Incidence of Treatment-Emergent Adverse Events by Severity (Part 2 of 2)
Study Part 1
(Safety Analysis Set)

	LB 266 mg (N = XX)			Placebo (N = XX)			All Subjects (N = XX		
System Organ Class Preferred Term	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Subjects with at Least One TEAE	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
System Organ Class 1	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Preferred Term 1	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Preferred Term 2	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
…									
System Organ Class 2	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Preferred Term 3	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Preferred Term 4	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
…									

LB = liposome bupivacaine, TEAE = treatment-emergent adverse event.
At each level of summation (overall, system organ class, preferred term), subjects are only counted once using the highest severity.

Reference: Listings 16.7.1.1 and 16.7.1.2.

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Table 14.3.1.5-1 (Page x of Y)
Incidence of Serious Treatment-Emergent Adverse Events
Study Part 1
(Safety Analysis Set)

System Organ Class Preferred Term	LB 67 mg (N=XX) n (%)	LB 133 mg (N=XX) n (%)	LB 266 mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
Subjects with at Least One TEAE	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
System Organ Class 1	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
….					
System Organ Class 2	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 3	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 4	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine, TEAE = treatment-emergent adverse event.
At each level of summation (overall, system organ class, preferred term), subjects are only counted once.

Reference: Listings 16.7.1.3 and 16.7.1.4.

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Table 14.3.2.1-1 (Page x of Y)
Vital Signs
Study Part 1
(Safety Analysis Set)

Parameter	Time Point	Statistics	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)
Heart Rate	Screening	n	00	00	00	00
		Mean	00.0	00.0	00.0	00.0
		SD	00.00	00.00	00.00	00.00
		Median	00.0	00.0	00.0	00.0
		Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	Baseline	n	00	00	00	00
		Mean	00.0	00.0	00.0	00.0
		SD	00.00	00.00	00.00	00.00
		Median	00.0	00.0	00.0	00.0
		Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	30 Minutes	n	00	00	00	00
		Mean	00.0	00.0	00.0	00.0
		SD	00.00	00.00	00.00	00.00
		Median	00.0	00.0	00.0	00.0
		Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
Etc.	Etc.					

LB = liposome bupivacaine.

Reference: Listing 16.8.

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Table 14.3.2.2-1 (Page x of Y)
Vital Signs Change from Baseline
Study Part 1
(Safety Analysis Set)

Parameter	Time Point	Statistics	LB 67 mg (N=XX)	LB 133 mg (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)
Heart Rate	30 Minutes	n	00	00	00	00
		Mean	00.0	00.0	00.0	00.0
		SD	00.00	00.00	00.00	00.00
		Median	00.0	00.0	00.0	00.0
		Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	1 Hour	n	00	00	00	00
		Mean	00.0	00.0	00.0	00.0
		SD	00.00	00.00	00.00	00.00
		Median	00.0	00.0	00.0	00.0
		Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	2 Hours	n	00	00	00	00
		Mean	00.0	00.0	00.0	00.0
		SD	00.00	00.00	00.00	00.00
		Median	00.0	00.0	00.0	00.0
		Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
Etc.						

LB = liposome bupivacaine.

Reference: Listing 16.8.

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Table 14.3.3-1 (Page x of Y)
Neurological Assessment
Study Part 1
(Safety Analysis Set)

Time Point	Assessment	LB 67 mg (N=XX) n/ N (%)	LB 133 mg (N=XX) n/ N (%)	LB 266 mg (N=XX) n/ N (%)	Placebo (N=XX) n/ N (%)	All Subjects (N=XX) n/ N (%)
Baseline	Oriented [1]	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	At Least one of the Events	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Numbness [2]	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Metallic Taste in Mouth	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Problems with Hearing	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Problems with Vision	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Muscles Twitching	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
15 Minutes	Oriented [1]	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	At Least one of the Events	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Numbness [2]	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Metallic Taste in Mouth	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Problems with Hearing	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Problems with Vision	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Muscles Twitching	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
Etc.						

LB = liposome bupivacaine. n/N = Number of subjects with an event / Number of subjects with a neurological assessment at the time point.
[1] The denominator does not include subjects who were not assessable at the time point.
[2] Numbness of the lips, the tongue, or around the mouth.

Reference: Listing 16.9.

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Table 14.3.4-1 (Page x of Y)
20-Meter Walk Test
Study Part 1
(Safety Analysis Set)

Time Point	Completed Status	LB 67 mg (N=XX) n (%)	LB 133 mg (N=XX) n (%)	LB 266 mg (N=XX) n/ (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
24 Hours	Yes	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
	No	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
72 Hours	Yes	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
	No	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Day 30	Yes	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
	No	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine.

Reference: Listing 16.10.

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Table 14.3.5-1 (Page x of Y)
Physician Satisfaction with Return of Sensory/Motor Function
Study Part 1
(Safety Analysis Set)

Time Point	Assessment	LB 67 mg (N=XX) n (%)	LB 133 mg (N=XX) n (%)	LB 266 mg (N=XX) n (%)	Placebo (N=XX) n (%)
72 Hours	Extremely Dissatisfied (1)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
	Dissatisfied (2)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
	Neither Satisfied or Dissatisfied (3)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
	Satisfied (4)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
	Extremely Satisfied (5)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Day 30	Extremely Dissatisfied (1)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
	Dissatisfied (2)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
	Neither Satisfied or Dissatisfied (3)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
	Satisfied (4)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
	Extremely Satisfied (5)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine.
Note: Percentages are based on number of subjects with a score at the time point.

Reference: Listing 16.11.

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Table 14.3.6-1 (Page x of Y)
Incidence of Transfusions
Study Part 1
(Safety Analysis Set)

Transfusion	LB 67 mg (N=XX) n (%)	LB 133 mg (N=XX) n (%)	LB 266 mg (N=XX) n/ (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
Yes	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
No	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine.

Reference: Listing 16.3.5.

STUDY PART 2 TABLES

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Table 14.1.1.1-2 (Page x of Y)
Subject Disposition
Study Part 2
(All Randomized Subjects)

	LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
Safety Analysis Set [1]	00 (00.0)	00 (00.0)	00 (00.0)
Efficacy Analysis Set [2]	00 (00.0)	00 (00.0)	00 (00.0)
PK Analysis Set [3]		NA	
Subjects Who Completed the Study	00 (00.0)	00 (00.0)	00 (00.0)
Subjects Who Terminated Early	00 (00.0)	00 (00.0)	00 (00.0)
Reason for Early Termination			
Subject Death	00 (00.0)	00 (00.0)	00 (00.0)
Adverse Event	00 (00.0)	00 (00.0)	00 (00.0)
Lack of Efficacy	00 (00.0)	00 (00.0)	00 (00.0)
Lost to Follow-up	00 (00.0)	00 (00.0)	00 (00.0)
Withdrawal by Subject			
Other	00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine.
[1] The safety analysis set includes all subjects who received study drug.
[2] The efficacy analysis set includes all subjects in the safety analysis set who underwent the planned surgery.
[3] The PK analysis set includes all subjects in the safety analysis set who received liposome bupivacaine, provided sufficient samples to allow for calculation of PK parameters required for analysis, and who did not receive conventional bupivacaine HCl postsurgically.

Reference: Listing 16.1.3.

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Table 14.1.1.2-2 (Page x of Y)
Subject Disposition by Site
Study Part 2
(All Randomized Subjects)

Site		LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
101	Safety Analysis Set [1]	00 (00.0)	00 (00.0)	00 (00.0)
	Efficacy Analysis Set [2]	00 (00.0)	00 (00.0)	00 (00.0)
	PK Analysis Set [3]		NA	
	Subjects Who Completed the Study	00 (00.0)	00 (00.0)	00 (00.0)
	Subjects Who Terminated Early	00 (00.0)	00 (00.0)	00 (00.0)
	Reason for Early Termination			
	Subject Death	00 (00.0)	00 (00.0)	00 (00.0)
	Adverse Event	00 (00.0)	00 (00.0)	00 (00.0)
	Lack of Efficacy	00 (00.0)	00 (00.0)	00 (00.0)
	Lost to Follow-up	00 (00.0)	00 (00.0)	00 (00.0)
	Withdrawal by Subject			
	Other	00 (00.0)	00 (00.0)	00 (00.0)
Etc				

LB = liposome bupivacaine.
[1] The safety analysis set includes all subjects who received study drug.
[2] The efficacy analysis set includes all subjects in the safety analysis set who underwent the planned surgery.
[3] The PK analysis set includes all subjects in the safety analysis set who received liposome bupivacaine, provided sufficient samples to allow for calculation of PK parameters required for analysis, and who did not receive conventional bupivacaine HCl postsurgically.

Reference: Listing 16.1.3.

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Table 14.1.2.1-2 (Page x of Y)
Demographic and Baseline Characteristics
Study Part 2
(Safety Analysis Set)

	LB XXX mg (N=XX)	Placebo (N=XX)	All Subjects (N=XX)
Age (years)			
n	00	00	00
Mean	00.0	00.0	00.0
SD	00.00	00.00	00.00
Median	00	00	00
Minimum, Maximum	00, 00	00, 00	00, 00
Age Category			
<65	00 (00.0)	00 (00.0)	00 (00.0)
>=65	00 (00.0)	00 (00.0)	00 (00.0)
Gender			
Male	00 (00.0)	00 (00.0)	00 (00.0)
Female	00 (00.0)	00 (00.0)	00 (00.0)
Ethnic Group			
Hispanic or Latino	00 (00.0)	00 (00.0)	00 (00.0)
Not Hispanic or Latino	00 (00.0)	00 (00.0)	00 (00.0)
Race [1]			
American Indian/Alaskan Native	00 (00.0)	00 (00.0)	00 (00.0)
Asian	00 (00.0)	00 (00.0)	00 (00.0)
Black or African American	00 (00.0)	00 (00.0)	00 (00.0)
Native Hawaiian/Other Pacific Islander	00 (00.0)	00 (00.0)	00 (00.0)
White	00 (00.0)	00 (00.0)	00 (00.0)
Other			

LB = liposome bupivacaine.
[1] Subjects may be counted in more than one category.
Reference: Listings 16.2 and 16.8.

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Table 14.1.2.1-2 (Page x of Y)
Demographic and Baseline Characteristics
Study Part 2
(Safety Analysis Set)

	LB XXX mg (N=XX)	Placebo (N=XX)	All Subjects (N=XX)
ASA Class			
1	00 (00.0)	00 (00.0)	00 (00.0)
2	00 (00.0)	00 (00.0)	00 (00.0)
3	00 (00.0)	00 (00.0)	00 (00.0)
Height (cm)			
n	00	00	00
Mean	00.0	00.0	00.0
SD	00.00	00.00	00.00
Median	00	00	00
Minimum, Maximum	00, 00	00, 00	00, 00
Weight (kg)			
n	00	00	00
Mean	00.0	00.0	00.0
SD	00.00	00.00	00.00
Median	00	00	00
Minimum, Maximum	00, 00	00, 00	00, 00

ASA = American Society of Anesthesiologists; LB = liposome bupivacaine.
[1] Subjects may be counted in more than one category.
Reference: Listings 16.2 and 16.8.

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Table 14.1.2.2-2 (Page x of Y)
Demographic and Baseline Characteristics
Study Part 2
(Efficacy Analysis Set)

	LB XXX mg (N=XX)	Placebo (N=XX)	All Subjects (N=XX)
Age (years)			
n	00	00	00
Mean	00.0	00.0	00.0
SD	00.00	00.00	00.00
Median	00	00	00
Minimum, Maximum	00, 00	00, 00	00, 00
Age Category			
<65	00 (00.0)	00 (00.0)	00 (00.0)
>=65	00 (00.0)	00 (00.0)	00 (00.0)
Gender			
Male	00 (00.0)	00 (00.0)	00 (00.0)
Female	00 (00.0)	00 (00.0)	00 (00.0)
Ethnic Group			
Hispanic or Latino	00 (00.0)	00 (00.0)	00 (00.0)
Not Hispanic or Latino	00 (00.0)	00 (00.0)	00 (00.0)
Race [1]			
American Indian/Alaskan Native	00 (00.0)	00 (00.0)	00 (00.0)
Asian	00 (00.0)	00 (00.0)	00 (00.0)
Black or African American	00 (00.0)	00 (00.0)	00 (00.0)
Native Hawaiian/Other Pacific Islander	00 (00.0)	00 (00.0)	00 (00.0)
White	00 (00.0)	00 (00.0)	00 (00.0)
Other			

LB = liposome bupivacaine.
[1] Subjects may be counted in more than one category.
Reference: Listings 16.2 and 16.8.

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Table 14.1.2.2-2 (Page x of Y)
Demographic and Baseline Characteristics
Study Part 2
(Efficacy Analysis Set)

	LB XXX mg (N=XX)	Placebo (N=XX)	All Subjects (N=XX)
ASA Class			
1	00 (00.0)	00 (00.0)	00 (00.0)
2	00 (00.0)	00 (00.0)	00 (00.0)
3	00 (00.0)	00 (00.0)	00 (00.0)
Height (cm)			
n	00	00	00
Mean	00.0	00.0	00.0
SD	00.00	00.00	00.00
Median	00	00	00
Minimum, Maximum	00, 00	00, 00	00, 00
Weight (kg)			
n	00	00	00
Mean	00.0	00.0	00.0
SD	00.00	00.00	00.00
Median	00	00	00
Minimum, Maximum	00, 00	00, 00	00, 00

ASA = American Society of Anesthesiologists; LB = liposome bupivacaine.
[1] Subjects may be counted in more than one category.
Reference: Listings 16.2 and 16.8.

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Table 14.1.3.1-2 (Page x of Y)
Prior Medications
Study Part 2
(Safety Analysis Set)

ATC Class WHO-DD Preferred Term	LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
Any Prior Medication	00 (00.0)	00 (00.0)	00 (00.0)
ATC Class 1	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 1	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 2	00 (00.0)	00 (00.0)	00 (00.0)
….			
ATC Class 2	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 3	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 4	00 (00.0)	00 (00.0)	00 (00.0)

ATC = Anatomical Therapeutic Chemical classification system; LB = liposome bupivacaine; WHO-DD = World Health Organization Drug Dictionary
Note: Prior medications are defined as medication with a stop date/time prior to study drug administration.
At each level of summation (overall, ATC class, and preferred term), subjects are only counted once.

Reference: Listing 16.3.4.

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Table 14.1.3.2-2 (Page x of Y)
Concomitant Medications
Study Part 2
(Safety Analysis Set)

ATC Class[1] WHO-DD Preferred Term	LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
Any Prior Medication	00 (00.0)	00 (00.0)	00 (00.0)
ATC Class 1	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 1	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 2	00 (00.0)	00 (00.0)	00 (00.0)
….			
ATC Class 2	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 3	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 4	00 (00.0)	00 (00.0)	00 (00.0)

ATC = Anatomical Therapeutic Chemical classification system; LB = liposome bupivacaine; WHO-DD = World Health Organization Drug Dictionary.
Note: Concomitant medications are defined as medications (other than rescue pain medication) taken on or after the start of study drug administration. This table does not include rescue pain medications.
At each level of summation (overall, ATC class, and preferred term), subjects are only counted once.

Reference: Listing 16.3.4.1.

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Table 14.2.1.1-2 (Page x of Y)
Study Drug Administration
Study Part 2
(Safety Analysis Set)

	LB XXX mg (N=XX)	Placebo (N=XX)
Duration of Injection (min)		
n	00	00
Mean	00.0	00.0
SD	00.00	00.00
Median	00	00
Minimum, Maximum	00, 00	00, 00
Volume of Study Drug Administered (mL)		
n	00	00
Mean	00.0	00.0
SD	00.00	00.00
Median	00	00
Minimum, Maximum	00, 00	00, 00

LB = liposome bupivacaine.

Reference: Listing 16.4.1.

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Table 14.2.1.2-2 (Page x of Y)
Surgery
Study Part 2
(Efficacy Analysis Set)

	LB XXX mg (N=XX)	Placebo (N=XX)
Duration of Surgery (min)		
n	00	00
Mean	00.0	00.0
SD	00.00	00.00
Median	00	00
Minimum, Maximum	00, 00	00, 00
Type of Anesthesia		
General	00 (00.0)	00 (00.0)
Spinal	00 (00.0)	00 (00.0)
Other	00 (00.0)	00 (00.0)
Incision Length (cm)		
n	00	00
Mean	00.00	00.00
SD	00.000	00.000
Median	00.00	00.00
Minimum, Maximum	00.0, 00.0	00.0, 00.0

LB = liposome bupivacaine.

Reference: Listing 16.4.2.

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Table 14.2.2.1.1-2 (Page x of Y)
AUC of NRS-R Pain Intensity Scores Through 72 Hours
wWOCF + LOCF Imputation for the Pain Scores
Study Part 2
(Efficacy Analysis Set)

Statistics	LB XXX mg (N=XX)	Placebo (N=XX)
n	00	00
Mean	000.0	000.0
SD	00.00	00.00
Median	0000	0000
Minimum, Maximum	000, 000	000, 000
LSM (Standard Error) [1]	00.0 (00.00)	00.0 (00.00)
LSM Difference (Standard Error) [2]	00.0 (00.00)	
95% CI for Difference [2]	00.0, 00.0	
P-value [2]	0.0000	

AUC = area under the curve calculated using the trapezoidal method; CI = confidence interval; LB = liposome bupivacaine; LSM = least squares mean; NRS-R = numeric rating scale at rest.
Scores are based on a numeric rating scale where 0 = no pain and 10 = worst possible pain.
wWOCF + LOCF = imputation using the worst observation prior to the use of rescue medication within a medication window and last-observation-carried-forward for missing values.
[1] From an analysis of covariance with treatment as the main effect and the baseline NRS-R pain intensity score as the covariate.
[2] Difference from placebo.

Reference: Listings 16.5.1.1 and 16.5.1.2.

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Table 14.2.2.1.2-2 (Page x of Y)
AUC of NRS-R Pain Intensity Scores Through 72 Hours by Site
wWOCF + LOCF Imputation for the Pain Scores
Study Part 2
(Efficacy Analysis Set)

Site	Statistics	LB XXX mg (N=XX)	Placebo (N=XX)
101	n	00	00
	Mean	000.0	000.0
	SD	00.00	00.00
	Median	0000	0000
	Minimum, Maximum	000, 000	000, 000
Etc.			

AUC = area under the curve calculated using the trapezoidal method; CI = confidence interval; LB = liposome bupivacaine, LSM = least squares mean; NRS-R = numeric rating scale at rest.
Scores are based on a numeric rating scale where 0 = no pain and 10 = worst possible pain.
wWOCF + LOCF = imputation using the worst observation prior to the use of rescue medication within a medication window and last-observation-carried-forward for missing values.

Reference: Listings 16.5.1.1 and 16.5.1.2.

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Table 14.2.2.1.3-2 (Page x of Y)
AUC of NRS-R Pain Intensity Scores Through 72 Hours
wWOCF + LOCF Imputation for the Pain Scores Excluding Subjects with PCA Interval Data
Study Part 2
(Efficacy Analysis Set)

Statistics	LB XXX mg (N=XX)	Placebo (N=XX)
n	00	00
Mean	000.0	000.0
SD	00.00	00.00
Median	0000	0000
Minimum, Maximum	000, 000	000, 000
LSM (Standard Error) [1]	00.0 (00.00)	00.0 (00.00)
LSM Difference (Standard Error) [2]	00.0 (00.00)	
95% CI for Difference [2]	00.0, 00.0	
P-value [2]	0.0000	

AUC = area under the curve calculated using the trapezoidal method; CI = confidence interval; LB = liposome bupivacaine; LSM = least squares mean; NRS-R = numeric rating scale at rest.
Scores are based on a numeric rating scale where 0 = no pain and 10 = worst possible pain.
wWOCF + LOCF = imputation using the worst observation prior to the use of rescue medication within a medication window and last-observation-carried-forward for missing values.
[1] From an analysis of covariance with treatment as the main effect and the baseline NRS-R pain intensity score as the covariate.
[2] Difference from placebo.

Reference: Listings 16.5.1.1 and 16.5.1.2.

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Table 14.2.2.2-2 (Page x of Y)
Total Postoperative Consumption (mg) of Opioid Rescue Pain Medication Through 72 Hours
Study Part 2
(Efficacy Analysis Set)

Statistics	LB 67 mg (N=XX)	Placebo (N=XX)
n	00	00
Mean	00.00	00.00
SD	00.000	00.000
Median	00.00	00.00
Minimum, Maximum	00.0, 00.0	00.0, 00.0
Geometric LSM [1]	00.00	00.00
Geometric LSM Ratio [2]	00.00	
95% CI for Ratio [2]	00.00, 00.00	
P-value [2]	0.0000	

CI = confidence interval; LB = liposome bupivacaine; LSM = least squares mean.
If the total amount of opioid used was 0 mg, the value was set to the lesser of 1 mg or one half of the smallest total amount observed in the study prior to being transformed into the natural logarithm.
[1] From an analysis of variance with treatment as the main effect on natural log transformed opioid amount.
Results are presented in the original, non-transformed scale.
[2] Geometric LSM Ratio is the anti-log LSM difference (LB/placebo).

Reference: Listing 16.5.2.1.

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Table 14.2.2.3.2 (Page x of Y)
Time to First Opioid Rescue
Study Part 2
(Efficacy Analysis Set)

	LB XXX mg (N=XX)	Placebo (N=XX)
Subjects Administered an Opioid Rescue [n (%)]	00 (00.00)	00 (00.00)
Censored Observations [n (%)]	00 (00.00)	00 (00.00)
Quartiles (hours) [1]		
First Quartile (25% Administered an Opioid)	000	000
Median (50% Administered an Opioid)	000	000
Third Quartile (75% Administered an Opioid)	000	000
Minimum, Maximum	00, 00*	00, 00*
95% CI of Median	(000, 000)	(000, 000)
P-value from Log-Rank Test	0.0000	0.0000

* indicates a censored observation.
CI = confidence interval; LB = liposome bupivacaine.
[1] Estimates from a Kaplan-Meier Analysis.

Reference: Listing 16.5.2.1.

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Table 14.2.2.4-2 (Page x of Y)
NRS-R Pain Intensity Scores
Study Part 2
(Efficacy Analysis Set)

Time Point	Statistics	LB XXX mg (N=XX)	Placebo (N=XX)
Baseline	n	00	00
	Mean	000.0	000.0
	SD	00.00	00.00
	Median	0000	0000
	Minimum, Maximum	000, 000	000, 000
First Request	n	00	00
	Mean	000.0	000.0
	SD	00.00	00.00
	Median	0000	0000
	Minimum, Maximum	000, 000	000, 000
	LSM (Standard Error) [1]	00.0 (00.00)	00.0 (00.00)
	LSM Difference (Standard Error) [2]	00.0 (00.00)	
	95% CI for Difference [2]	00.0, 00.0	
	P-value [2]	0.0000	
2 Hours	n	00	00
	Mean	000.0	000.0
	SD	00.00	00.00
	Median	0000	0000
	Minimum, Maximum	000, 000	000, 000
Etc.			

CI = confidence interval; LB = liposome bupivacaine; LSM = least squares mean; NRS-R = numeric rating scale at rest.
Scores are based on a numeric rating scale where 0 = no pain and 10 = worst possible pain.
[1] From an analysis of covariance with treatment as the main effect and the baseline NRS-R pain intensity score as the covariate.
[2] Difference from placebo.
Reference: Listing 16.5.1.1.

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Table 14.2.2.5-2 (Page x of Y)
NRS-A Pain Intensity Scores
Study Part 2
(Efficacy Analysis Set)

Time Point	Statistics	LB XXX mg (N=XX)	Placebo (N=XX)
Baseline	n	00	00
	Mean	000.0	000.0
	SD	00.00	00.00
	Median	0000	0000
	Minimum, Maximum	000, 000	000, 000
First Request	n	00	00
	Mean	000.0	000.0
	SD	00.00	00.00
	Median	0000	0000
	Minimum, Maximum	000, 000	000, 000
	LSM (Standard Error) [1]	00.0 (00.00)	00.0 (00.00)
	LSM Difference (Standard Error) [2]	00.0 (00.00)	
	95% CI for Difference [2]	00.0, 00.0	
	P-value [2]	0.0000	
2 Hours	n	00	00
	Mean	000.0	000.0
	SD	00.00	00.00
	Median	0000	0000
	Minimum, Maximum	000, 000	000, 000
Etc.			

CI = confidence interval; LB = liposome bupivacaine; LSM = least squares mean; NRS-A = numeric rating scale with activity.
Scores are based on a numeric rating scale where 0 = no pain and 10 = worst possible pain.
[1] From an analysis of covariance with treatment as the main effect and the baseline NRS-A pain intensity score as the covariate.
[2] Difference from placebo.
Reference: Listing 16.5.1.1.

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Table 14.2.2.6-2 (Page x of Y)
AUC of NRS-R Pain Intensity Scores Through 24, 36, 48, and 60 Hours
wWOCF + LOCF Imputation for the Pain Scores
Study Part 2
(Efficacy Analysis Set)

Time Point	Statistics	LB XXX mg (N=XX)	Placebo (N=XX)
24 Hours	n	00	00
	Mean	000.0	000.0
	SD	00.00	00.00
	Median	0000	0000
	Minimum, Maximum	000, 000	000, 000
	LSM (Standard Error) [1]	00.0 (00.00)	00.0 (00.00)
	LSM Difference (Standard Error) [2]	00.0 (00.00)	
	95% CI for Difference [2]	00.0, 00.0	
	P-value [2]	0.0000	
36 Hours	n	00	00
	Mean	000.0	000.0
	SD	00.00	00.00
	Median	0000	0000
	Minimum, Maximum	000, 000	000, 000
Etc.			

AUC = area under the curve calculated using the trapezoidal method; CI = confidence interval; LB = liposome bupivacaine; LSM = least squares mean; NRS-R = numeric rating scale at rest.
Scores are based on a numeric rating scale where 0 = no pain and 10 = worst possible pain.
wWOCF + LOCF = imputation using the worst observation prior to the use of rescue medication within a medication window and last-observation-carried-forward for missing values.
[1] From an analysis of covariance with treatment as the main effect and the baseline NRS-R pain intensity score as the covariate.
[2] Difference from placebo.
Reference: Listings16.5.1.1 and 16.5.1.2.

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Table 14.2.2.7-2 (Page x of Y)
AUC of NRS-A Pain Intensity Scores Through 24, 36, 48, 60, and 72 Hours
wWOCF + LOCF Imputation for the Pain Scores
Study Part 2
(Efficacy Analysis Set)

Time Point	Statistics	LB XXX mg (N=XX)	Placebo (N=XX)
24 Hours	n	00	00
	Mean	000.0	000.0
	SD	00.00	00.00
	Median	0000	0000
	Minimum, Maximum	000, 000	000, 000
	LSM (Standard Error) [1]	00.0 (00.00)	00.0 (00.00)
	LSM Difference (Standard Error) [2]	00.0 (00.00)	
	95% CI for Difference [2]	00.0, 00.0	
	P-value [2]	0.0000	
48 Hours	n	00	00
	Mean	000.0	000.0
	SD	00.00	00.00
	Median	0000	0000
	Minimum, Maximum	000, 000	000, 000
Etc.			

AUC = area under the curve calculated using the trapezoidal method; CI = confidence interval; LB = liposome bupivacaine; LSM = least squares mean; NRS-A = numeric rating scale with activity.
Scores are based on a numeric rating scale where 0 = no pain and 10 = worst possible pain.
wWOCF + LOCF = imputation using the worst observation prior to the use of rescue medication within a medication window and last-observation-carried-forward for missing values.
[1] From an analysis of covariance with treatment as the main effect and the baseline NRS-A pain intensity score as the covariate.
[2] Difference from placebo.
Reference: Listings 16.5.1.1 and 16.5.1.2.

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Table 14.2.2.8-2 (Page x of Y)
AUC of NRS-R Pain Intensity Scores 24-48 and 48-72 Hours
wWOCF + LOCF Imputation for the Pain Scores
Study Part 2
(Efficacy Analysis Set)

Time Point	Statistics	LB XXX mg (N=XX)	Placebo (N=XX)
24-48 Hours	n	00	00
	Mean	000.0	000.0
	SD	00.00	00.00
	Median	0000	0000
	Minimum, Maximum	000, 000	000, 000
	LSM (Standard Error) [1]	00.0 (00.00)	00.0 (00.00)
	LSM Difference (Standard Error) [2]	00.0 (00.00)	
	95% CI for Difference [2]	00.0, 00.0	
	P-value [2]	0.0000	
48-72 Hours	n	00	00
	Mean	000.0	000.0
	SD	00.00	00.00
	Median	0000	0000
	Minimum, Maximum	000, 000	000, 000
	LSM (Standard Error) [1]	00.0 (00.00)	00.0 (00.00)
	LSM Difference (Standard Error) [2]	00.0 (00.00)	
	95% CI for Difference [2]	00.0, 00.0	
	P-value [2]	0.0000	

AUC = area under the curve calculated using the trapezoidal method; CI = confidence interval; LB = liposome bupivacaine, LSM = least squares mean; NRS-R = numeric rating scale at rest.
Scores are based on a numeric rating scale where 0 = no pain and 10 = worst possible pain.
wWOCF + LOCF = imputation using the worst observation prior to the use of rescue medication within a medication window and last-observation-carried-forward for missing values.
[1] From an analysis of covariance with treatment as the main effect and the baseline NRS-R pain intensity score as the covariate.
[2] Difference from placebo.
Reference: Listings 16.5.1.1 and 16.5.1.2.

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Table 14.2.2.9-2 (Page x of Y)
Percentage of Subjects who are Pain Free at Each Time Point
Study Part 2
(Efficacy Analysis Set)

Time Point	LB XXX mg (N=XX) n/ N (%)	Placebo (N=XX) n/ N (%)	P-value [1]
2 Hours	00/00 (00.0)	00/00 (00.0)	0.0000
4 Hours	00/00 (00.0)	00/00 (00.0)	0.0000
8 Hours	00/00 (00.0)	00/00 (00.0)	0.0000
12 Hours	00/00 (00.0)	00/00 (00.0)	0.0000
24 Hours	00/00 (00.0)	00/00 (00.0)	0.0000
36 Hours	00/00 (00.0)	00/00 (00.0)	0.0000
Etc			

.

LB = liposome bupivacaine. n/N = Number of subjects with a pain score of 0 or 1 / Number of subjects with a pain score at the time point.
Pain Free is defined as an NRS-R pain intensity score of 0 or 1
[1] P-value is from a chi-square test.

Reference: Listing 16.5.1.1.

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Table 14.2.2.10-2 (Page x of Y)
Total Postoperative Consumption (mg) of Opioid Rescue Pain Medication Through 24, 36, 48, and 60 Hours
Study Part 2
(Efficacy Analysis Set)

Time Point	Statistics	LB 67 mg (N=XX)	Placebo (N=XX)
24 Hours	n	00	00
	Mean	00.00	00.00
	SD	00.000	00.000
	Median	00.00	00.00
	Minimum, Maximum	00.0, 00.0	00.0, 00.0
	Geometric LSM [1]	00.00	00.00
	Geometric LSM Ratio [2]	00.00	
	95% CI for Ratio [2]	00.00, 00.00	
	P-value [2]	0.0000	
Etc.			

CI = confidence interval; LB = liposome bupivacaine, LSM = least squares mean.
If the total amount of opioid used was 0 mg, the value was set to the lesser of 1 mg or one half of the smallest total amount observed in the study prior to being transformed into the natural logarithm.
[1] From an analysis of variance with treatment as the main effect on natural log transformed opioid amount.
Results are presented in the original, non-transformed scale.
[2] Geometric LSM ratio is the anti-log LSM difference (LB/placebo).

Reference: Listing 16.5.2.1.

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Table 14.2.2.11-2 (Page x of Y)
Subjects Who Received Rescue Medication Through 72 Hours
Study Part 2
(Efficacy Analysis Set)

	LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	P-value [1]
Received No Rescue Medication	00 (00.0)	00 (00.0)	
Received Only the First Rescue	00 (00.0)	00 (00.0)	
Received the First Rescue and a Second Opioid Rescue	00 (00.0)	00 (00.0)	
Received all Three Rescues	00 (00.0)	00 (00.0)	

LB = liposome bupivacaine.
[1] P-value is from a chi-square test

Reference: Listings 16.5.2.1 and 16.5.2.2.

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Table 14.2.2.12-2 (Page x of Y)
Overall Benefit of Analgesia Score Questionnaire (Total Scores)
Study Part 2
(Efficacy Analysis Set)

Time Point	Statistics	LB XXX mg (N=XX)	Placebo (N=XX)	P-value [1]
24 Hours	n	00	00	0.0000
	Mean	000.0	000.0	
	SD	00.00	00.00	
	Median	0000	0000	
	Minimum, Maximum	000, 000	000, 000	
48 Hours	n	00	00	0.0000
	Mean	000.0	000.0	
	SD	00.00	00.00	
	Median	0000	0000	
	Minimum, Maximum	000, 000	000, 000	
72 Hours	n	00	00	0.0000
	Mean	000.0	000.0	
	SD	00.00	00.00	
	Median	0000	0000	
	Minimum, Maximum	000, 000	000, 000	

CI = confidence interval; LB = liposome bupivacaine.
Note: The lower the score, the better the overall analgesic treatment.
[1] P-value is from a Wilcoxon Rank Sum test.

Reference: Listing 16.5.3.

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Table 14.2.2.13-2 (Page x of Y)
Subject Satisfaction with Postsurgical Pain Control
Study Part 2
(Efficacy Analysis Set)

Time Point	Assessment	LB XXX mg (N=XX) n/N (%)	Placebo (N=XX) n/N (%)	P-value [1]
72 Hours	Extremely Dissatisfied (1)	00/00 (00.0)	00/00 (00.0)	
	Dissatisfied (2)	00/00 (00.0)	00/00 (00.0)	
	Neither Satisfied or Dissatisfied (3)	00/00 (00.0)	00/00 (00.0)	
	Satisfied (4)	00/00 (00.0)	00/00 (00.0)	
	Extremely Satisfied (5)	00/00 (00.0)	00/00 (00.0)	
Day 30	Extremely Dissatisfied (1)	00/00 (00.0)	00/00 (00.0)	
	Dissatisfied (2)	00/00 (00.0)	00/00 (00.0)	
	Neither Satisfied or Dissatisfied (3)	00/00 (00.0)	00/00 (00.0)	
	Satisfied (4)	00/00 (00.0)	00/00 (00.0)	
	Extremely Satisfied (5)	00/00 (00.0)	00/00 (00.0)	

LB = liposome bupivacaine. n/N = Number of subjects with a subject satisfaction score of 1, 2, 3, 4, or 5 / Number of subjects with a subject satisfaction score at the time point.
Note: Percentages are based on number of subjects with a score at the time point.
[1] P-value is from a Wilcoxon Rank Sum test.

Reference: Listing 16.5.4.

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Table 14.2.2.14-2 (Page x of Y)
Time to Sensitivity to Cold
Study Part 2
(Efficacy Analysis Set)

	LB XXX mg (N=XX)	Placebo (N=XX)
Subjects with Sensitivity to Cold [n (%)]	00 (00.00)	00 (00.00)
Censored Observations [n (%)]	00 (00.00)	00 (00.00)
Quartiles (hours) [1]		
First Quartile (25% with Sensitivity to Cold)	000	000
Median (50% with Sensitivity to Cold)	000	000
Third Quartile (75% with Sensitivity to Cold)	000	000
Minimum, Maximum	00, 00*	00, 00*
95% CI of Median	(000, 000)	(000, 000)
P-value from Log-Rank Test	0.0000	0.0000

* indicates a censored observation.
CI = confidence interval; LB = liposome bupivacaine,
[1] Estimates from a Kaplan-Meier Analysis.

Reference: Listing 16.5.5.

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Table 14.3.1.1-2 (Page x of Y)
Overview of Treatment-Emergent Adverse Events
Study Part 2
(Safety Analysis Set)

	Part 2			Part 1 and Part 2 Combined		
	LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)	LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
Subjects with at Least One TEAE	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Maximum Severity: Mild	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Maximum Severity: Moderate	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Maximum Severity: Severe	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
At Least One TEAE Related to Study Drug	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
At Least One Serious TEAE	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Subjects Discontinued Because of a TEAE	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Deaths on Study	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine, TEAE = treatment-emergent adverse event.

Reference: Listings 16.7.1.1 and 16.7.1.2.

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Table 14.3.1.2-2 (Page x of Y)
Incidence of Treatment-Emergent Adverse Events
Study Part 2
(Safety Analysis Set)

	Part 2			Part 1 and Part 2 Combined		
System Organ Class Preferred Term	LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)	LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
Subjects with at Least One TEAE	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
System Organ Class 1	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 1	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 2	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
….						
System Organ Class 2	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 3	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 4	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine, TEAE = treatment-emergent adverse event.
At each level of summation (overall, system organ class, preferred term), subjects are only counted once.

Reference: Listings 16.7.1.1 and 16.7.1.2.

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Table 14.3.1.3-2 (Page x of Y)
Incidence of Study Drug Related Treatment-Emergent Adverse Events
Study Part 2
(Safety Analysis Set)

	Part 2			Part 1 and Part 2 Combined		
System Organ Class Preferred Term	LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)	LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
Subjects with at Least One TEAE	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
System Organ Class 1	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 1	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 2	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
….						
System Organ Class 2	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 3	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 4	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine, TEAE = treatment-emergent adverse event.
At each level of summation (overall, system organ class, preferred term), subjects are only counted once.

Reference: Listings 16.7.1.1 and 16.7.1.2..

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Table 14.3.1.4-2 (Page x of Y)
Incidence of Treatment-Emergent Adverse Events by Severity (Part 1 of 2)
Study Part 2
(Safety Analysis Set)

	Part 2								
	LB XXX mg (N = XX)			Placebo (N = XX)			All Subjects (N = XX		
System Organ Class Preferred Term	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Subjects with at Least One TEAE	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
System Organ Class 1	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Preferred Term 1	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Preferred Term 2	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
…									
System Organ Class 2	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Preferred Term 3	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Preferred Term 4	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
…									

LB = liposome bupivacaine, TEAE = treatment-emergent adverse event.
At each level of summation (overall, system organ class, preferred term), subjects are only counted once using the highest severity.

Reference: Listings 16.7.1.1 and 16.7.1.2..

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Table 14.3.1.4-2 (Page x of Y)
Incidence of Treatment-Emergent Adverse Events by Severity (Part 2 of 2)
Study Part 2
(Safety Analysis Set)

	Part 1 and Part 2 Combined								
	LB XXX mg (N = XX)			Placebo (N = XX)			All Subjects (N = XX		
System Organ Class Preferred Term	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Subjects with at Least One TEAE	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
System Organ Class 1	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Preferred Term 1	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Preferred Term 2	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
…									
System Organ Class 2	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Preferred Term 3	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
Preferred Term 4	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)	00 (00.00)
…									

LB = liposome bupivacaine, TEAE = treatment-emergent adverse event.
At each level of summation (overall, system organ class, preferred term), subjects are only counted once using the highest severity.

Reference: Listings 16.7.1.1 and 16.7.1.2.

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Table 14.3.1.5-2 (Page x of Y)
Incidence of Serious Treatment-Emergent Adverse Events
Study Part 2
(Safety Analysis Set)

	Part 2			Part 1 and Part 2 Combined		
System Organ Class Preferred Term	LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)	LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
Subjects with at Least One TEAE	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
System Organ Class 1	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 1	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 2	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
….						
System Organ Class 2	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 3	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Preferred Term 4	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine, TEAE = treatment-emergent adverse event.
At each level of summation (overall, system organ class, preferred term), subjects are only counted once.

Reference: Listings16.7.1.3 and 16.7.1.4. .

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Table 14.3.2.1-2 (Page x of Y)
Vital Signs
Study Part 2
(Safety Analysis Set)

			Part 2		Part 1 and Part 2 Combined	
Parameter	Time Point	Statistics	LB 266 mg (N=XX)	Placebo (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)
Heart Rate	Screening	n	00	00	00	00
		Mean	00.0	00.0	00.0	00.0
		SD	00.00	00.00	00.00	00.00
		Median	00.0	00.0	00.0	00.0
		Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	Baseline	n	00	00	00	00
		Mean	00.0	00.0	00.0	00.0
		SD	00.00	00.00	00.00	00.00
		Median	00.0	00.0	00.0	00.0
		Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	30 Minutes	n	00	00	00	00
		Mean	00.0	00.0	00.0	00.0
		SD	00.00	00.00	00.00	00.00
		Median	00.0	00.0	00.0	00.0
		Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
Etc.	Etc.					

LB = liposome bupivacaine.

Reference: Listing 16.8.

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Table 14.3.2.2-2 (Page x of Y)
Vital Signs Change from Baseline
Study Part 2
(Safety Analysis Set)

			Part 2		Part 1 and Part 2 Combined	
Parameter	Time Point	Statistics	LB 266 mg (N=XX)	Placebo (N=XX)	LB 266 mg (N=XX)	Placebo (N=XX)
Heart Rate	30 Minutes	n	00	00	00	00
		Mean	00.0	00.0	00.0	00.0
		SD	00.00	00.00	00.00	00.00
		Median	00.0	00.0	00.0	00.0
		Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	1 Hour	n	00	00	00	00
		Mean	00.0	00.0	00.0	00.0
		SD	00.00	00.00	00.00	00.00
		Median	00.0	00.0	00.0	00.0
		Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
	2 Hours	n	00	00	00	00
		Mean	00.0	00.0	00.0	00.0
		SD	00.00	00.00	00.00	00.00
		Median	00.0	00.0	00.0	00.0
		Minimum, Maximum	00, 00	00, 00	00, 00	00, 00
Etc.						

LB = liposome bupivacaine.

Reference: Listing 16.8.

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Table 14.3.3-2 (Page x of Y)
Neurological Assessment
Study Part 2
(Safety Analysis Set)

		Part 2			Part 1 and Part 2 Combined		
Time Point	Assessment	LB XXX mg (N=XX) n/ N (%)	Placebo (N=XX) n/ N (%)	All Subjects (N=XX) n/ N (%)	LB XXX mg (N=XX) n/ N (%)	Placebo (N=XX) n/ N (%)	All Subjects (N=XX) n/ N (%)
Baseline	Oriented [1]	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	At Least one of the Events	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Numbness [2]	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Metallic Taste in Mouth	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Problems with Hearing	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Problems with Vision	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Muscles Twitching	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
15 Minutes	Oriented [1]	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	At Least one of the Events	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Numbness [2]	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Metallic Taste in Mouth	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Problems with Hearing	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Problems with Vision	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
	Muscles Twitching	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)	00/00 (00.0)
Etc.							

LB = liposome bupivacaine. n/N = Number of subjects with an event / Number of subjects with a neurological assessment at the time point.
[1] The denominator does not include subjects who were not assessable at the time point.
[2] Numbness of the lips, the tongue, or around the mouth.

Reference: Listing 16.9.

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Table 14.3.4-2 (Page x of Y)
20-Meter Walk Test
Study Part 2
(Safety Analysis Set)

		Part 2			Part 1 and Part 2 Combined		
Time Point	Completed Status	LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)	LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
24 Hours	Yes	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
	No	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
72 Hours	Yes	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
	No	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
Day 30	Yes	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
	No	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine.

Reference: Listing 16.10.

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Table 14.3.5-2 (Page x of Y)
Physician Satisfaction with Return of Sensory/Motor Function
Study Part 2
(Safety Analysis Set)

		Part 2			Part 1 and Part 2 Combined		
Time Point	Assessment	LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	P-value [1]	LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
72 Hours	Extremely Dissatisfied (1)	00 (00.0)	00 (00.0)	0.0000	00 (00.0)	00 (00.0)	00 (00.0)
	Dissatisfied (2)	00 (00.0)	00 (00.0)		00 (00.0)	00 (00.0)	00 (00.0)
	Neither Satisfied or Dissatisfied (3)	00 (00.0)	00 (00.0)		00 (00.0)	00 (00.0)	00 (00.0)
	Satisfied (4)	00 (00.0)	00 (00.0)		00 (00.0)	00 (00.0)	00 (00.0)
	Extremely Satisfied (5)	00 (00.0)	00 (00.0)		00 (00.0)	00 (00.0)	00 (00.0)
Day 30	Extremely Dissatisfied (1)	00 (00.0)	00 (00.0)	0.0000	00 (00.0)	00 (00.0)	00 (00.0)
	Dissatisfied (2)	00 (00.0)	00 (00.0)		00 (00.0)	00 (00.0)	00 (00.0)
	Neither Satisfied or Dissatisfied (3)	00 (00.0)	00 (00.0)		00 (00.0)	00 (00.0)	00 (00.0)
	Satisfied (4)	00 (00.0)	00 (00.0)		00 (00.0)	00 (00.0)	00 (00.0)
	Extremely Satisfied (5)	00 (00.0)	00 (00.0)		00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine.
Note: Percentages are based on number of subjects with a score at the time point.
[1] P-value is from a Wilcoxon Rank Sum test.

Reference: Listing 16.11.

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Table 14.3.6-2 (Page x of Y)
Incidence of Transfusions
Study Part 2
(Safety Analysis Set)

	Part 2			Part 1 and Part 2 Combined		
Transfusion	LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)	LB XXX mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
Yes	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)
No	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine.

Reference: Listing 16.3.5.

LISTINGS

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Listing 16.1.1 (Page x of Y)
Eligibility

Study Part: X Treatment Group: YYY

Subject ID	Date Informed Consent Form Signed	Randomization Date/Time	Randomization Number	Met Inc./Exc. Criteria?	Criteria Not Met	Waiver	
						Granted?	Date

Inc./Exc. = inclusion/exclusion.

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Listing 16.1.2 (Page x of Y)
Unblinding

Study Part: X Treatment Group: YYY

Subject ID	Blind Broken?	Date of Unblinding	Reason

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Listing 16.1.3 (Page x of Y)
Subject Populations and Discontinuations

Study Part: X Treatment Group: YYY

	Subject Included in:					
Subject ID	Safety Analysis Set [1]	Efficacy Analysis Set [2]	PK Analysis Set [3]	Complete the Study?	Date of Completion or Early Discontinuation	Reason for Early Discontinuation

[1] The safety analysis set includes all subjects who received study drug.
[2] The efficacy analysis set includes all subjects in the safety analysis set who underwent the planned surgery.
[3] The PK analysis set includes all subjects in the safety analysis set who received liposome bupivacaine, provided sufficient samples to allow for calculation of PK parameters required for analysis, and who did not receive conventional bupivacaine HCl postsurgically.

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Listing 16.1.4 (Page x of Y)
Hospital Discharge

Study Part: X Treatment Group: YYY

	Hospital Discharge	
Subject ID	Date	Time

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Listing 16.2 (Page x of Y)
Demographics

Study Part: X Treatment Group: YYY

Subject ID	Initials	Date of Birth	Age	Gender	Ethnicity	Race	ASA Class

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Listing 16.3.1 (Page x of Y)
Medical History
Past and/or Concomitant Diseases and Past Surgeries

Study Part: X Treatment Group: YYY

Subject ID	Visit Date	Body System	Condition	Onset Date	Currently Active?

Programmer note: Sort categories as on the CRFs, not alphabetically.

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Listing 16.3.2 (Page x of Y)
Physical Examination

Study Part: X Treatment Group: YYY

Subject ID	Performed?	Date

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Listing 16.3.3 (Page x of Y)
Electrocardiogram Recording (Holter Monitoring)

Study Part: X Treatment Group: YYY

Subject ID	Performed?	Start Date	Start Time	Stop Date	Stop Time

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Listing 16.3.4
Prior and Concomitant Medications (Except for Rescue Pain Medications)

Study Part: X Treatment Group: YYY

Subject ID	Anatomical Main Group/ Preferred Term / Verbatim Term	Prior / Concomitant [1]	Reason for Use	Start Date / Time	End Date / Time	Dose / Unit	Route	Frequency

Prior medications are defined as medication with a stop date/time prior to study drug administration.
Concomitant medications are defined as medications (other than protocol defined and other rescue pain medication) taken on or after the start of study drug administration.

Programmer note: If a subject has no medications, then put "NONE" in the 2nd column.
If the medication is Ongoing, then put "Ongoing" in the "End Date / Time" column.
Use formatted terms as much as possible. If you have to use codes, then add footnotes to explain the codes.

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Listing 16.3.5
Transfusions After Study Drug Administration

Study Part: X Treatment Group: YYY

Subject ID	Anatomical Main Group/ Preferred Term / Verbatim Term	Reason for Use	Start Date / Time	End Date / Time	Dose / Unit	Route	Frequency

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Listing 16.4.1
Study Drug Exposure

Study Part: X Treatment Group: YYY

		Study Drug Administration					
Subject ID	Study Drug Administered?	Date Administered	Start Time	End Time	Duration (minutes)	Volume (mL)	Time of Femoral Nerve Catheter Insertion

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Listing 16.4.2
Surgery

Study Part: X Treatment Group: YYY

Subject ID	Date	Surgery Start Time	Surgery Stop Time	Duration (minutes)	Type of Anesthesia	Other Type	Procedure	Incision Length (cm)

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Listing 16.5.1.1
Pain Intensity Scores at Rest and with Activity

Study Part: X Treatment Group: YYY

				NRS-R			NRS-A	
Subject ID	Time Point	Actual Date	Actual Time	Hours Since End of Surgery	Actual Score	Imputed Score	Actual Score	Imputed Score

NRS-R = numeric rating scale at rest. NRS-A = numeric rating scale with activity.
Scores are based on a numeric rating scale where 0 = no pain and 10 = worst possible pain.

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Listing 16.5.1.2
AUC of NRS-R and NRS-A Pain Intensity Scores
wWOCF + LOCF - Imputation for the Pain Scores

Study Part: X Treatment Group: YYY

		AUC						
Subject ID	NRS Pain Intensity:	0-24	0-36	0-48	0-60	0-72	24-48	48-72
	At Rest							
	With Activity							

AUC = area under the curve calculated using the trapezoidal method, LB = liposome bupivacaine, LSM = least squares means, CI = confidence interval, NA = not applicable.
Scores are based on a numeric rating scale where 0 = no pain and 10 = worst possible pain.
wWOCF + LOCF = imputation using the worst observation prior to the use of rescue medication within a medication window and last-observation-carried-forward for missing values.

Programmer Note: The Time Intervals should be 0-24, 0-36, 0-48, 0-72, 24-48, and 48-72. For the intervals 24-48 and 48-72 put NA in the 'With Activity' column.

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Listing 16.5.2.1
Postoperative Consumption of Opioid Rescue Pain Medication

Study Part: X Treatment Group: YYY

Subject ID	First or Second Rescue	Medication	Date/Time Administered	Hours from End of Surgery	Amount Taken (Units)	Converted Amount (mg) [1]	Cumulative Amount (mg)

[1] Opioids are converted to a morphine-equivalent amount.

Programmer note: If subject took no postoperative opioid pain medications, put 'NONE' in the 2nd column.

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Listing 16.5.2.2

Postoperative Consumption of Rescue Pain Medication via PCA Pump (Interval Data)

Study Part: X Treatment Group: YYY

Subject ID	Medication	Date/Time Started	Hours from End of Surgery	Date/Time Stopped	Total Dose (units)

Ropivacaine used as a rescue pain medication is also included in the listing.

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Listing 16.5.2.3

Postoperative Consumption of Conventional Bupivacaine HCl Rescue Pain Medication

Study Part: X Treatment Group: YYY

Subject ID	Date/Time Started	Hours from End of Surgery	Date/Time Stopped	Concentration (%)	Rate (mL/Hour)

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Listing 16.5.3
Overall Benefit of Analgesia Score Questionnaire

Study Part: X Treatment Group: YYY

				Distress and Bother with [2]:						
Subject ID	Time Point	Date/Time of Assessment	Current Pain at Rest [1]	Vomiting	Itching	Sweating	Freezing	Dizziness	Satisfaction with Pain Treatment [2]	Total Score

[1] 0 = Minimal Pain, 4 = Maximal imaginable pain.
[2] 0 = Not at all, 4 = Very much.
Total score is the sum of the first six questions plus 4 minus the score of the seventh question.

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Listing 16.5.4
Subject Satisfaction with Postsurgical Pain Control

Study Part: X Treatment Group: YYY

Subject ID	Time Point	Date of Assessment	Time of Assessment	Assessment

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Listing 16.5.5
Sensitivity to Cold

Study Part: X Treatment Group: YYY

Subject ID	Time Point	Date of Assessment	Time of Assessment	Sensitivity to Cold

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Listing 16.5.6
Predefined Treatment-Emergent Opioid-Related Adverse Events at 72 Hours (Study Part 1)

Study Part: X Treatment Group: YYY

Subject ID	Date of Assessment	Diffuse Pruritus	Overt Respiratory Depression	Urinary Retention [1]	Constipation	Sedation	Confusion	Delirium	Vomiting	Need for Antiemetic Medication

[1] Urinary retention was measured by need for postsurgical bladder catheterization.

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Listing 16.6.1
Scheduled Bupivacaine Plasma Concentrations (Study Part 1)

Treatment Group: YYY

Subject ID	Dose Time [1]	Date of Sample	Time of Sample	Time Point	Elapsed Time (hours) [2]	Total Bupivacaine Plasma Concentration (ng/mL)	Unbound Bupivacaine Plasma Concentration (ng/mL)

[1] Dose time is the start time of study drug administration.
[2] Elapsed time is the time the sample was collected relative to the time of dose.

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Listing 16.6.2
Bupivacaine Plasma Pharmacokinetic Parameters (Study Part 1)
Treatment Group: YYY

Subject ID	Cmax (ng/mL	Tmax (hours)	AUC 0-last (h*ng/mL)	AUC 0-inf (h*ng/mL)	t1/2 (hours)

[1] Dose time is the start time of study drug administration.
[2] Elapsed time is the time the sample was collected relative to the time of dose.

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Listing 16.6.3
Unscheduled Bupivacaine Plasma Concentrations

Study Part XX Treatment Group: YYY

Subject ID	Dose Time [1]	Date of Sample	Time of Sample	Reason for Collection	Elapsed Time (hours) [2]	Bupivacaine Plasma Concentration (ng/mL)

[1] Dose time is the start time of study drug administration.
[2] Elapsed time is the time the sample was collected relative to the time of dose.

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Listing 16.7.1.1
Adverse Events (Part 1 of 2)

Study Part: X Treatment Group: YYY

Subject ID	SOC / Preferred Term / Verbatim Term	Start Date / Time	End Date / Time	Solicited From: Neuro. [1]	Solicited From: ORAE [2]	Serious	Severity	Relationship to Study Drug	Outcome

* Indicates that the event is not treatment-emergent.
[1] Neurological assessment.
[2] Predefined treatment-emergent opioid-related adverse events questionnaire.

Programmer note: If the subject has no adverse events, then put 'NONE' in the "SOC/Preferred Term/Verbatim Term" column. Use formatted terms as much as possible. If you have to use codes, then add footnotes to explain the codes.

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Listing 16.7.1.2
Adverse Events (Part 2 of 2)

Study Part: X Treatment Group: YYY

Subject ID	SOC / Preferred Term / Verbatim Term	Start Date / Time	End Date / Time	Action Taken with Subject				
				None	Medication	Non-Pharmaceutical Therapy	Discontinued from Study	Other

* Indicates that the event is not treatment-emergent.

Programmer note: If the subject has no adverse events, then put 'NONE' in the "SOC/Preferred Term/Verbatim Term" column. Use formatted terms as much as possible. If you have to use codes, then add footnotes to explain the codes.

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Listing 16.7.1.3
Serious Adverse Events (Part 1 of 2)

Study Part: X Treatment Group: YYY

Subject ID	SOC / Preferred Term / Verbatim Term	Start Date / Time	End Date / Time	Solicited From: Neuro. [1]	Solicited From: ORAE[2]	Severity	Relationship to Study Drug	Outcome

* Indicates that the event is not treatment-emergent.
[1] Neurological assessment.
[2] Predefined treatment-emergent opioid-related adverse events questionnaire.

Programmer note: If the subject has no adverse events, then put 'NONE' in the "SOC/Preferred Term/Verbatim Term" column. Use formatted terms as much as possible. If you have to use codes, then add footnotes to explain the codes.

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Listing 16.7.1.4
Serious Adverse Events (Part 2 of 2)

Study Part: X Treatment Group: YYY

Subject ID	SOC / Preferred Term / Verbatim Term	Start Date / Time	End Date / Time	Action Taken with Subject: None	Medication	Non-Pharmaceutical Therapy	Discontinued from Study	Other

* Indicates that the event is not treatment-emergent.

Programmer note: If the subject has no adverse events, then put 'NONE' in the "SOC/Preferred Term/Verbatim Term" column. Use formatted terms as much as possible. If you have to use codes, then add footnotes to explain the codes.

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Listing 16.7.1.5
Deaths

Study Part: X Treatment Group: YYY

Subject ID	Date of Death	Primary Cause	Autopsy Performed?	Report Obtained?

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Listing 16.8
Height, Weight, and Vital Signs

Study Part: X Treatment Group: YYY

Subject ID	Time Point	Date of Assessment	Time of Assessment	Height (cm)	Weight (kg)	Heart Rate (bpm)	Blood Pressure (mmHg)	
							Systolic	Diastolic

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Listing 16.9
Neurological Assessment

Study Part: X Treatment Group: YYY

Subject ID	Time Point	Date of Assessment	Time of Assessment	Oriented	Numbness [1]	Metallic Taste in Mouth	Problems with Hearing	Problems with Vision	Muscles Twitching

[1] Numbness of the lips, the tongue, or around the mouth.

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Listing 16.10
20-Meter Walk Test

Study Part: X Treatment Group: YYY

Subject ID	Time Point	Date of Assessment	Time of Assessment	Able to Perform the Test?	If No, Provide Reason

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Listing 16.11
Physician Satisfaction with Return of Sensory/Motor Function

Study Part: X Treatment Group: YYY

Subject ID	Time Point	Date of Assessment	Time of Assessment	Assessment