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STATISTICAL ANALYSIS PLAN

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

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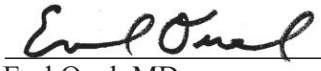 Erol Onel, MD **Executive Medical Director**	01 March 2013 Date
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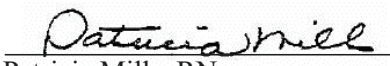
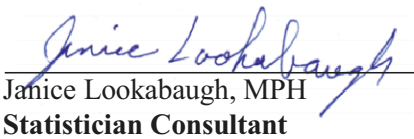
 Patricia Mills, RN **Sr. Director, Drug Safety and Pharmacovigilance**	01 March 2013 Date
 Janice Lookabaugh, MPH **Statistician Consultant**	01 March 2013 Date

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1. LIST OF ABBREVIATIONS

AE	Adverse event
ANCOVA	Analysis of covariance
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
$AUC_{(0\text{-last})}$	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
$C_{(t)}$	Last observed quantifiable concentration
eCRF	Electronic case report form
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit

IM	Intramuscular
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
t_{last}	Time to last quantifiable concentration
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-322 titled "A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Assess the Efficacy and Safety of Intercostal Nerve Block with Liposome Bupivacaine in Subjects Undergoing Posterolateral Thoracotomy".

The structure and content of this SAP provide 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-322 Amendment 1 issued on 23 September 2012.
- Case report forms (CRFs) for Protocol 402-C-322.
- 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

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

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

4. STUDY OVERVIEW

This is a Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled study in subjects undergoing posterolateral thoracotomy.

After completing screening procedures, eligible subjects will be randomized 1:1 to receive either liposome bupivacaine or placebo. Study drug will be administered after the posterolateral thoracotomy is completed (i.e., just prior to the surgical site closure).

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.

Postsurgical Rescue Medication

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

First Rescue Medication

The first rescue medication will be intravenous (IV) fentanyl 100 mcg, which will be administered once via bolus only.

Second Rescue Medication

For the US sites only, 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 of the following recommended doses: (1) on-demand morphine boluses of 1.5 mg with a lockout interval of 6 minutes and an initial maximum hourly dose of 15 mg or (2) on-demand hydromorphone boluses of 0.2 mg with a lockout interval of 10 minutes and an initial maximum hourly dose of 1.2 mg. The recommended bolus doses may be adjusted according to local hospital practice; however, adding a basal rate is prohibited.

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

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

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

Postsurgical Assessments

Subjects will be evaluated for pain using the numeric rating scale (NRS) at rest (NRS-R) at baseline and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours following surgery, at first request for rescue pain medication, and on Day 12. Subjects will also be evaluated for pain with activity using the NRS with activity (NRS-A) at baseline, and 24, 48, and 72 hours following surgery and on Day 12.

Neurological assessments will be conducted at baseline, 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 60, and 72 hours after surgery. The cardiac assessment (i.e., ECG

recordings) will be started at baseline (approximately 1 hour prior to surgery) and continue for a total of 72 hours. The sensory function assessment (i.e., cold test) will be conducted at baseline, when the subject wakes up after surgery, and at 2, 4, 12, 24, 36, 48, 60, and 72 hours after surgery, or until the subject's sensitivity to cold has returned in two consecutive evaluations.

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

Pharmacokinetic Assessments

Blood samples for PK analysis will be obtained from subjects at specific sites at baseline, 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after the end surgery.

Unscheduled blood samples also may be collected 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 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 and who provide sufficient samples to allow for calculation of the PK parameters required for analysis.

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.

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 266 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 7.1.2. 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.

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, (either a per-protocol opioid or a non-per protocol opioid) or a non-opioid analgesic postsurgically, their NRS scores recorded within the window of controlled type of rescue medication (see the table below for the windows for the per-protocol 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 from the subject will be used instead.

Medication	Route	Window Used to Impute NRS
Fentanyl	IV	6 hours
Oxycodone	PO	6 hours
Morphine	IV	4 hours
Hydromorphone	IV	2 hours

IV = intravenous; NRS = numeric rating scale; PO = oral.
If non-per protocol rescue medications are given then the window will be determined post-hoc prior to breaking the blind. For non-opioid analgesics the half-life of the analgesic, if known, will be used for the window.

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).

e) 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 postsurgical 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.

Rescue Pain Medication

For calculation of the total rescue pain medication usage (morphine equivalent) through a 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) matches the date of the administration of study drug, 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 (23:59).

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.

Adverse Event 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

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

7.1.4. Multiplicity Adjustments

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). 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 30 sites/centers in the US and Europe will enroll subjects in this study. The primary efficacy results will be summarized by site and region (US and Europe) but site will not be included in any models. Region will be included in the 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. In addition, the same summary will be produced by site and region.

7.3. Description of Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group and for all subjects for the safety 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.

If any subjects are randomized to the liposome bupivacaine group and receive placebo or any subjects are randomized to the placebo group and receive liposome bupivacaine then a similar table will be created using the efficacy analysis set.

7.4. Prior and Concomitant Medications

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 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 protocol-specified rescue pain medications.

7.5. Measurements of Treatment Compliance

Study drug administration will be summarized by treatment group 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 for the efficacy analysis set. The variables to be included in the summary are length of surgery (end time minus start time, in minutes), level of index nerve injected, length of time in the Intensive Care Unit (ICU) (hours), and number and percentage of subjects with at least one chest tube and length of time from end of surgery to removal of last chest tube, for subjects who have a chest tube inserted.

7.6. Efficacy Analysis

All summaries of the efficacy variables will use the efficacy analysis set, which will be based on randomized treatment.

7.6.1. Efficacy Variables

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

The secondary efficacy variables are:

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

The 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-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 medication.
    - Subjects who only receive IV fentanyl as a rescue medication.
    - Subjects who receive IV fentanyl and a second opioid medication.
- Overall benefit of analgesia score questionnaire at 24, 48, and 72 hours.

- Subject satisfaction with postsurgical pain control at 72 hours, Day 12, and Day 30.
- Time to sensitivity to cold (listed in the protocol as "Proportion of subjects at each time point with sensitivity to cold anywhere within the dermatomes supplied by any of the nerves to which study drug was administered").
- Incidence of predefined treatment-emergent opioid-related AEs (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.

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 calculated using the wWOCF + LOCF imputation method described in Section 7.1.2.

Liposome bupivacaine will be compared to placebo using analysis of covariance (ANCOVA) with treatment and region (US and Europe) as main effects and the baseline NRS-R pain intensity score as a 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.

Descriptive statistics of the primary efficacy variable will also be shown by region and site.

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. Projected amounts, for subjects who discontinue early, will be calculated as described in Section 7.1.3.

Medication	Unit	Route	Conversion (Multiplication) Factor
Fentanyl	mcg	IV	0.1
Oxycodone	mg	PO	0.5
Morphine	mg	IV or IM	1
Hydromorphone	mg	IV	6.7

IV = intravenous; PO = oral.
If any other opioids are administered, then the conversion factor will be determined post-hoc prior to breaking the blind.

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 liposome bupivacaine and placebo, an analysis of variance (ANOVA) with treatment and region (US and Europe) as main effects will be used. Based on the model, the geometric LS means, geometric LS mean ratio of liposome bupivacaine to placebo, 95% CI for the geometric LS mean ratio of liposome bupivacaine to 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. A Log-rank test with region (US and Europe) as a stratifying variable will be used to compare liposome bupivacaine to placebo.

The secondary 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

The following describes the statistical analyses to be performed.

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

For the tertiary efficacy variables NRS-R, NRS-A, and the AUC of the NRS-R 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 variable of 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 received no rescue medication' is defined as subjects who did not receive any medication reported on the three Rescue Medication eCRFs.

The category of 'Subjects who only received IV fentanyl as a rescue medication' is defined as subjects who received IV fentanyl based on the First Rescue Medication eCRF and did not receive any medication based on all of the Second Rescue Medication eCRFs.

The category of 'Subjects who received IV fentanyl and a second opioid medication' is defined as subjects who received IV fentanyl based on the First Rescue Medication eCRF and who either received a medication based on any of the Second Rescue Medication eCRFs or reported an opioid on the Concomitant Medications eCRF (with a start date within 72 hours of the end of surgery).

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. A log-rank test will be used to compare liposome bupivacaine to placebo.

Incidence of Predefined Treatment-Emergent Opioid-Related Adverse Events

The determination of whether a subject had a treatment-emergent ORAE will be based solely on responses on the Predefined Treatment-Emergent ORAEs eCRF. 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 individual 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

Pharmacokinetic parameters will be calculated by noncompartmental analysis method from concentration-time data using WinNonlin Professional 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 the last observed quantifiable concentration ($C_{(t)}$) and the time to last quantifiable concentration (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 $\ln 2/\lambda_Z$.

- The 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. Only data from the subjects in the liposome bupivacaine treatment group will be presented in the summary tables and listings.

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

Plasma concentrations will be summarized 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. 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 in linear and semi-logarithmic scale.

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.

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.

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. 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.

Physician's Satisfaction with Wound Healing

The physician's satisfaction with wound healing will be assessed as 'Extremely dissatisfied', 'Dissatisfied', 'Neither satisfied nor dissatisfied', 'Satisfied', or 'Extremely satisfied' 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.

7.9. Interim Analysis

No interim analyses are planned.

8. SAMPLE SIZE CALCULATIONS

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

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-322. 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.

Planned Tables

Table Number	Table Title
14.1.1.1	Subject Disposition (All Subjects)
14.1.1.2	Subject Disposition by Region and Site (All Subjects)
14.1.2	Demographic and Baseline Characteristics (Safety Analysis Set)
14.1.3.1	Prior Medications (Safety Analysis Set)
14.1.3.2	Concomitant Medications (Safety Analysis Set)
14.2.1.1	Study Drug Administration (SafetyAnalysis Set)
14.2.1.2	Surgery (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 (Efficacy Analysis Set)
14.2.2.1.2	AUC of NRS-R Pain Intensity Scores Through 72 Hours by Region and Site wWOCF + LOCF Imputation for the Pain Scores (Efficacy Analysis Set)
14.2.2.2	Total Postoperative Consumption (mg) of Opioid Rescue Pain Medication Through 72 Hours (Efficacy Analysis Set)

Planned Tables Continued

Table Number	Table Title
14.2.2.3.2	Time to First Opioid Rescue (Efficacy Analysis Set)
14.2.2.4	NRS-R Pain Intensity Scores (Efficacy Analysis Set)
14.2.2.5	NRS-A Pain Intensity Scores (Efficacy Analysis Set)
14.2.2.6	AUC of NRS-R Pain Intensity Scores Through 24, 36, 48, and 60 Hours wWOCF + LOCF Imputation for the Pain Scores (Efficacy Analysis Set)
14.2.2.7	AUC of NRS-R Pain Intensity Scores 24-48 and 48-72 Hours wWOCF + LOCF Imputation for the Pain Scores (Efficacy Analysis Set)
14.2.2.8	Percentage of Subjects who are Pain Free at Each Time Point (Efficacy Analysis Set)
14.2.2.9	Total Postoperative Consumption (mg) of Opioid Rescue Pain Medication Through 24, 36, 48, and 60 Hours (Efficacy Analysis Set)
14.2.2.10	Subjects who Received Rescue Medication Through 72 Hours (Efficacy Analysis Set)
14.2.2.11	Overall Benefit of Analgesia Score Questionnaire (Total Scores) (Efficacy Analysis Set)
14.2.2.12	Subject Satisfaction with Postsurgical Pain Control (Efficacy Analysis Set)
14.2.2.13	Time to Sensitivity to Cold (Efficacy Analysis Set)
14.2.2.14	Incidence of Predefined Treatment-Emergent Opioid-Related Adverse Events (Efficacy Analysis Set)
14.2.3.1	Bupivacaine Plasma Concentrations (ng/mL) Study Part 1 (PK Analysis Set)
14.2.3.2	Bupivacaine Plasma Pharmacokinetic Parameters Study Part 1 (PK Analysis Set)
14.3.1.1	Overview of Treatment-Emergent Adverse Events (Safety Analysis Set)
14.3.1.2	Incidence of Treatment-Emergent Adverse Events (Safety Analysis Set)
14.3.1.3	Incidence of Study Drug Related Treatment-Emergent Adverse Events (Safety Analysis Set)

Planned Tables Continued

Table Number	Table Title
14.3.1.4	Incidence of Treatment-Emergent Adverse Events by Severity (Safety Analysis Set)
14.3.1.5	Incidence of Serious Treatment-Emergent Adverse Events (Safety Analysis Set)
14.3.2.1	Vital Signs (Safety Analysis Set)
14.3.2.2	Vital Signs Change from Baseline (Safety Analysis Set)
14.3.3	Neurological Assessment (Safety Analysis Set)
14.3.4	Physician Satisfaction with Wound Healing (Safety 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 and Baseline Characteristics
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 Protocol-Defined Rescue Pain Medications)
16.4.1	Study Drug Exposure
16.4.2	Surgery
16.4.3	Intensive Care Unit and Chest Tube Removal
16.5.1.1	Pain Intensity Scores at Rest and with Activity
16.5.1.2	AUC of NRS-R Pain Intensity Scores wWOCF + LOCF Imputation for the Pain Scores
16.5.2	Postoperative Consumption of Opioid 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
16.6.1	Scheduled Bupivacaine Plasma Concentrations
16.6.2	Bupivacaine Plasma Pharmacokinetic Parameters
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	Physician's Satisfaction with Wound Healing

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Table 14.1.1.1 (Page x of Y)
Subject Disposition
(All Subjects)

	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)
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	00 (00.0)	00 (00.0)	00 (00.0)
Other	00 (00.0)	00 (00.0)	00 (00.0)

LB = liposome bupivacaine; PK = pharmacokinetic.
[1] The safety analysis set includes all subjects who received study drug and is based on actual treatment received.
[2] The efficacy analysis set includes all subjects in the safety analysis set and is based on randomized treatment.
[3] The PK analysis set includes all subjects in the safety analysis set who received liposome bupivacaine and provided sufficient samples to allow for calculation of the PK parameters required for analysis.

Reference: Listing 16.1.3.

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Table 14.1.1.2 (Page x of Y)
Subject Disposition by Region and Site
(All Subjects)

Region	Site		LB 266 mg (N=XX) n (%)	Placebo (N=XX) n (%)	All Subjects (N=XX) n (%)
US	All Sites	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	00 (00.0)	00 (00.0)	00 (00.0)
		Other	00 (00.0)	00 (00.0)	00 (00.0)
	Etc				

LB = liposome bupivacaine; PK = pharmacokinetic.
[1] The safety analysis set includes all subjects who received study drug and is based on actual treatment received.
[2] The efficacy analysis set includes all subjects in the safety analysis set and is based on randomized treatment.
[3] The PK analysis set includes all subjects in the safety analysis set who received liposome bupivacaine and provided sufficient samples to allow for calculation of the PK parameters required for analysis.

Reference: Listing 16.1.3.

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Table 14.1.2 (Page x of Y)
Demographic and Baseline Characteristics
(Safety Analysis Set)

	LB 266 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: Listing 16.2.

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Table 14.1.2 (Page x of Y)
Demographic and Baseline Characteristics
(Safety Analysis Set)

	LB 266 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: Listing 16.2.

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Table 14.1.3.1 (Page x of Y)
Prior Medications
(Safety Analysis Set)

ATC Class WHO-DD Preferred Term	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)
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)
Etc.			

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 (Page x of Y)
Concomitant Medications
(Safety Analysis Set)

ATC Class WHO-DD Preferred Term	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)
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)
Etc.			

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.

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

	LB 266 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 (Page x of Y)
Surgery
(Efficacy Analysis Set)

	LB 266 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
Level of Index Nerve Injected		
T3	00 (00.0)	00 (00.0)
T4	00 (00.0)	00 (00.0)
Etc.		
Location of Index Nerve Injected		
Left	00 (00.0)	00 (00.0)
Right	00 (00.0)	00 (00.0)
At Least One Chest Tube Inserted		
Yes	00 (00.0)	00 (00.0)
No	00 (00.0)	00 (00.0)
Time With Chest Tube(s) Inserted (min) [1]		
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
Time in ICU (hours)		

n	00	00
Mean	00.0	00.0
SD	00.00	00.00
Median	00	00
Minimum, Maximum	00, 00	00, 00

ICU = Intensive Care Unit; LB = liposome bupivacaine.
[1] Since end of surgery. Only includes subjects who had at least one chest tube inserted.

Reference: Listing 16.4.2 and 16.4.3.

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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
(Efficacy Analysis Set)

Statistics	LB 266 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 carried forward 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 and region (US and Europe) as main effects and the baseline NRS-R pain intensity score as a 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 (Page x of Y)
AUC of NRS-R Pain Intensity Scores Through 72 Hours by Region and Site
wWOCF + LOCF Imputation for the Pain Scores
(Efficacy Analysis Set)

Region	Site	Statistics	LB 266 mg (N=XX)	Placebo (N=XX)
US	All Sites	n	00	00
		Mean	000.0	000.0
		SD	00.00	00.00
		Median	0000	0000
		Minimum, Maximum	000, 000	000, 000
Etc.	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 carried forward 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 14.2.2.2 (Page x of Y)
Total Postoperative Consumption (mg) of Opioid Rescue Pain Medication Through 72 Hours
(Efficacy Analysis Set)

Statistics	LB 266 mg (N=XX)	Placebo (N=XX)
n	00	00
Mean	00.00	00.00
Geometric 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 by the natural logarithm.
[1] From an analysis of variance with treatment and region (US and Europe) as main effects 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.

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

	LB 266 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 [2]	0.0000	

* indicates a censored observation.
CI = confidence interval; LB = liposome bupivacaine.
[1] Kaplan-Meier estimates.
[2] Log-rank test with region (US and Europe) as a stratifying variable.

Reference: Listing 16.5.2.

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

Time Point	Statistics	LB 266 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 and region (US and Europe) as main effects and the baseline NRS-R pain intensity score as a covariate.
[2] Difference from placebo.

Reference: Listing 16.5.1.1.

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

Time Point	Statistics	LB 266 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 and region (US and Europe) as main effects and the baseline NRS-A pain intensity score as a covariate.
[2] Difference from placebo.

Reference: Listing 16.5.1.1.

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Table 14.2.2.6 (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
(Efficacy Analysis Set)

Time Point	Statistics	LB 266 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-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 carried forward 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 and region (US and Europe) as main effects and the baseline NRS-R pain intensity score as a covariate.
[2] Difference from placebo.
Reference: Listings16.5.1.1 and 16.5.1.2.

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Table 14.2.2.7 (Page x of Y)
AUC of NRS-R Pain Intensity Scores 24-48 and 48-72 Hours
wWOCF + LOCF Imputation for the Pain Scores
(Efficacy Analysis Set)

Time Point	Statistics	LB 266 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 carried forward 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 and region (US and Europe) as main effects and the baseline NRS-R pain intensity score as a 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 (Page x of Y)
Percentage of Subjects who are Pain Free at Each Time Point
(Efficacy Analysis Set)

Time Point	LB 266 mg (N=XX) n/N (%)	Placebo (N=XX) n/N (%)	P-value [1]
1 Hour	00/00 (00.0)	00/00 (00.0)	0.0000
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			

Pain free is defined as a pain intensity score at rest of 0 or 1.
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.
[1] P-value is from a chi-square test.

Reference: Listing 16.5.1.1.

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Table 14.2.2.9 (Page x of Y)
Total Postoperative Consumption (mg) of Opioid Rescue Pain Medication Through 24, 36, 48, and 60 Hours
(Efficacy Analysis Set)

Time Point	Statistics	LB 266 mg (N=XX)	Placebo (N=XX)
24 Hours	n	00	00
	Mean	00.00	00.00
	Geometric 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 by the natural logarithm.
[1] From an analysis of variance with treatment and region (US and Europe) as main effects 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.

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Table 14.2.2.10 (Page x of Y)
Subjects Who Received Rescue Medication Through 72 Hours
(Efficacy Analysis Set)

	LB 266 mg (N=XX) n (%)	Placebo (N=XX) n (%)	P-value [1]
Received No Rescue Medication	00 (00.0)	00 (00.0)	0.0000
Received Only the First Rescue	00 (00.0)	00 (00.0)	0.0000
Received the First Rescue and a Second Opioid Rescue	00 (00.0)	00 (00.0)	0.0000

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

Reference: Listings 16.5.2.

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Table 14.2.2.11 (Page x of Y)
Overall Benefit of Analgesia Score Questionnaire (Total Scores)
(Efficacy Analysis Set)

Time Point	Statistics	LB 266 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	

LB = liposome bupivacaine.
Note: The lower the score, the greater the benefit of analgesia.
[1] P-value is from a Wilcoxon Rank Sum test.

Reference: Listing 16.5.3.

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Table 14.2.2.12 (Page x of Y)
Subject Satisfaction with Postsurgical Pain Control
(Efficacy Analysis Set)

Time Point	Assessment	LB 266 mg (N=XX) n (%)	Placebo (N=XX) n (%)	P-value [1]
72 Hours	Extremely Dissatisfied (1)	00 (00.0)	00 (00.0)	0.0000
	Dissatisfied (2)	00 (00.0)	00 (00.0)	
	Neither Satisfied nor Dissatisfied (3)	00 (00.0)	00 (00.0)	
	Satisfied (4)	00 (00.0)	00 (00.0)	
	Extremely Satisfied (5)	00 (00.0)	00 (00.0)	
Day 12	Extremely Dissatisfied (1)	00 (00.0)	00 (00.0)	0.0000
	Dissatisfied (2)	00 (00.0)	00 (00.0)	
	Neither Satisfied nor Dissatisfied (3)	00 (00.0)	00 (00.0)	
	Satisfied (4)	00 (00.0)	00 (00.0)	
	Extremely Satisfied (5)	00 (00.0)	00 (00.0)	
Day 30	Extremely Dissatisfied (1)	00 (00.0)	00 (00.0)	0.0000
	Dissatisfied (2)	00 (00.0)	00 (00.0)	
	Neither Satisfied nor Dissatisfied (3)	00 (00.0)	00 (00.0)	
	Satisfied (4)	00 (00.0)	00 (00.0)	
	Extremely Satisfied (5)	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 16.5.4.

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Table 14.2.2.13 (Page x of Y)
Time to Sensitivity to Cold
(Safety Analysis Set)

	LB 266 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 [2]	0.0000	0.0000

* indicates a censored observation.
CI = confidence interval; LB = liposome bupivacaine,
[1] Kaplan-Meier Estimates.
[2] Log-rank test with region (US and Europe) as a stratifying variable.

Reference: Listing 16.5.5.

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Table 14.2.2.14 (Page x of Y)
Incidence of Predefined Treatment-Emergent Opioid-Related Adverse Events
(Efficacy Analysis Set)

	LB 266 mg (N=XX) n (%)	Placebo (N=XX) n (%)	P-value [2]
Subjects with at Least One Event	00 (00.0)	00 (00.0)	0.0000
Diffuse Pruritus	00 (00.0)	00 (00.0)	
Overt Respiratory Depression	00 (00.0)	00 (00.0)	
Urinary Retention [1]	00 (00.0)	00 (00.0)	
Constipation	00 (00.0)	00 (00.0)	
Sedation	00 (00.0)	00 (00.0)	
Confusion	00 (00.0)	00 (00.0)	
Delirium	00 (00.0)	00 (00.0)	
Vomiting	00 (00.0)	00 (00.0)	
Need for Antiemetic Medication	00 (00.0)	00 (00.0)	

LB = liposome bupivacaine.
[1] Urinary retention was measured by need for postsurgical bladder catheterization.
[2] P-value is from a chi-square test.

Reference: Listing 16.5.6.

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

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

LB = liposome bupivacaine.

Reference: Listing 16.6.1.

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Table 14.2.3.2 (Page x of Y)
Bupivacaine Plasma Pharmacokinetic Parameters
(PK Analysis Set)

Parameter	Statistics	LB 266 mg (N=XX)
Cmax (ng/mL)	n	00
	Mean	000.00 0
	SD	0.0000
	%CV	000.00
	Geometric Mean	00.0
	Median	0.000
	Minimum, Maximum	00.00, 00.00
Tmax (hours)	n	00
	Mean	000.00 0
	SD	0.0000
	Median	0.000
	Minimum, Maximum	00.00, 00.00
AUC0-last (h*ng/mL)	n	00
	Mean	000.00 0
	SD	0.0000
	%CV	000.00
	Geometric Mean	00.0
	Median	0.000
	Minimum, Maximum	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). %CV and geometric mean will not be shown for Tmax and half-life

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

	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)
Maximum Severity: Mild	00 (00.0)	00 (00.0)	00 (00.0)
Maximum Severity: Moderate	00 (00.0)	00 (00.0)	00 (00.0)
Maximum Severity: Severe	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)
At Least One Serious TEAE	00 (00.0)	00 (00.0)	00 (00.0)
Subjects Discontinued Due to a TEAE	00 (00.0)	00 (00.0)	00 (00.0)
Deaths on Study	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 (Page x of Y)
Incidence of Treatment-Emergent Adverse Events
(Safety Analysis Set)

System Organ Class Preferred Term	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)
System Organ 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)
….			
System Organ 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)
Etc.			

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

System Organ Class Preferred Term	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)
System Organ 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)
….			
System Organ 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)
Etc.			

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 (Page x of Y)
Incidence of Treatment-Emergent Adverse Events by Severity
(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 (Page x of Y)
Incidence of Serious Treatment-Emergent Adverse Events
(Safety Analysis Set)

System Organ Class Preferred Term	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)
System Organ 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)
….			
System Organ 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)
Etc.			

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 (Page x of Y)
Vital Signs
(Safety Analysis Set)

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

LB = liposome bupivacaine.

Reference: Listing 16.8.

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

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

LB = liposome bupivacaine.

Reference: Listing 16.8.

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Table 14.3.3 (Page x of Y)
Neurological Assessment
(Safety Analysis Set)

Time Point	Assessment	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)
	At Least one of the Events	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)
	Metallic Taste in Mouth	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)
	Problems with Vision	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)
15 Minutes	Oriented [1]	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)
	Numbness [2]	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)
	Problems with Hearing	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)
	Muscles Twitching	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.
[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 (Page x of Y)
Physician's Satisfaction with Wound Healing
(Safety Analysis Set)

Time Point	Assessment	LB 266 mg (N=XX) n (%)	Placebo (N=XX) n (%)	P-value [1]
72 Hours	Extremely Dissatisfied (1)	00 (00.0)	00 (00.0)	0.0000
	Dissatisfied (2)	00 (00.0)	00 (00.0)	
	Neither Satisfied or Dissatisfied (3)	00 (00.0)	00 (00.0)	
	Satisfied (4)	00 (00.0)	00 (00.0)	
	Extremely Satisfied (5)	00 (00.0)	00 (00.0)	
Day 30	Extremely Dissatisfied (1)	00 (00.0)	00 (00.0)	0.0000
	Dissatisfied (2)	00 (00.0)	00 (00.0)	
	Neither Satisfied or Dissatisfied (3)	00 (00.0)	00 (00.0)	
	Satisfied (4)	00 (00.0)	00 (00.0)	
	Extremely Satisfied (5)	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 16.10.

LISTINGS

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Listing 16.1.1 (Page x of Y)
Eligibility

Treatment Group: YYY

Subject ID	Date Informed Consent Form Signed	Randomization Date/Time	Randomization Number	Visit	Met Eligibility Requirements?	Criteria Not Met	Waiver Granted?	Waiver Date

Programmer note: Visit should be Registration, Screening, and Baseline. For Screening, the waiver questions should be blank.

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Listing 16.1.2 (Page x of Y)
Unblinding

Treatment Group: YYY

Subject ID	Blind Broken?	Date of Unblinding	Reason	Person Who Performed Unblinding

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

Treatment Group: YYY

Subject ID	Subject Included In: 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	If Lost to Follow-up, Date of Last Contact

PK = pharmacokinetic.
[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.
[3] The PK analysis set includes all subjects in the safety analysis set who received liposome bupivacaine and provided sufficient samples to allow for calculation of the PK parameters required for analysis.

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Listing 16.1.4 (Page x of Y)
Hospital Discharge

Treatment Group: YYY

	Hospital Discharge	
Subject ID	Date	Time

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Listing 16.2 (Page x of Y)
Demographics and Baseline Characteristics

Treatment Group: YYY

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

ASA = American Society of Anesthesiologists.

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Listing 16.3.1 (Page x of Y)
Medical History
Past Medical Findings or Surgical Procedures

Treatment Group: YYY

Subject ID	Visit Date	Body System	Finding/ Procedure	Start Date	Currently Ongoing?

Programmer note: Sort categories as on the CRFs, not alphabetically. If Other is checked for Body System then report as Other: specify.

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Listing 16.3.2 (Page x of Y)
Physical Examination

Treatment Group: YYY

Subject ID	Performed?	Date

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

Treatment Group: YYY

Subject ID	Started?	Start Date	Start Time	Stop Date	Stop Time

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

Treatment Group: YYY

Subject ID	Anatomical Main Group/ Preferred Term / Verbatim Term	Prior / Concomitant	Reason for Use	AE Number or NA	Start Date / Time	End Date / Time	Dose / Unit	Route	Frequency

AE = adverse event; NA = Not applicable.
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 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 16.4.1
Study Drug Exposure

Treatment Group: YYY

Subject ID	Study Drug Administered?	Date Administered	Study Drug Administration			
			Start Time	End Time	Duration (minutes)	Total Volume (mL)

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Listing 16.4.2
Surgery

Treatment Group: YYY

	Surgery				Index Nerve Injected		
Subject ID	Date	Start Time	Stop Time	Duration (minutes)	Level	Side	At Least One Chest Tube Inserted?

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Listing 16.4.3
Intensive Care Unit and Last Chest Tube Removal

Treatment Group: YYY

		ICU		Last Chest Tube Removed	
Subject ID	Start Time	Time Admitted	Time Discharged	Date	Time

ICU = Intensive Care Unit.

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Listing 16.5.1.1
Pain Intensity Scores at Rest and with Activity

Treatment Group: YYY

				NRS-R		NRS-A	
Subject ID	Time Point	Actual Date	Actual Time	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 Pain Intensity Scores
wWOCF + LOCF Imputation for the Pain Scores

Treatment Group: YYY

Subject ID	Time Interval (hours)	AUC

AUC = area under the curve calculated using the trapezoidal method; NRS-R = numerical 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 carried forward 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.

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Listing 16.5.2
Postoperative Consumption of Opioid Rescue Pain Medication

Treatment Group: YYY

Subject ID	First or Second Rescue	Medication	Date/Time Administered	Hours from End of Surgery	Amount Taken (Units)	Route	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 16.5.3
Overall Benefit of Analgesia Score Questionnaire

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.

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Listing 16.5.4
Subject Satisfaction with Postsurgical Pain Control

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

Treatment Group: YYY

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

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Listing 16.5.6
Predefined Treatment-Emergent Opioid-Related Adverse Events at 72 Hours

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

Treatment Group: YYY

Subject ID	Dose Time [1]	Date of Sample	Time of Sample	Time Point	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 16.6.2
Bupivacaine Plasma Pharmacokinetic Parameters

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)

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Listing 16.6.3
Unscheduled Bupivacaine Plasma Concentrations

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)

Treatment Group: YYY

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

SOC = system organ class
* 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)

Treatment Group: YYY

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

SOC = system organ class.
* 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)

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

SOC = system organ class.
* 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)

Treatment Group: YYY

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

SOC = system organ class.
* 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

Treatment Group: YYY

Subject ID	Date	Primary Cause	Autopsy Performed?	Date of Autopsy

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Listing 16.8
Height, Weight, and Vital Signs

Treatment Group: YYY

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

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Listing 16.9
Neurological Assessment

Treatment Group: YYY

Subject ID	Time Point	Date	Time	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
Physician's Satisfaction with Wound Healing

Treatment Group: YYY

Subject ID	Time Point	Date of Assessment	Time of Assessment	Assessment

Cardiac ECG Clinical Statistical Plan

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

Sponsor Reference: 402-C-322

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DATE: 30Jul2013

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TABLE OF CONTENTS

1 INTRODUCTION

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

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

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

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

1.1 Objectives

1.1.1 Primary Objective

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

1.1.2 Secondary Objectives

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

1.2 Study Design

This is a Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled study conducted to investigate the efficacy and safety of liposome bupivacaine (total of 266 mg in 20 mL) divided into three equal doses in three syringes of approximately 88 mg in 6.6 mL volume per nerve and administered to each of three nerve segments (index nerve, nerve above, and nerve below) compared with saline placebo nerve block. This study is to enroll 180 patients in up to 30 sites in the US and Europe.

After completing screening procedures, eligible subjects undergoing posterolateral thoracotomy will be randomized 1:1 to receive either liposome bupivacaine or placebo. Study drug will be administered after the posterolateral thoracotomy is completed (i.e., just prior to the surgical site closure).

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

Exclusion criteria will include current or historical evidence of any clinically significant disease or condition, especially cardiovascular or neurological conditions that, in the opinion of the Investigator, may increase the risk of surgery or complicate the subject's postsurgical course or interfere with the determination of pain intensity related solely to the surgery.

1.3 ECG Selection

ECGs will be obtained by recording digital 12 lead ECGs on a Holter recorder (MORTARA H12+) started at baseline (approximately 1 hour prior to surgery) and will continue for a total of 72 hours. All subjects will have an ECG extracted at baseline and then post-treatment ECG(s) will be extracted at the determination of the T_{max} of bupivacaine for each study participant. Subjects who are treated with EXPAREL and have PK blood draws will have a single post-treatment ECG collected at actual T_{max}. Subjects who are treated with placebo or who do not have PK blood draws will have post-treatment ECGs extracted at both the mean and median T_{max}. The unblinded statistician will supply the mean and median T_{max} time points for these subjects based on the mean and median T_{max} observed in the EXPAREL treated subjects who have PK blood draws.

1.4 Analysis of 12-Lead ECGs

Digital 12-lead holter ECGs will be recorded using the Mortara Instrument Digital H12+™ ECG continuous recorder (Mortara Instrument, Inc., Milwaukee, Wisconsin), which will continuously record all 12 leads simultaneously from baseline (approximately 1 hour prior to surgery) and continue for 72 hours. The ECG signal will be recorded on compact flash memory cards provided to the sites. The subject's unique identification number and demographic information will be recorded for each flash card. Without knowledge of subject treatment assignment, the central laboratory, eResearchTechnology, Inc. (ERT; Philadelphia, PA, USA), will generate a 10-second, 12-lead digital ECG at baseline and at Tmax (see Section 1.3). If targeted ECG time points are artifactual and of poor quality, the central laboratory will capture analyzable 10-second ECGs as close as possible to the targeted time points.

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

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

$$QTcB = QT/\sqrt{RR}$$

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

$$RR = 60/HR$$

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

Electrocardiogram changes in HR, RR, PR, QRS, QT, QTcF, and QTcB will be examined at T_{max}.

2 ECG STATISTICAL PLAN

2.1 Subject Populations

The ECG analysis will be performed on all enrolled subjects with at least one available pre-dose Day 1 baseline ECG and one post-dose ECG.

All data collected will be presented in data listings. Unscheduled ECG data, if available, will not be included in formal ECG analysis tables, but will be included in subject data listings.

Data from subjects excluded from an analysis population will be presented in the data listings, but will not be included in the calculation of summary statistics.

2.2 Central Tendency Analysis

The **baseline** ECG interval value will be obtained from the ECG extracted prior to study drug administration.

Descriptive statistics (e.g., frequency, percent, mean, standard deviation (SD), median, maximum and minimum) will be used to summarize the ECG variables and the corresponding changes from the baseline to the ECG(s) obtained at actual T_{max} when it is obtained, and when not, both the median and mean Tmax values will be used in each subject (see Section 1.3). This will provide a time point analysis which is detailed in the tables separately for placebo and liposome bupivacaine.

2.3 Outlier Analyses

An outlier analysis will supplement the central tendency analysis by determining if there are subjects who had an exaggerated effect on any ECG interval that would not be revealed in a mean change from baseline central tendency analysis.

Therefore, the data will be presented as the frequency and percent of subjects with each type of outlier. The following criteria ("study endpoints") are defined for this analysis ("new" means not present at baseline and becomes present on a post-dose ECG time point):

- Heart rate: A value for a subject is considered to be an outlier if the heart rate measurement at the post-dose time point is <50 bpm and the measure is at least a 25% decrease from the subject's baseline heart rate (i.e., a bradycardic event) or if the heart rate measurement at the post-dose time point is >100 bpm and the measure is at least a 25% increase from the baseline heart rate (i.e., a tachycardic event).
- PR interval: A value for a subject is considered to be an outlier if the PR interval at the post-dose time point is >200 ms and it is at least a 25% increase from the subject's baseline PR interval.

- QRS interval: A value for a subject is considered to be an outlier if the QRS interval at the post-dose time point is >100 ms and it is at least a 25% increase from the subject's baseline QRS interval.
- QT interval: A value for a subject is considered to be an outlier if the QT interval at the post-dose time point is >500 ms and the subject's baseline QT interval is ≤500 ms.
- QTcF: A value for a subject is considered to be an outlier if the QTcF interval at the post-dose time point is >500 ms and the subject's baseline QTcF interval is ≤500 ms. Outlier values will also be presented if the QTcF interval at the post-dose time point is >480 ms when the subject's baseline QTcF interval is ≤480 ms and when the post-dose time point is >450 ms when the subject's baseline QTcF interval is ≤450 ms. In addition, the proportion of subjects with changes from baseline of >30-60 ms and >60 ms will be presented.
- QTcB: A value for a subject is considered to be an outlier if the QTcB interval at the post-dose time point is >500 ms and the subject's baseline QTcB interval is ≤500 ms. Outlier values will also be presented if the QTcB interval at the post-dose time point is >480 ms when the subject's baseline QTcB interval is ≤480 ms and when the post-dose time point is >450 ms when the subject's baseline QTcB interval is ≤450 ms. In addition, the proportion of subjects with changes from baseline of >30-60 ms and >60 ms will be presented.

The data will be presented by time point (actual T_{max}, mean T_{max} and median T_{max}) separately for liposome bupivacaine and placebo.

A categorical or outlier analysis will be considered exploratory since the study was not powered to pick up unusual individual responses to the potential effects of drugs. Outlier analyses will produce data as the percentage of subjects in each treatment group that meet the criteria as defined for this analysis. All outliers will be summarized by treatment group on the basis of incidence rates. The outlier summary tables will include counts of subjects.

2.4 Morphological Analysis

Morphological analyses will be performed with regard to the ECG waveform interpretation as defined by the central ECG laboratory's cardiologist. Changes from baseline to the post-dose ECG(s) will be done.

All findings will be presented in the ECG listings. New onset (presented as percentage of subjects meeting the new criteria) for the following variables will be detailed in the tables:

- Atrial fibrillation or flutter
- Second degree heart block,

- Third degree heart block,
- Complete right bundle branch block,
- Complete left bundle branch block,
- ST segment depression,
- ST segment elevation,
- T wave abnormalities (negative T waves only),
- Myocardial infarction pattern, and
- Any new abnormal U waves.

The data will be presented in the tables by time point (actual T_{max}, mean T_{max} and median T_{max}) separately for the liposome bupivacaine and placebo groups as detailed above for the central tendency analyses.

3 DEVIATIONS IN ANALYSIS FROM STATISTICAL PLAN AND OTHER ISSUES

Deviations of the actual final statistical analysis from the statistical plan will be described and justified in the final report.