STATISTICAL ANALYSIS PLAN

Protocol Title	A Multicenter, Randomized, Double-blind, Active-controlled Study to Evaluate the Safety and Efficacy of EXPAREL When Administered via Infiltration into the Transversus Abdominis Plane (TAP) Versus Bupivacaine Alone in Subjects Undergoing Elective Cesarean Section.
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Study Phase	4
IND Number	069,198
Sponsor	Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 Tel: 973-254-3560
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1. SIGNATURE PAGE

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3. LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse event
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
ATC	Anatomical therapeutic class
BMI	Body mass index
bpm	Beats per minute
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CSR	Clinical study report
d	Day
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
FNB	Femoral nerve block
hr, h	hour
ICF	Informed consent form
ICH	International Conference on Harmonization
ICU	Intensive care unit
IV	Intravenous
LOCF	Last observation carried forward
LS	Least square
MedDRA	Medical dictionary for regulatory affairs
MMRM	Mixed model repeated measures
MPADSS	Modified Postanesthesia Discharge Scoring System
min	minutes
OMED	Oral morphine equivalent dose in mg
n	Number of subjects
OBAS	Overall benefit of analgesia
OR	Operating room
PACU	Postanesthesia care unit
PCA	Patient-controlled analgesia
PK	Pharmacokinetics
PO	Oral
ROW	Rest of world
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SPIS	Sum of pain intensity scores
TAP	Transversus abdominis plane

Abbreviation	Description
TEAE	Treatment-emergent adverse event
TKA	Total knee arthroplasty
TLF	Table, listings and figures
TUG	Timed up-and-go
TWT	Timed walk test
VAS	Visual analog scale
WHO	World Health Organization
WHO-DD	World Health Organization – Drug Dictionary
wWOCF	Windowed worst observation carried forward

4. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analysis and reporting of the clinical study 402-C-411 titled "A Multicenter, Randomized, Double-blind, Active-controlled Study to Evaluate the Safety and Efficacy of EXPAREL Plus Bupivacaine When Administered via Infiltration into the Transversus Abdominis Plane (TAP) Versus Bupivacaine Alone in Subjects Undergoing Elective Cesarean Section."

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 Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials (1998). All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association (1999) and the Royal Statistical Society (1993), 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 the clinical study report (CSR), regulatory submissions, or manuscripts. Post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc, unplanned, or exploratory analyses performed will be clearly identified as such in the final CSR.

The following documents related to clinical study Protocol 402-C-411 were reviewed in preparation of this SAP:

- Protocol Amendment 3, issued 7 May 2018.
- ICH Guidance on Statistical Principles for Clinical Trials (E9).

The reader of this SAP is encouraged to also read the clinical 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.

5. STUDY OBJECTIVES

5.1. Primary Objective

The primary objective of this study is to compare total opioid consumption through 72 hours following EXPAREL+Bupivacaine HCl infiltration into the transversus abdominis plane (TAP) after spinal anesthesia to active bupivacaine HCl TAP infiltration after spinal anesthesia in subjects undergoing an elective cesarean section (C-section).

5.2. Secondary Objectives

The secondary objectives are to assess efficacy and safety parameters and patient satisfaction.

6. STUDY OVERVIEW

This is a Phase-4, multicenter, randomized, double-blind, active-controlled study in approximately 186 adult subjects undergoing elective C-section. All subjects will remain in the hospital for up to 72 hours postsurgery.

Subjects will be randomized in a 1:1 allocation ratio to receive either:

- EXPAREL+bupivacaine TAP infiltration following spinal anesthesia hereafter referred to as EXPAREL+Bupivacaine.
- Active bupivacaine TAP infiltration following spinal anesthesia hereafter referred to as Bupivacaine.

Hereafter, treatment group “EXPAREL+bupivacaine” will sometimes be labeled as “EXPAREL 266 mg” and “Active bupivacaine” will be labeled as “IR Buipivacaine”. Subjects will be allowed rescue medication upon request to control their pain. Rescue medication will be oral (PO) immediate release oxycodone. If subject cannot tolerate PO medication, intravenous (IV) morphine or hydromorphone may be used as rescue medication.

Pain will be assessed using a 10 cm visual analog scale (VAS). Pain will be assessed at multiple prescheduled time points during the study and prior to taking any rescue medication. Subjects will remain in the hospital for up to 72 hours postsurgery.

Other postsurgical assessments include:

- Opioid use
- Time of first unassisted ambulation
- Pain intensity scores using a 10-cm VAS at rest
- Discharge readiness
- Subject's satisfaction with postsurgical pain control

- Overall benefit of anesthesia score (OBAS) questionnaire
- Quality of recovery 15-item questionnaire (QoR-15)

7. DEFINITIONS

Study Day

If event occurs earlier than the start of study drug, Study Day is calculated as the date of event minus the date of the start of study drug administration. Otherwise Study Day is calculated as the date of event minus the date of the start of study drug administration plus one (+1). Study Day is based on the calendar dates, thus days before the date of surgery have negative values while those on or after the date of surgery are positive.

Treatment-emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are the adverse events started on/after the study drug administration.

Time 0 (zero)

Time 0 is defined as the date and time of the end of surgery.

Time Periods

All scheduled times have a window associated with them (see Time and Events Schedule for individual time point windows). Various time frames are used in the data analyses which are dependent on these windows.

Table 1: Time Window for VAS Assessment

Defined time VAS Time Point (hrs)	Acceptable Window (hrs)
6	± 0.5
12, 18, 24	± 1
30, 36, 42, 48	± 2
72	± 4

If there are two or more VAS data points that fit into the same time window, the data point close to the center of the window will be used. If two data points are of equal distance to the center, the one with higher VAS score will be used for analysis. For programming purpose, the VAS time point for analysis (ANL01FL=Y) will be numbered by their schedule, eg, ATPTN = 6, 12, 18, …, 72. Other VAS time points will be numbered by the VAS time relative to the surgical end time in hours (with 1 decimal point), eg, 47.5.

If after applying the time window, the VAS data point for the scheduled window becomes missing, it will be imputed as per Section 9.1.1.2.

Baseline

Baseline is defined as the last available measurement or assessment prior to the start of study treatment.

Ready for Discharge

Ready for discharge is defined as a total score of 9 or more on the Modified Postanesthesia Discharge Scoring System (MPADSS). The total score is the sum of all scores. If there are missing data, then the total score will not be calculated.

Discharge Time

Discharge time is defined as Discharge day - admission day + 1.

Summed Pain Intensity Score (SPIS)

Sum of pain intensity scores (SPIS) are calculated by summing the observed or imputed VAS scores for the time-frames of interest. Only the scheduled VAS assessments will be used to derive SPIS.

Time to Event

Time to event will be calculated as the time from end of surgery to time of event in hours.

Opioid-free

Opioid-free is defined as not received opioid rescue medication during the time interval.

Opioid-sparing

Subjects meet the opioid sparing criteria if the following conditions are satisfied:

- For 0-72 hours opioid consumption, all doses add up to ≤15mg (oral morphine equivalent dose [OMED]) AND the OBAS score = 0 for all of the following questions,
    - Questions 2, 3, 4, 5, and 6.
    - If any of the above OBAS score is missing, then opioid-sparing is set to missing.

Opioid Window

Opioid window is a time interval starting when the opioid medication is administered through the time when the medication's analgesic effect is worn out.

8. ANALYSIS SETS

The safety analysis set includes all subjects who receive study drug. All analyses based on the safety set will be by actual treatment received.

The modified intent-to-treat principal (MITT) analysis set will be used for efficacy analysis. It includes all randomized subjects in the safety analysis set who undergo C-section, receive study drug on/after 17 February 2018, and whose ultrasound images show correct TAP infiltration. Note before 17 February 2018 subjects were dosed based on the protocol with dosing error. Incorrect TAP infiltration was noted by the independent data reviewing committee. Both errors affect the evaluation of the effectiveness of the study drug. All analyses based on the efficacy analysis set will be by randomized treatment regardless of the actual treatment received.

9. STATISTICAL METHODS OF ANALYSIS

9.1. General Principles

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). All analyses and tabulations will be performed using SAS® Version 9.4 or later. Continuous variables will be summarized using descriptive statistics [sample size (n), mean, standard deviation (SD), minimum, median, and maximum]. Categorical variables will be tabulated with number and percentage of unique subjects. Unless otherwise noted, percentages will be calculated using the number of subjects in the respective treatment group and analysis set as the denominator and presented with only those categories appearing in the data.

Individual subject data will be provided in listings. All listings will be sorted by treatment, site, subject, and, if applicable, collection date and time.

9.1.1. ling Missing Values

9.1.1.1. Total postsurgery opioid consumption

For the calculation of the total postsurgical opioid consumption, both opioid rescue medication before hospital discharge and opioid pain medication in the daily diary after discharge will be included. If opioid is taken on the discharge day but time of dosing is missing, it will be imputed as time of discharge or 12:00 pm on the discharge day, whichever is later. If opioid is taken after the day of discharge and time of dosing is missing, it will be imputed as 12:00 pm the day after discharge.

If patient does not return her patient daily diary at the end of study, then for the primary efficacy endpoint of total postsurgery opioid consumption through 72 hours (inclusive), if a patient is discharged at $x < 36$ hours after end of surgery, her total postsurgical opioid consumption through 72 hours will be calculated as $72/x \cdot y$, where y is the opioid consumption during the initial x hours (inclusive) postsurgery. If a patient is discharged at $36 \leq x \leq 72$ hours, her total postsurgery opioid consumption through 72 hours will be

calculated as $D_{0,x} + D_{2x-72,x}$, where $D_{2x-72,x}$ is the opioid consumption from $2x - 72$ hours (exclusive) through x hours (inclusive). For example, if a patient is discharged at x=70 hours, her postsurgerical 0 to 72 hours opioid consumption will be calculated as her consumption during the first 70 hours plus the consumption between 70 and 72 hours, which is imputed by the consumption between 68 and 70 hours.

9.1.1.2. VAS Pain Intensity Scores and Area Under the VAS-Time Curve

Pain scores obtained during the opioid medication window will be replaced with the worst observation carried forward (wWOCF). For this study the prescribed opioid rescue medication is oxycodone. However, morphine, hydromorphone, or other opioids may be used. The durations of the analgesic effect for various opioids are listed in **Error! Reference source not found.**.

Table 2: Opioid Rescue Medication Window

Medication	Route	Window Used to Impute VAS
Oxycodone, Oxycocet, Percocet, acetaminophen-oxycodone, Oxycontin	PO, IM, IV, SC	6 hours
Morphine	IV, PO, SC	4 hours
Hydromorphone (Dilaudid), Hydromorphone hydrochloride	IV	2 hours
Hydromorphone (Dilaudid), Hydromorphone hydrochloride	PO, IM, SC	4 hours
Hydrocodone	PO	6 hours
Fentanyl	IV, PO, IM	6 hours
Hydrocodone combination product - Vicodin, Norco, Lorcet, Lortab, hydrocodone-acetaminophen	PO	6 hours
Codeine combination product - Tylenol 3, acetaminophen-coedine, Paracetamol Forte, Tylenol 4	PO	6 hours
Ultram, Tramadol, Tramacol hydrochloride	PO	6 hours
PO = oral, IV = intravenous, IM = Intramuscular, SC = subcutaneous, VAS = visual analog scale.		

If other rescue medications not listed above are given, the window will be determined post-hoc. If a combination opioid product is given, the window will be determined by the opioid part of the medication.

For the secondary analysis endpoint of VAS pain score, missing data at each scheduled time point will be imputed assuming VAS scores missing at random. Rubin's (1987) multiple imputation procedure will be applied to replace each missing value with a set of plausible values that represent the uncertainty about the right value to impute. For the AUC and SPIS

calculation, the windowed worst observation carried forward (wWOCF) multiple imputation procedure will be used in the following order:

a) Windowed worst observation carried forward (wWOCF) for rescue medications.

   For subjects who take a rescue medication, their VAS scores recorded within the window of controlled type of rescue medication (see **Error! Reference source not found.**) will be replaced by the 'worst' observation. The worst observation will be the highest VAS score from the end of previous rescue window or the end of surgery whichever is later. The VAS score of rescue will be included in this calculation. Note (1) the VAS score in the window that is higher than the worst value to be carried forward, this "higher" value will not be overwritten. Instead, the worst value will be replaced by this "higher" value and continue carrying forward until the end of the window. (2) if the scheduled VAS score within the window is missing, it will be imputed with this worst value.

b) After the wWOCF imputation, described in Step a, subject data still missing with a non-monotone missing pattern (i.e., intermittent missing) will have missing scores imputed using the Markov Chain Monte Carlo (MCMC) method (Schafer 1997) within each treatment by SAS PROC MI. Multiple imputations will be conducted to simulate 30 datasets with only monotone missing data. In order to achieve the stationary distribution and to avoid dependency within samples generated by MCMC method, the number of iteration for the burn-in period will be set to 2000 and the number of iterations between two consecutive samples will be set to 1000 (i.e., NBITER=2000 and NITER=1000.)

c) The resulting data from Step b will then have the monotone missing pattern. The remaining missing data will then be imputed by a parametric regression method (Rubin 1987) that assumes multivariate normality distribution.

   Only missing data at the scheduled time points are imputed by above Steps b and c. The imputed VAS score will have the time from end of surgery assigned exactly the scheduled time, eg, 48.0 hr and 72.0 hr.

d) AUC of VAS score will be derived using all scheduled and unscheduled VAS scores

e) The AUC and SPIS at various time intervals will be derived from the imputed VAS scores resulting from Step c. There will be 30 sets of AUC and SPIS from the 30 imputed data sets. See Section 9.7.1.4 and 9.7.1.5 for detail.

f) The endpoints derived in Step d will be analyzed as described in Section 9.7.1 for each imputation.

g) Rubin's (1987) synthesizing procedure for the multiple imputed data will be applied to synthesize analysis results for each imputation. SAS PROC MIANALYZE will be used for this procedure. The mean parameter estimates, the asymptotic variance for this mean from the imputed data analysis in Step e will be computed using Rubin and Schenker method (1986).

The SAS pseudo-code for multiple imputations and analysis is as follows.

```
** Step 1 use Markov-Chain Monte-Carlo (MCMC) method to create a monotonic missing pattern
** Note the value for the random seed is fixed to be 123 so that the results are reproducible, MIN=0 and
   MAX=10 are to bound the imputed VAS score within 0-10, ROUND=0.1 is to round the imputed VAS
   score with 1 decimal place. The Box-Cox transformation is to reduce the skewness of the data
   distribution **
proc mi data=adef seed=123 nimpute=30 out=output_step1 min=0
max=10 round=0.1;
      by treatment;
      mcmc impute=monotone nbiter=2000 niter=1000;
      var t6 t12 t18 t24 t30 t36 t42 t48 t72 ;
      transform boxcox (t6 t12 t18 t24 t30 t36 t42 t48 t72 /
      c=0.5 lambda=0) ;* this is log(t+0.5) transformation ;
run;

** Step 2 – use regression on output dataset from Step 1 to impute missing values **;
proc mi data=output_step1 seed=987 nimpute=1 out=output_step2
min=0 max=10 round=0.1;
      by _imputation_ treatment ;
      monotone reg(t12 = t6 / details);
      monotone reg(t18 = t6 t12 / details);
      monotone reg(t24 = t6 t12 t18/ details);
      monotone reg(t30 = t6 t12 t18 t24/ details);
      monotone reg(t36 = t6 t12 t18 t24 t30/ details);
      monotone reg(t42 = t6 t12 t18 t24 t30 t36/ details);
      monotone reg(t48 = t6 t12 t18 t24 t30 t36 t42/ details);
      monotone reg(t72 = t6 t12 t18 t24 t30 t36 t42 t48/
      details);
      var t6 t12 t18 t24 t30 t36 t42 t48 t72;
      transform boxcox (t6 t12 t18 t24 t30 t36 t42 t48 t72 /
      c=0.5 lambda=0) ;
run;

** Step 3 derive endpoint_variable using appropriate techniques by variable _IMPUTATION_ **;

*** Step 4 analyze imputed data set **;
ods output Diffs=diff LSMeans=lsm ;
proc mixed data=auc1 ;
      by impute ;
      class usubjid trtpn siteid ;
      model aval = trtpn siteid age height ;
```

```
      lsmestimate trtpn "Trt1-Trt2 Noninferior" 1 -1 / lower
      testvalue=36 cl alpha=0.025 ;
      lsmestimate trtpn "Trt1-Trt2 Superior"    1 -1 / lower
      testvalue=0  cl alpha=0.025 ;
      lsmeans trtpn / pdiff cl alpha=0.05 ;
run ;

ods output ParameterEstimates=lsmdif ;
proc mianalyze data=diff alpha=0.05 ;
      modeleffects estimate ;
      stderr stderr ;
run ;

ods output ParameterEstimates=lsmeans ;
proc mianalyze data=lsm alpha=0.05 ;
      by trtpn ;
      modeleffects estimate ;
      stderr stderr ;
run ;

** Step 5 builds report from SUMMARYSTATSB and MIXEDSTATSB **;
```

9.1.1.3. Exposure, Surgery, and Rescue Medication Date or Time

It is expected that all necessary information on study drug exposure, surgery, and postsurgical rescue medication dates and times 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 plus 1 minute.

9.1.1.4. Adverse Event or Concomitant Medications Dates or Times

For AEs with missing or partially missing start date/time, the following imputation rules will be applied for the determination of treatment-emergent status:

For partial start date/time:

- If the year is unknown, then the date will be assigned the date and time of first dose of study treatment.
- If the year is known to be different from the year of the first dose, then missing month and day will be imputed as the first month and first day of the month.
- If the year is known to be the year of the first dose,
    a) If the month is unknown or is the same as the month of the first dose, then the missing month and day will be imputed by the month and day of the first dose.

b) If the month is known to be different from the month of the first dose, then the missing day is imputed as 01 (first day of the month).

- If the time is unknown, then:

a) If the date (day, month, and year) matches the date of the administration of study drug, then the time of the study treatment will be used to impute the missing time.

b) Otherwise, '00:00' will be assigned.

For medications with missing or partially missing dates, Section 9.5 provides rules for the determination of prior or concomitant status.

9.1.1.5. 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' and will be footnoted for the table to indicate this imputation. If relationship to study drug is not reported for an AE, then for tables of study-drug related AEs, the event will be assigned the relationship of 'definite'. Tables presenting related AEs will include all AEs with relationships of 'possible', 'probable' or 'definite' as assessed by the investigator.

9.1.1.6. Time to Event

For calculating time to an event when only the hour is reported, the minutes will be set to zero.

9.1.2. ling Erroneous Values

Subject 263-0134's 200mg oxycodone record (7 July 2018 16:00) will be removed due to data entry error. This subject data are locked in the eCRF, hence cannont be removed via database query/resolution.

9.1.3. Multiplicity Adjustments

For the efficacy analyses, EXPAREL+Bupivacaine HCl TAP infiltration following spinal anesthesia will be compared to bupivacaine HCl TAP infiltration following spinal anesthesia using the 1-sided 0.025 alpha level for the efficacy analysis set.

No multiplicity adjustments will be made.

9.1.4. By-Center Analyses

By-site summaries will be presented for disposition, demographics, primary efficacy endpoint and secondary efficacy endpoints. In the by-site analysis, analysis stratified by site or adjusted for site as covariate, the small sites below will be pooled into one psudo site, numbered as SITEID 999:

- SITEID 264, 265, 266, 267, 269, 276, and 277.

9.2. Subject Disposition

Subject disposition summaries will include the number of subjects

- Screened,
    - Screen failure
    - Enrolled (ie, randomized)
- Randomized
    - Randomized not treated,
    - Randomized treated,
- In the safety analysis set,
- Subjects whose TAP infiltration were performed
    - Inorrectly based on ultrasound image
- Subjects who were dosed before 17 February 2018,
- In the efficacy analysis set,
- Protocol
    - Enrolled under Amendment 2 or 3
    - Enrolled under Amendment 1
    - Enrolled under Original Protocol
- Completed the study as planned,
- Discontinued from the study, and
    - Reasons for discontinuation from the study.

Percentages will be reported for the screen failures and enrolled using the number of subjects screened as the denominator; other percentages will use the number of subjects randomized and treated as denominator, unless otherwise noted.

The safety analysis set and enrollment data will be presented as treated. All other data will be presented as randomized.

The disposition summary will present the data for each treatment group. This summary table will present overall sites and for each site separately.

9.3. Description of Demographics and Baseline Characteristics

9.3.1. Demographics

The summary of demographic data will present:

- Age (years) – descriptive statistics
- Sex – n (%)
- Ethnicity – n (%)
- Race – n (%)
- Country – n (%)

Age is calculated from the date the subject signed the informed consent form (ICF) and birth. It is presented as the number of years between, rounding down to the nearest integer year.

The demographic summary will present the data for each treatment group. Summaries will be provided for each (safety and efficacy) analysis set separately.

9.3.2. Baseline Characteristics

The summary of baseline characteristic data will present:

- American Society of Anesthesiologists (ASA) Classification – n (%)
- Baseline ECG interpretation
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m^2)
- Baseline vital signs
    - Heart rate (bpm)
    - Systolic blood pressure (mmHg)
    - Diastolic blood pressure (mmHg)

The formula for BMI is $w/(h^2)$, where w is weight in kilograms and h is height in meters. Weight in pounds will be converted to kilograms using the conversion factor of 2.2046 pounds to 1 kilogram. Height in inches will be converted to centimeters using the conversion factor of 2.54 centimeters to 1 inch.

Baseline characteristics summaries will present the data for each treatment group. Summaries will be provided for each (safety and efficacy) analysis set separately.

Descriptive statistics (n, mean, SD, median, minimum and maximum) will be provided for continuous variables. The number and percent of subjects will be tabulated for the categorical variables.

9.4. Surgery Characteristics

Surgery characteristics including duration of surgery will be summarized using descriptive statistics. Summaries will be provided for each (safety and efficacy) analysis set.

Duration of surgery is calculated as the difference between the end of surgery and start of surgery times and reported in hours.

9.5. Intraoperative, Prior and Concomitant Medications

All medications will be coded using the World Health Organization Drug Dictionary (WHODDE Sep 2018) and will be classified according to the anatomical therapeutic chemical classification term (ATC4) and preferred term (PT).

Pre-operative and intraoperative medications are defined as medications given as part of the surgical procedure. These may include anesthesia, opioids or other medications with start and stop dates on the day of surgery and start and stop times overlapping with the surgery start and stop times.

Prior and Concomitant medications are medications collected on the Prior/Concomitant Medication eCRF page.

Prior medications are defined as medications with a stop date and time prior to the start of 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).

For the determination of the prior and concomitant status, the follow fules will be followed for incomplete dates.

- If the medication stop date is partially missing,
    - If the year and month indicate the stop date is before study drug drug administration, it is Prior medication.
    - Otherwise, it is concomitant medication.
- If the medication stop date is completely missing, it is concomitant medication.

Pre- and intraoperative, prior, and concomitant medications will be summarized separately using n (%) of subjects for each treatment group and across treatment groups by ATC4 term and PT for the safety analysis set. Subjects may have more than one medication per ATC4 and PT. At each level of subject summarization, a subject will be counted once if one or more medications are reported by the same subject at that level.

All medications (Combined Spinal Epidural Medications, Pre-Operative Medications, Intraoperative Medications, Multimodal Pain Medication, Rescue Medications, Prescription Daily Pain Medications, and Prior/Concomitant Medications) will be included in the data listing.

9.6. Measurements of Treatment Compliance

Study treatment is administered by the site personnel, therefore compliance is assured.

9.7. Efficacy Analysis

For Primary and Secondary Efficacy Analyses, descriptive statistics that are appropriate for the efficacy variable will also be shown by site, but no statistical analyses will be performed within a site. All efficacy analyses will be performed on the efficacy analysis set.

9.7.1. Efficacy Endpoints

9.7.1.1. Primary Efficacy

The primary endpoint is the total postsurgical opioid consumption (mg) in oral morphine equivalent dose (OMED) through 72 hours.

9.7.1.2. Secondary Efficacy

The following secondary endpoints will be analyzed as described in Section 9.1.3:

- AUC of the VAS pain intensity scores through 72 hours presented as $AUC_{0\text{-}72}$.
- Total postsurgical opioid consumption through 24 and 48 hours, and Day 7 (168 hours) and Day 14 (336 hours).
- Percentage of opioid-free subjects from end of surgery through 72 hours.
- Percentages of opioid-sparing subjects from end of surgery through 72 hours.
- Time to first opioid rescue medication from end of surgery.

9.7.1.3. Tertiary Efficacy

- The AUC of the VAS pain intensity scores from 0 to 12 hours, 0 to 24 hours, 0 to 48 hours, 24 to 48 hours, 24 to 72 hours and 48 to 72 hours
- Sum of VAS pain intensity scores at rest from end of surgery through 72 hours presented as $SPIS_{0\text{-}72}$.
- Sum of VAS pain intensity scores at rest from postsurgical 0 to 12 hours, 0 to 24 hours, 0 to 48 hours, 0 to 72 hours, 24 to 48 hours, 24 to 72 hours and 48 to 72 hours presented as $SPIS_{0\text{-}12}$, $SPIS_{0\text{-}24}$, $SPIS_{0\text{-}48}$, $SPIS_{0\text{-}72}$, $SPIS_{24\text{-}48}$, $SPIS_{24\text{-}72}$, $SPIS_{48\text{-}72}$.
- Integrated rank assessment using the VAS pain intensity score at rest at postsurgery 24, 48, and 72 hours and the total amount of postsurgical opioids consumed from end of surgery through 24, 48, and 72 hours (Silverman 1993[5]).
- Overall benefit of analgesia scores (OBAS) at each assessed time point.

- Time spent in the post-anesthesia care unit (PACU).
- Time to first unassisted ambulation.
- Proportion of subjects meeting Modified Post Anesthesia Discharge Scoring System (MPADSS) criteria for discharge readiness at each assessed time point.
- Overall assessment of the subject's satisfaction with postsurgical pain control (using a 5-point Likert scale) at 72 hours after surgery (or at hospital discharge if earlier than 72 hours).
- Responses to the QoR-15 questionnaire at 72 hours after surgery (or at hospital discharge if earlier than 72 hours).
- Number of unscheduled phone calls or office visits related to pain from discharge through Day 14

9.7.1.4. Area under the Curve

Area under the pain-time curve is derived using the trapezoidal rule (see formula below) on the pain scores adjusted for rescue medication use using the observed and imputed values (see Section 9.1.1.2). AUC will start with the first pain assessment obtained after surgery and use all following pain assessments up to 72 hours post surgery including those collected prior to rescue medication and unscheduled. Exact assessment times will be used in deriving AUC.

$$AAA = \sum_{i=2}^{n} (p_i + p_{(i-1)})(t_i - t_{(i-1)})/2$$

Where p_i is the VAS pain score at time i and t_i is the time, in hours, from end of surgery. Note t_1 is 6 hours post surgery. It is the first time VAS score is collected.

In calculating $AUC_{0\text{-}72}$, if the exact 72 hour VAS score is not collected, it will be interpolated using the two nearest before and after data points. If the last 72 hour assessment is before 72.0 hours, then the exact 72 hour VAS score for the AUC calculation will use this last observation carried forward. Similarly for the 6 hour VAS score, if it is not collected at the exact 6 hour post surgery, it will be interpolated using the two nearest before and after data points. If the first 6 hour assessment is after 6.0 hour, then the exact 6 hour VAS score for the AUC calculation will use this first observation carried backward.

9.7.1.5. Summed Pain Intensity Score

SPIS will be calculated using the observed or imputed VAS scores only at the scheduled time points,

$$SSSS_{0-72} = \sum_{6,12,18,24,30,36,42,48,72\ hrr} VAS.$$

Refer to Section 7 Time Periods for the derivation of scheduled time points. For the multiply-imputed VAS scores, the average will be used for the SPIS calculation. No synthesizing procedure (Section 9.1.1.2 Step g) will be applied for this analysis.

9.7.1.6. Opioid Dose Conversion

Opioids dose will be converted to oral morphine equivalent dose (OMED mg) using the conversion factor from **Error! Reference source not found.** for all summaries. Total opioid dose is the oral morphine equivalent sum of all opioids taken after surgery up to the time point of interest. Subjects with no opioid use during the period in question will be assigned a dose of 0 mg for summaries.

Table 3. Conversion Factors to IV and Oral Morphine Equivalent Dose from Other Opioids

Medication	Unit	Route	IV Morphine Conversion (Multiplication) Factor	Oral Morphine Conversion (Multiplication) Factor
Oxycodone, Oxycocet, Percocet, acetaminophen-oxycodone	mg	PO	0.5	1.5
Morphine	mg	IV,IM,SC	1	3
Morphine	mg	PO	0.33	1
Hydromorphone (Dilaudid)	mg	IV,IM,SC	6.67	20
Hydromorphone (Dilaudid)	mg	PO	1.3	4
Fentanyl	mg	IV,PO,IM	100	300
Hydrocodone combination product - Vicodin, Norco, Lorcet, Lortab, hydrocodone-acetaminophen, Ketobemidone	mg	PO	0.33	1
Codeine combination product - Tylenol 3, acetaminophen-coedine, Paracetamol Forte, Tylenol 4	mg	PO	0.05	0.15
Ultram, Tramadol, Tramacol hydrochloride	mg	PO, IM	0.08	0.25
Demerol, Meperidine, Pethidine	mg	IV, SC	0.1	0.3
Demerol, Meperidine, Pethidine	mg	PO	0.033	0.1
Ketobemidone, Oxycodone	mg	IV	1	3
Nalbuphine/Nallouphine (Nubain/Manfine)	mg	IV, IM,SC	1	3

PO = oral, IV = intravenous, IM = Intramuscular, SC = subcutaneous, VAS = visual analog scale.
If other rescue medications not listed above are given, the window will be determined post-hoc. If a combination opioid product is given, the window will be determined by the opioid part of the medication.

9.7.1.7. Overall Benefit of Analgesia Score (OBAS)

The OBAS is derived as follows:

1. Add all the scores of questions 1 to 6.
2. To this number, add four.
3. Subtract the score of question 7 from this number.

If a response is missing to any question in the OBAS, the total score will not be calculated.

9.7.1.8. Safety Endpoints

- Incidence of AEs/SAEs starting after the start of anesthesia through Day 14.
- Vital signs at scheduled time points.

9.7.2. Methods of Analysis

For Primary and Secondary Efficacy Analyses, descriptive statistics appropriate for the efficacy variable will be presented overall and by site. No statistical comparison will be made within a site.

9.7.2.1. Primary Efficacy Analysis

Postsurgical opioid consumption (OMED mg) will be summarized by treatment group for the total dose consumed between 6 and 72 hours after the end of surgery. For the frequency count of number of subjects receiving opioid medications, subjects will be counted only once regardless of how many times subjects have received the medications. This summary table will show summaries overall.

Tests for the treatment effect will be based on the following null hypothesis (Ho) and two-sided alternative hypothesis (Ha):

$$\text{Ho: } \mu_s = \mu_p \text{ versus Ha: } \mu_s \neq \mu_p$$

where μ_s and μ_p are the mean of the 0-72 hour Postsurgical opioid consumption (OMED mg) for the EXPAREL+Bupivacaine TAP infiltration following spinal anesthesia, and Bupivacaine TAP infiltration following spinal anesthesia, respectively. A one-sided test will be performed at 2.5% level of significance comparing the two treatment groups. The treatment effect of EXPAREL+Bupivacaine will be considered significantly better than that of Bupivacaine if the null hypothesis of no difference is rejected and a difference in the observed mean is in favor of EXPAREL+Bupivacaine (mean for EXPAREL+Bupivacaine less than the mean for Bupivacaine).

To test for significant differences between EXPAREL+Bupivacaine and Bupivacaine, an analysis of covariance (ANCOVA) model with treatment and site as the main effects, age and height as covariates will be used. The LS means for each treatment group, LS mean difference between

the two treatment groups, two-sided 95% CI for the LS mean difference, and the one-sided p-value will be reported.

In addition to the presentation for the between group difference, the percent reduction in total postsurgical OMED will also be presented. The % reduction is derived as follows,

$$\% \text{ Reduction} = \{LSM_{Bupivacaine} - LSM_{EXPAREL+Bupivacaine}\}/LSM_{Bupivacaine}$$

where LSM is least square mean estimated from ANCOVA.

The primary analysis for the primary endpoint is based on the Efficacy evaluable population.

9.7.2.1.1. Subgroup Analysis of Primary Efficacy Endpoint

The analysis of the primary endpoint will be repeated for selected subgroups such as

- Age (<35, and ≥35),
- Race (White and Non-White),
- BMI (<25, 25 to <30, and ≥30+ kg/m^2)
- Number of prior C-sections (0, 1+),
- Discharge Time (Discharged on or before Day 3, Discharged on or after Day 4), and
- Subjects with or without anxiety medical history.

Note because of the small sample sizes, all subgroup analysis will be performed without adjusting/stratifiying by site

9.7.2.2. Secondary Efficacy Analyses

9.7.2.2.1. Opioid-Sparing at 72 Hours and Opioid-free at 48 Hours

The Percentage of opioid-sparing subjects through 72 hours and percentage of opioid-free subjects through 72 hours will be additionally analyzed using the logistic regression model with treatment, site, age, and height as explanatory variables. Odds ratio (EXPAREL+Bupivacaine / Bupivacaine), and 95% CI for the odds ratio and p-value will be presented. In addition, the number and percentage of subject's opioid-free and opioid-sparing will also be tabulated.

Pseudo-code for logistic regression method:

```
ods output OddsRatios=or /* ODDS RATIO AND 95% CL*/
     Diffs=diff(keep=probz) /* 1-SIDED P-VALUE */
     LSMeans=lsm(keep=trtpn mu) /* PROB OF YES */ ;
proc logistic data=ef1 plots=none ;
  class siteid trtpn / param=glm ;
  model avalc(event="Yes")=trtpn siteid age heightbl ;
  lsmeans trtpn / pdiff=controll('2') ilink ;
run ;
```

9.7.2.2.2. AUC for Pain Intensity Score

AUC_{0-72} for pain intensity from 0 to 72 hours will be analyzed using ANCOVA with treatment and site as main effects, age and height as covariates. Note higher AUC means more pain over time. Based on the model, the LS mean and SE of the LS mean will be reported for each treatment. The LS Mean for treatment difference for EXPAREL+Bupivacaine minus Bupivacaine and 95% CI for the LSM difference will be used to test the following two hypotheses:

- Hypothesis 1 (non-inferiority):
    - Ho: EXPAREL+Bupivacaine group is inferior to Bupivacaine group with respect to AUC for pain intensity.
    - Ha: EXPAREL+Bupivacaine group is not inferior to Bupivacaine group with respect to AUC for pain intensity.
- Hypothesis 2 (superiority):
    - Ho: EXPAREL+Bupivacaine group is not different from Bupivacaine group with respect to AUC for pain intensity.
    - Ha: EXPAREL+Bupivacaine group is superior to Bupivacaine group with respect to AUC for pain intensity.

The statistical test will be conducted using a stepdown approach by inspecting the 95% confidence interval for the between EXPAREL+Bupivacaine and Bupivacaine group difference as follows:

- Non-inferiority Test for Hypothesis 1.
    - If the upper bound of the 2-sided 95% confidence interval for the LSM for the difference of AUC_{0-72} (EXPAREL+Bupivacaine) – AUC_{0-72} (Bupivacaine) is > NIM, where NIM (non-inferiority margin) = 50% x 72 hrs, then stop the hypothesis tests and declare that the non-inferiority result is not achieved.
    - If the upper bound of the 2-sided 95% CI is ≤ NIM then declare that the non-inferiority of EXPAREL+Bupivacaine to Bupivacaine is achieved. Move on to test for Hypothesis 2.
- Superiority Test for Hypothesis 2
    - If the upper bound of the 2-sided 95% CI is ≥0, then stop the test and declare that the superiority of EXPAREL+Bupivacaine to Bupivacaine is not achieved.
    - If the upper bound is <0 then declare that the superiority of EXPAREL+Bupivacaine to Bupivacaine is achieved.

In the table presentation for the between group comparion, if the superiority test passes, only the 1-sided superiority test p-value will be displayed. If the superiority test fails, only the 1-sided non-inferiority test p-value will be displayed.

Additionally, descriptive statistics of the AUC of VAS pain score will also be shown by site but no statistical analyses will be performed within a site.

9.7.2.2.3. Time to First Opioid Rescue Medication

Time to first opioid rescue medication will be computed in hours as the date and time of the first opioid rescue medication minus the date and time of the end of surgery. If a subject is not administered an opioid rescue medication, the time to first administration will be censored at their last visit/follow up time (last VAS, start time of last concomitant medication, start time of last prescription daily pain medication, start time of last AE, hospital discharge, Subject Satisfaction with Postsurgical Pain Control questionnaire, QoR-15, and last OBAS). Note missing time will be set to 12:00 PM of the day.

Time to first opioid rescue will be analyzed by the Cox regression model with treatment and site as factors, and age and height as covariates. The between group comparison will be carried out

by the χ^2 test. The n (%) of subjects administered an opioid as well as the n (%) of censored observations will be presented for each treatment group. Median, quartiles, and their associated 95% confidence intervals will be estimated from the adjusted survival curve with site, age, and height as confounders (Nieto and Coresh 1996). In addition, the plot of adjusted survival curve will be presented for both treatment groups.

9.7.2.2.4. Total Postsurgical Opioid Consumption through 24 and 48 Hours, and Day 7 (168 Hours) and Day 14 (336 Hours)

These endpoints will be analyzed similar to Section 9.7.2.1.

9.7.2.3. Tertiary Efficacy Analyses

9.7.2.3.1. AUC in Visual Analog Scale (VAS) from 0 to 12 Hours, 0 to 24 Hours, 0 to 48 Hours, 24 to 48 Hours, and 48 to 72 Hours

These endpoints will be analyzed similar to Section 9.7.2.2.2.

9.7.2.3.2. Summ of VAS Pain Intensity Scores at Rest from End of Surgery through 72 Hours ($SPIS_{0\text{-}72}$)

Summed Pain Intensity Score through 72 hours ($SPIS_{0-72}$) will be analyzed similarly to Section 9.7.2.2.2. The non-inferiority margin for this analysis is defined as 50% x 9, where 9 is the number of time points in the $SPIS_{0-72}$ calculation.

9.7.2.3.3. Opioid-Free at 72 Hours

These endpoints will be analyzed similar to Section 9.7.2.2.1.

9.7.2.3.4. Sum of VAS Pain Intensity Scores (SPIS) at Rest from 0 to 12 Hours, 0 to 24 Hours, 0 to 48 Hours, 24 to 48 Hours, and 48 to 72 Hours

These endpoints will be analyzed similar to Section **Error! Reference source not found.**.

9.7.2.3.5. Integrated Rank Assessment Using the VAS Pain Intensity Score at Rest

In this analysis, $SPIS_{0-72}$ is combined with the cumulative dose (oral MED) of the rescue opioid medications up to the time of the 72 hour pain assessment. If opioid pain medication information stops being collected before the pain assessment time, the projected amount will be calculated and used as described in Section 9.1.1.1. The integrated analysis of the pain score and opioid rescue medication will be carried out according to the methods of D.G. Silverman et al (1993) as follows.

- Both the SPIS score and the amount of opioid medication will be separately ranked in the combined treatment groups (the average of respective ranks will be used in the case of ties).
- Each subject's SPIS rank and total opioid medication usage rank will then be subtracted by the mean rank [(n+1)/2] of all subjects and expressed as a percent (%) difference from the mean rank, where n is the total number of subjects in the analysis.
- A subject's integrated score is the sum of the % difference in the SPIS score and the % difference in the total opioid pain medication usage.

The integrated score will be summarized with descriptive statistics by treatment and analyzed for the between treatment difference using the method described in Section **Error! Reference source not found.**.

9.7.2.3.6. Overall Benefit of Analgesia (OBAS)

The OBAS total score will be summarized and individual question responses tabulated by treatment at each assessment time points. For the OBAS total score, the between group comparison will be carried out at each time point using the Cochran-Mantel-Haenszel (CMH) test for row mean score difference (RMS) with modified ridit score.

9.7.2.3.7. Time Spent in the Post-Anesthesia Care Unit (PACU)

The time spent (hours) in PACU is defined as date/time of admission to PACU subtracted by date/time of discharge from PACU. This endpoint will be analyzed by treatment group using ANCOVA as described in Section **Error! Reference source not found.**.

9.7.2.3.8. Time to First Unassisted Ambulation

Time to first unassisted ambulation will be computed in hours as the date and time of the first unassisted ambulation minus the date and time of the end of surgery. If a subject is not administered an ambulation, the time to first unassisted ambulation will be censored at 72 hours after surgery or at the time of last follow-up, whichever is early. Time to first unassisted ambulation will be analyzed by the method similar to time to first opioid rescue medication secondary endpoint (see Section 9.7.2.2.3).

9.7.2.3.9. Discharge Readiness

Percentage of subjects meeting MPADSS criteria for discharge readiness (total score ≥9, Section 7) will be analyzed similarly to Section 9.7.2.2.1 using logistic regression at each assessed time point.

If a subject is discharge ready at an early timepoint, the subject will be considered discharge ready at all subsequent (future) timepoints. If a subject has a discharge readiness total score of less than 9 or if the total score is missing, the subject will be considered not discharge ready, unless they were previously considered discharge ready.

9.7.2.3.10. Subject Satisfaction with Overall Analgesia

Subject satisfaction with overall analgesia (obtained using a 5-point Likert scale) will be summarized with mean and SD and tabulated with n (%) by treatment and assessment time point. The between group comparison will be carried out using the same method as described in Section 9.7.2.3.6.

9.7.2.3.11. QoR-15 Questionnaire

This analysis will only be done on subjects with correct QoR-15. Listing of subjects with correct QoR-15 and incorrect QoR-15 will be provided.

Quality of Recovery questionnaire is comprised of two Parts. Part A has 10 items and Part B has 5 items, both on the feeling and experience in the last 24 hours. For each subject, the mean score of Part A and the mean score of Part B will be calculated using all the available item scores. If ≥4 item scores are missing for Part A, or ≥2 item scores are missing for Part B, the respective mean score will be set to missing. The total score for the questionnaire is defined as the average of the Part A and Part B mean scores. If either Part A or Part B mean score is missing, the total score is set to missing. See Appendix 1 for the QoR-15 questionnaire.

The total score as well as scores for Questions 3, 4, 14, 15 will be summarized (n, mean, SD, median, minimum and maximum) for each treatment group at 72 hours postsurgery or prior to hospital discharge, whichever occurs first. The between group comparison will be carried out using the same method as described in Section 9.7.2.3.6.

9.7.2.3.12. Phone Calls after Discharge

The number of unscheduled pain-related phone calls per subject after discharge through postsurgical Day 14 will be summarized with mean and SD and tabulated with n (%) of subjects with 0, 1, 2, 3, etc. phone call by treatment. The between group comparison will be carried out using the same method as described in Section 9.7.2.3.6.

9.7.2.3.13. Total Opioid Consumption through Day 7 and Day 14

Subject's opioid consumption in hospital and on patient diary after discharge will be summed together to get total opioid consumption through Day 7 and Day 14. These two endpoints will be derived as the sum of total opioid consumption through 72 hours (primary efficacy endpoint) and from 72 hours (exclusive) through Day 7 and Day 14 (inclusive), respectively. The opioid consumption from 72 hrs through Day 7 and Day 14 will be based on the Prescription Daily Pain Medication recorded in the Patient Diary. No imputation or projection will be carried out for the missing diaries. These two endpoints will be analyzed similar to Section 9.7.2.1.

9.7.2.4. By-Subgroup Analysis

In addition, total opioid consumption through 72 hours will be analyzed for the following subgroup.

- Age (<35, 35+ years)
- Race (White, Non-White)
- BMI (<25, 25 to <30, and 30+ kg/m2)
- Number of prior C-sections (0, 1+)
- Discharge Time (Discharged on or before Day 3, Discharged on or after Day 4)
- Medical history of anxiety (yes, no)

Note because of the small sample sizes, all subgroup analysis will be performed without adjusting/stratifiying by site.

9.8. Safety Analyses

Safety assessments in this study consist of adverse events (AEs) and vital signs (VS)

9.8.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v21.1).

An AE will be considered TEAE if it starts on/after the time of the study drug administration.

If an AE has a partial onset date and time the imputed start dates and time will be used to determine treatment-emergence (Section 9.1.1.4). All AE summaries will present TEAEs only. AEs that are not treatment-emergent will be included in listings but not summarized.

AEs will be summarized using subject incidence table. An overview of TEAE will be presented. This table will include n (%) of subjects with

- Any TEAE
  - Maximum severity: Mild
  - Maximum severity: Moderate
  - Maximum severity: Severe
- At least one related TEAE
- At least one serious TEAE
- Subjects discontinued due to a TEAE
- Died on study

Additionally, n (%) are calculated based on the number of unique subjects within each MedDRA category (eg, preferred term) by treatment group. A subject reporting multiple events of the same category will be counted only once for that category. For summary purpose, AE relationship to the study drug will be grouped into “Unrelated” for “unrelated” or “unlikely related” and “Related” for “possibly”, “probably”, or “definitely related”. For subjects with more than one event coded to the same PT, the subjects will be counted for the categories with the strongest relationship and the greatest severity. The following subject incidence tables will be presented.

- TEAEs by PT (Preferred Term) sorted by the decreasing order of subject incidence in the combined group
- TEAEs by SOC (System Organ Class) and PT sorted alphabetically
- TEAEs by study drug-relationship by SOC and PT
- TEAEs by severity and by SOC and PT
- TEAE of special interest (TEAESI) by SOC and PT

A subject data listing will be provided for all adverse events. Included in the listing are the reported term, PT, SOC, TEAE flag, study day when AE starts, duration, relationship, severity, action taken, outcome, and seriousness category.

Separate data listings will be provided for subjects who die on study, experience SAEs, have TEAEs leading to study discontinuation, or AEs of special interest.

AE of special interest will be extracted based on the MedDRA terms below.

Table 4. Adverse Events of Special Interest

Group	MedDRA System Organ Class	MedDRA Preferred Terms
FALL	Injury, poisoning and procedural complications	Fall
LAST	Cardiac Disorders	Arrhythmia
	Cardiac Disorders	Atrial Fibrillation
	Cardiac Disorders	Atrial Tachycardia
	Cardiac Disorders	Atrioventricular Block
	Cardiac Disorders	Atrioventricular Block First Degree
	Cardiac Disorders	Bradycardia
	Cardiac Disorders	Bundle Branch Block Left
	Cardiac Disorders	Bundle Branch Block Right
	Cardiac Disorders	Cardiac Arrest
	Cardiac Disorders	Cardiac Failure Acute
	Cardiac Disorders	Cardiac Failure Congestive
	Cardiac Disorders	Conduction Disorder
	Cardiac Disorders	Myocardial Infarction
	Cardiac Disorders	Sinus Arrest
	Cardiac Disorders	Sinus Arrhythmia
	Cardiac Disorders	Sinus Bradycardia
	Cardiac Disorders	Sinus Tachycardia
	Cardiac Disorders	Supraventricular Tachyarrhythmia
	Cardiac Disorders	Supraventricular Tachycardia
	Cardiac Disorders	Tachyarrhythmia
	Cardiac Disorders	Tachycardia
	Cardiac Disorders	Ventricular Extrasystoles
	Cardiac Disorders	Ventricular Tachycardia
	Nervous System	Dizziness
	Nervous System	Dysgeusia
	Nervous System	Somnolence
	Nervous System	Tremors

A listing of the mapping of the system organ class and preferred terms to verbatim terms will be presented.

9.8.2. Vital Signs

Vitals signs are resting heart rate (bpm), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg). Vital signs will be summarized by treatment group at each assessment time point. Summaries will present both actual and change-from-baseline results.

9.8.3. Interim Analysis

The objective of the interim analysis is to evaluate efficacy and re-estimate the sample size. The first planned interim analysis, with 80 subjects out of planned 152 subjects for the primary efficacy analysis, was to test the null hypothesis of no between-group difference using the O'Brien-Fleming's 2-sided boundary of 0.0078. Predictive probability (Saville et al 2014) was computed to evaluate the futility of the trial.

The possible outcomes of the interim analysis are

- Stop trial for futility, if the predictive probability is <30%
- Stop trial for overwhelming efficacy, if the p-value is <0.0078
- Continue the study with the planned total sample size of 144 subjects, if the predictive probability is ≥70%
- Continue the study with total sample size increased up to 200 subjects, if the predictive probability is ≥30% but <70%. The expansion in the sample size is to achieve the predictive probability >70%

If the study continues to its completion, the critical value for the final analysis is as follows.

Table 5. Critical Values (2-sided) for the Final Analysis

Maximum Sample Size	144	152	160	168	176	184	192	200
Critical Value	0.0472	0.0476	0.0480	0.0484	0.0486	0.0488	0.0490	0.0492

For detail of the interim analysis, please refer to "402-C-411_interim_SAP_final" dated 07June2017 and "402-C-411_2nd_interim_SAP_draft_final.docx.pdf" dated 15August2018.

Results of the Interim Analysis

The first interim analysis was carried out after 80 patients (40 per group) enrolled under Amendment 2 or later version of the protocol and provided their primary efficacy outcome (Section 9.7.1.1). All randomized subjects who underwent planned surgery and received study drug were included in this interim analysis. After this analysis, it was decided to continue the trial without change to the sample size. The second interim analysis was carried out when 120 patients enrolled under Amendment 2 or later version and provided their primary efficacy outcome and key secondary outcome (VAS pain intensity score). As result of this analysis, total sample size was increased to 184.

10. SAMPLE SIZE CALCULATIONS

The sample size for this study was based Quale et al (2016). The coefficient of variation (CV) from this poster was approximately 60%. Assuming a log-normal distribution for total opioid consumption with a 60% CV, 5% alpha, a 1:1 randomization ratio, and 80% power 72 subjects per treatment arm is sufficient to detect a 30% difference between treatments. Assuming 5% of the subjects are not evaluable a total sample size of approximately 152 subjects are needed to ensure 144 evaluable subjects

11. REFERENCES

Newcombe, RG, Interval Estimation for the Difference between Independent Proportions: Comparison of Eleven Methods. Statist. Med. 17, 873-890 (1998).

Nieto, FJ and J Coresh. Adjusting Survival Curvs for Confounders: A Review and a New Method. American Journal of Epidemiology. 1996. Vol. 143, No. 10.

Rubin, DB. (1987). Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons.

Quale, M, G Cunningham, C Foster, and J Hutchins. Addition of transversus abdominis plane infiltration with liposomal bupivacaine to intrathecal morphine for postoperative analgesia after Caesarean delivery: a retrospective study. Abstract 1497. American Society of Regional Anesthesia and Pain Management. 41st Annual Regional Anesthesiology and Acute Pain Medicine Meeting. 31-Mar-2016 to 02-Apr-2016. New Orleans, LA, US.

Saville, BR, JT Connor, GD Ayers, J Alvarez. The Utility of Bayesian Predictive Probabilities for Interim Monitoring of Clinical Trials. Clinical Trials. May 2014, p485-493, Vol. 11, No. 4.

Schafer, JL. (1997). Analysis of Incomplete Multivariate Data. New York: Chapman & Hall.

Silverman, DG, TZ O'Connor, SJ Brull. Integrated assessment of pain scores and rescue morphine use during studies of analgesic efficacy. *Anesth Analg*. 1993;77:168-170.

12. TIME AND EVENTS SCHEDULE OF STUDY PROCEDURES

Please see the Protocol for the full “Time and Events Schedule of Study Procedures”.

13. LAYOUT OF TABLES, LISTINGS AND FIGURES

The following are planned summary tables. 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 mock-ups will be displayed in the produced output unless otherwise specified. Notes to programmers will not be included in the tables.

Tables and listings will have 10 point font size. Listings font size may be reduced to 9 point if needed. The TLFs will have either Times New Roman, Courier New or SAS Monospace type face. All final TLFs will be provided in both PDF and Word (or RTF) file formats.

Percentages should not appear if the count is zero.

Italicized text in the TLF mock-ups indicate notes to programmers and is not to appear on any TLF.

Note headers and footers on mock-ups are reflective of the SAP document and are not intended to appear on the TLFs.

Titles on the TLFs in the mock-ups are presented left-justified as a single line of text. However, the presentation for final TFLs should be center-justified with the TLF number on one line and the remaining titles on multiple lines of text where the line breaks are delimited by hyphens (-) in the TLF mock-ups titles. For example, for Table 14.2-1.1.1 the title in the mock-up appears as:

```
Table 14.2-1.1.1: Analysis of Postsurgical Total Opioid Consumption (MED mg)
through 72 hours – Efficacy Analysis Set
```

but should appear as follows on the final TLF:

```
                          Table 14.2-1.1.1
Analysis of Postsurgical Total Opioid Consumption (OMED mg) through 72 hours
                        Efficacy Analysis Set
```

The title format in the mock-ups is due to limitations of MS Word. The mock-up format enables MSWord to generate a table of contents for the mock-ups.

For categorical variables, if subjects have missing values (example Race), a “missing” category will be added as appropriate.

All tables will present treatment EXPAREL 266 mg (for EXPAREL+Bupivacaine) and IR Bupivacaine as separate columns.

On all figures, EXPAREL 266 mg will be represented in red with solid lines and dots, and Bupivacaine will be represented in blue with solid lines and filled squares.

On all listings the treatments, in the order of appearance, are: EXPAREL 266 mg, IR Bupivacaine and, if applicable, NOT RANDOMIZED. Always insert a page break between treatments.

On all listings sort within treatment by site, subject, with further sorts dependent on listing.

The shell provides a general guidance for how the data will be presented. The actual presentation may be modified to accommodate the page size restriction.

For TFLs with multiple pages, page numbers will be included.

All TFLs will have SAS program names and folder names and date/time stamp in the footnote for tracking purpose.

14. LIST OF TABLES

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Table 14.1-1: Summary of Subject Disposition – All Screened Subjects

Site: Overall

	EXPAREL 266 mg (N=XX) n (%)	IR Bupivacaine (N=XX) n (%)	Total (N=XX) n (%)
Screened [1]			xx
Screen Failure			xx (xx.x)
Enrolled			xx (xx.x)
Randomized	xx	xx	xx
Not Treated	xx	xx	xx
Treated	xx	xx	xx
TAP Infiltration Error per Ultrasound Image	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study Drug Administered Before 17 February 2018	xx (xx.x)	xx (xx.x)	xx (xx.x)
Safety Analysis Set [2]#	xx (xx.x)	xx (xx.x)	xx (xx.x)
Efficacy Analysis Set [3]@	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol			
Enrolled under Protocol v3	xx (xx.x)	xx (xx.x)	xx (xx.x)
Enrolled under Protocol v2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Enrolled under Protocol v1			
Completed Study@	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued from Study@	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reasons for Discontinuation	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of Efficacy	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to Follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal by Subject	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)

= as treated @ = as randomized
[1] Signed the informed consent form [2] Received study drug [3] Received study drug and surgery
Percentages for screen failure and enrolled based on number screened; others on number randomized.
Subjects randomized to EXPAREL 266 mg but treated with IR Bupivacaine: *list subjects*
Subjects randomized to IR Bupivacaine but treated with EXPAREL 266 mg: *list subjects*

Note to programmer: *First page will present overall sites; subsequent pages will present each site – one site per page. For reasons for discontinuation only those reasons that appear in the data will appear on the table. For individual sites the label should be the site number. For the footnotes "Subjects treated with..." if no subjects were mistreated, then omit footnote.*

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Table 14.1-2.1: Summary of Subject Demographics - Safety Analysis Set

Site: Overall

	Statistic	EXPAREL+Bupivacaine (N=XX)	IR Bupivacaine (N=XX)	Total (N=XX)
Age (yrs)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
Sex				
Female	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Male	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity				
Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race				
American Indian/Alaska Native	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black/African American	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
White	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian/Pacific Islander	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note to programmer: *Only categories available in the data will appear on the table. First page will present overall sites; subsequent pages will present each site – one site per page. For individual sites the label should be the site number.*

Use this mock-up also for table:

Table 14.1-2.2: Summary of Subject Demographics – Efficacy Analysis Set

Pacira Pharmaceuticals (Page 1 of 3) Protocol: 402-C-411

Table 14.1-3.1: Summary of Subject Baseline Characteristics - Safety Analysis Set

	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)	Total (N=XX)
ECG				
Normal, NCS	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Abnormal, NCS	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Abnormal, CS	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
VAS Score (cm)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
ASA Classification				
1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
≥ 4	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Height(cm)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx

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Table 14.1-3.1: Summary of Subject Baseline Characteristics - Safety Analysis Set

	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)	Total (N=XX)
Weight (kg)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
	Maximum	xx	xx	xx
Body Mass Index (kg/m^2)				
	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
	Maximum	xx	xx	xx

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Table 14.1-3.1: Summary of Subject Baseline Characteristics - Safety Analysis Set

	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)	Total (N=XX)
Heart Rate (bpm)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
Systolic Blood Pressure (mmHg)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
Diastolic Blood Pressure (mmHg)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
	Maximum	xx	xx	xx

Use Table 14.1-2.1 shell for

Table 14.1-3.2: Summary of Subject Baseline Characteristics - Efficacy Analysis Set

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Table 14.1-4.1: Summary of Surgery Characteristics - Safety Analysis Set

Characteristic	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)	Total (N=XX)
Duration of Surgery (hours)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx	xx	xx
	Minimum	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
Tourniquet				
Used Not	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Used	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Duration (hours)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx	xx	xx
	Minimum	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
Drain				
Used Not	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Used	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Duration (hours)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx	xx	xx
	Minimum	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx

Use this mock-up also for tables:

Table 14.1-4.2: Summary of Surgery Characteristics – Efficacy Analysis Set

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Table 14.1-5: Incidence of Intraoperative Medications - Efficacy Analysis Set

Anatomical Therapeutic Class (ATC) Preferred Name	EXPAREL 266 mg (N=XX) n (%)	IR Bupivacaine (N=XX) n (%)	Total (N=XX) n (%)
Subjects taking at least one medication	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PN1.1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PN1.2	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC2	xx (xx.x)	xx (xx.x)	xx (xx.x)
PN2.1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PN2.2	xx (xx.x)	xx (xx.x)	xx (xx.x)
	xx (xx.x)	xx (xx.x)	xx (xx.x)
ETC.			

Medications are coded using World Health Organization Drug Dictionary (WHODD Sepember 2018).
Sorted by descending total incidence by ATC and preferred name within ATC.
Intraoperatives medications are those indicated as such by the investigator.
Subjects using the same prior medication more than once are counted only once at each summary level.

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Table 14.2-1.1a: Analysis of Postsurgical Total Opioid Consumption (OMED mg) Through 72 hours – Efficacy Analysis Set

Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
LS Mean [1]	xxx.x	xxx.x
Standard Error of LS Mean [1]	xxx.xx	xxx.xx
% Reduction [2]	xxx.x	
LSM Treatment Difference Difference [1][3]	xx.x	
95% Confidence Interval [1][3]	(xx.x, xx.x)	
P-value, 1-sided [1][3]	0.xxx	

LS = Least Square; LSM2 = LS Means in IR Bupivacaine group; LSM1 = LS Means in EXPAREL 266 mg group.
[1] From an ANCOVA with main effects of treatment and site and covariates of age and height on total opioid consumption. Subjects without any opioid use are assigned a value of 0 mg for summaries.
[2] % Reduction in Total Opioid Dose is calculated as (LSM2-LSM1)/LSM2*100%.
[3] Test of Ha: LSM (EXPAREL 266 mg) < LSM (IR Bupivacaine).

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Table 14.2-1.1b: Summary of Postsurgical Total Opioid Consumption (OMED mg) Through 72 hours by Site - Efficacy Analysis Set

Site	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
101	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
102	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
...	...	...	...
999	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
Overall	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx

Note to programmer: *Present for each site. Do not split a site's statistics across pages.*

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Table 14.2-1.2a: Analysis of Postsurgical Total Opioid Consumption (OMED mg) Through 24 and 48 hours, and Day 7 (168 hours) and Day 14 (336 hours) - Efficacy Analysis Set

	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
0-24 hrs	LS Mean [1]	xxx.x	xxx.x
	Standard Error of LS Mean [1]	xxx.xx	xxx.xx
	% Reduction [2]	xxx.xx	
	LSM Treatment Difference Difference [1][3]	xx.x	
	95% Confidence Interval [1][3]	(xx.x, xx.x)	
	P-value, 1-sided [1][3]	0.xxx	
0-48 hrs	LS Mean [1]	xxx.x	xxx.x
	Standard Error of LS Mean [1]	xxx.xx	xxx.xx
	% Reduction [2]	xxx.xx	
	LSM Treatment Difference Difference [1][3]	xx.x	
	95% Confidence Interval [1][3]	(xx.x, xx.x)	
	P-value, 1-sided [1][3]	0.xxx	
. . .			

LS = Least Square; LSM2 = LS Means in IR Bupivacaine group; LSM1 = LS Means in EXPAREL 266 mg group.
[1] From an ANCOVA with main effects of treatment and site and covariates of age and height on total opioid consumption. Subjects without any opioid use are assigned a value of 0 mg for summaries.
[2] % Reduction in Total Opioid Dose is calculated as (LSM2-LSM1)/LSM2*100%.
[3] Test of Ha: LSM (EXPAREL 266 mg) < LSM (IR Bupivacaine).

Note to programmer: *Time periods to appear on this table, in order, are 0-24 hrs, 0-48 hrs, 0-Day 7 (168 hrs) and 0-Day 14 (336 hrs). Do not split a time period statistics across pages.*

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Table 14.2-1.2b: Summary of Postsurgical Total Opioid Consumption (OMED mg) Through 24 and 48 Hours, and Day 7 (168 hrs) and Day 14 (336 hours) by Site - Efficacy Analysis Set

Site Time Interval	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
101			
0-24 hrs	N	xx	xx
	Mean	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Min, Max	xx, xx	xx, xx
0-48 hrs	N	xx	xx
	Mean	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Min, Max	xx, xx	xx, xx
0-Day 7 (168 hrs)			
0-Day 14 (336 hrs)			
999			
0-24 hrs	. . .		
0-48 hrs	. . .		
Overall			
. . .			

Use Table 14.2-1.1a and 1.1b shells for

Table 14.2-1.3a: Analysis of Postsurgical Total Opioid Consumption (OMED mg) Through Day 7 – Efficacy Analysis Set

Table 14.2-1.4a: Analysis of Postsurgical Total Opioid Consumption (OMED mg) Through Day 14 – Efficacy Analysis Set

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Table 14.2-1.5a: Subgroup Analysis of Postsurgical Total Opioid Consumption (OMED mg) Through 72 hours by Age – Efficacy Analysis Set

Age	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
<35 years	LS Mean [1]	xxx.x	xxx.x
	Standard Error of LS Mean [1]	xxx.xx	xxx.xx
	% Reduction [2]	xxx.x	
	LSM Treatment Difference Difference [1][3]	xx.x	
	95% Confidence Interval [1][3]	(xx.x, xx.x)	
	P-value, 1-sided [1][3]	0.xxx	
>= 35 years	LS Mean [1]	xxx.x	xxx.x
	Standard Error of LS Mean [1]	xxx.xx	xxx.xx
	% Reduction [2]	xxx.x	
	LSM Treatment Difference Difference [1][3]	xx.x	
	95% Confidence Interval [1][3]	(xx.x, xx.x)	
	P-value, 1-sided [1][3]	0.xxx	

LS = Least Square; LSM2 = LS Means in IR Bupivacaine group; LSM1 = LS Means in EXPAREL 266 mg group.
[1] From an ANCOVA with main effects of treatment and covariates of age and height on total opioid consumption. Subjects without any opioid use are assigned a value of 0 mg for summaries.
[2] % Reduction in Total Opioid Dose is calculated as (LSM2-LSM1)/LSM2*100%.
[3] Test Ha: LSM (EXPAREL 266 mg) < LSM (IR Bupivacaine).

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Table 14.2-1.5b: Subgroup Summary of Postsurgical Total Opioid Consumption (OMED mg) Through 72 hours by Age – Efficacy Analysis Set

Age	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
<35 years	N	xx	xx
	Mean	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Min, Max	xx, xx	xx, xx
>= 35 years	N	xx	xx
	Mean	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Min, Max	xx, xx	xx, xx

Use Table 14.2-1.5a and 1.5b shell for (see SAP Section 9.7.2.1.1 for subgroup categories)

Table 14.2-1.6a: Subgroup Analysis of Postsurgical Total Opioid Consumption (OMED mg) Through 72 hours by Race – Efficacy Analysis Set

Table 14.2-1.6b: Subgroup Summary of Postsurgical Total Opioid Consumption (OMED mg) Through 72 hours by Race – Efficacy Analysis Set

Table 14.2-1.7a: Subgroup Analysis of Postsurgical Total Opioid Consumption (OMED mg) Through 72 hours by BMI Status – Efficacy Analysis Set

Table 14.2-1.7b: Subgroup Summary of Postsurgical Total Opioid Consumption (OMED mg) Through 72 hours by BMI Status – Efficacy Analysis Set

Table 14.2-1.8a: Subgroup Analysis of Postsurgical Total Opioid Consumption (OMED mg) Through 72 hours by Number of Prior C-Sections – Efficacy Analysis Set

Table 14.2-1.8b: Subgroup Summary of Postsurgical Total Opioid Consumption (OMED mg) Through 72 hours by Number of Prior C-Sections – Efficacy Analysis Set

Table 14.2-1.9a: Subgroup Analysis of Postsurgical Total Opioid Consumption (OMED mg) Through 72 hours by Discharge Time – Efficacy Analysis Set

Table 14.2-1.9b: Subgroup Summary of Postsurgical Total Opioid Consumption (OMED mg) Through 72 hours by Discharge Time – Efficacy Analysis Set

Table 14.2-1.10a: Subgroup Analysis of Postsurgical Total Opioid Consumption (OMED mg) Through 72 hours by Anxiety Medical History – Efficacy Analysis Set

Table 14.2-1.10b: Subgroup Summary of Postsurgical Total Opioid Consumption (OMED mg) Through 72 hours by Anxiety Medical History – Efficacy Analysis Set

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Table 14.2-2.1: Analysis of Opioid-Sparing Subjects through 72 hours - Efficacy Analysis Set

	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
No Opioid-Spared Percentage [1]	(%)	xx.x	xx.x
Opioid-Spared Percentage	(%)	xx.x	xx.x
	Odds Ratio [2]	xx.x	
	95% CI for Odds Ratio	(xx.x, xx.x)	
	P-value, 1-sided [3]	0.xxxx	

[1] LS Means probability from the logistic regression with treatment, site, age, and height as explanatory variables.
[2] OR of EXPAREL 266 mg over IR Bupivacaine.
[3] Test of Ha: Odds Ratio >1.

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Table 14.2-2.2: Summary of Opioid-Sparing Subjects through 72 hours by Site - Efficacy Analysis Set

Site Opioid Use	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
101			
Opioid-Spared	n (%)	xx (xx.x)	xx (xx.x)
No Opioid-Spared	n (%)	xx (xx.x)	xx (xx.x)
...			
999			
Opioid-Spared	n (%)	xx (xx.x)	xx (xx.x)
No Opioid-Spared	n (%)	xx (xx.x)	xx (xx.x)
Overall			
Opioid-Spared	n (%)	xx (xx.x)	xx (xx.x)
No Opioid-Spared	n (%)	xx (xx.x)	xx (xx.x)

Note to programmer: *Present for each site. Do not split a site's statistics across pages.*

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Table 14.2-3.1a: Analysis of AUC for VAS Pain Intensity Scores Through 72 hours – Efficacy Analysis Set - Multiple Imputation Results

Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
LS Mean [1]	xxx.x	xxx.x
Standard Error of LS Mean	xxx.xx	xxx.xx
LSM Treatment Difference Difference [1]	xx.x	
95% Confidence Interval [2]	(xx.x, xx.x)	
Noninferiority Test P-value, 1-sided	0.xxx	
Superiority Test P-value, 1-sided	0.xxx	

LS = least squares.
AUC = area under the curve calculated using the trapezoidal method.
VAS = 10 cm visual analog scale for pain, where 0 = no pain and 10 = worst possible pain.
[1] From an ANCOVA with main effects of treatment and site and covariates of age and height.
[2] The non-inferiority of EXPAREL 266 mg to IR Bupivacaine is demonstrated if the upper limit is <=36. The superiority is demonstrated if the upper limit is <0.

Programming note: if Superiority test fails, ie, p>0.05, then keep non-inferiority test and remove superiority test. Otherwise, remove non-inferiority test and keep superiority test.

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Table 14.2-3.1b: Summary of AUC for VAS Pain Intensity Scores Through 72 hours by Site – Efficacy Analysis Set

Site	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
101	N	xx	xx
	Mean	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Min, Max	xx, xx	xx, xx
...	...	...	...
999	N	xx	xx
	Mean	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Min, Max	xx, xx	xx, xx
	Min, Max	xx	xx
Overall	N	xx	xx
	Mean	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Min, Max	xx, xx	xx, xx

AUC = area under the curve calculated using the trapezoidal method.
VAS = 10 cm visual analog scale for pain, where 0 = no pain and 10 = worst possible pain.

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Table 14.2-3.2a: Analysis of AUC for VAS Pain Intensity Scores at Rest from 0 to 12 hours, 0 to 24 hours, 0 to 48 hours, 24 to 48 hours, and 48 to 72 hours - Efficacy Analysis Set

Time Point	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
0-24	LS Mean [1]	xxx.x	xxx.x
	Standard Error of LS Mean	xxx.xx	xxx.xx
	LSM Treatment Difference [1]	xx.x	
	95% Confidence Interval	(xx.x, xx.x)	
	P-value, 1-sided [2]	0.xxxx	
Etc.	LS Mean [1]	xxx.x	xxx.x
	Standard Error of LS Mean	xxx.xx	xxx.xx
	LSM Treatment Difference [1]	xx.x	
	95% Confidence Interval	(xx.x, xx.x)	
	P-value, 1-sided [2]	0.xxxx	

LS = least squares;
AUC = area under the curve calculated using the trapezoidal method;
VAS = 10 cm visual analog scale for pain, where 0 = no pain and 10 = worst possible pain;
[1] From an ANCOVA with main effects of treatment and site and covariates of age and height.
[2] Test of Ha: LSM (EXPAREL 266 mg) < LSM (IR Bupivacaine).

Note to programmer: VAS Pain Intensity Score to be presented on this table are, in order, 0-12, 0-24, 0-48, 24-48, 24-48 and 48-72. Do not break statistics across pages.

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Table 14.2-3.2b: Summary of AUC for VAS Pain Intensity Scores at Rest from 0 to 12 hours, 0 to 24 hours, 0 to 48 hours, 24 to 48 hours, and 48 to 72 hours - Efficacy Analysis Set

Time Point	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
0-24	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xxx.x	xxx.x
	Min, Max	xx, xx	xx, xx
Etc.	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xxx.x	xxx.x
	Min, Max	xx, xx	xx, xx

Note to programmer: VAS Pain Intensity Score to be presented on this table are, in order, 0-12, 0-24, 0-48, 24-48, 24-48 and 48-72. Do not break statistics across pages.

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Table 14.2-4: Analysis of Time to First Opioid Rescue Medication Use (hours) - Efficacy Analysis Set

	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
Number of Subjects on			
Rescue Medication (Opioid)	n (%)	xx (xx.x)	xx (xx.x)
No Rescue Medication (censored)	n (%)	xx (xx.x)	xx (xx.x)
Time to Rescue			
Quartiles [1]			
First (25% rescued)	Estimate	xx.xx	xx.xx
	(95% CI)	(xx.xx, xx.xx)	(xx.xx, xx.xx)
Median (50% rescued)	Estimate	xx.xx	xx.xx
	(95% CI)	(xx.xx,xx.xx)	(xx.xx,xx.xx)
Third (75% rescued)	Estimate	xx.xx	xx.xx
	(95% CI)	(xx.xx,xx.xx)	(xx.xx,xx.xx)
Minimum	Observed	xx.xx	xx.xx
Maximum	Observed	xx.xx*	xx.xx
P-value, 2-sided [2]		0.xxxx	

* indicates censored observation. CI = confidence interval
[1] Estimates from the adjusted survival curve with site, age, and height as confounders.
[2] P-value for the EXPAREL 266 mg to IR Bupivacaine comparison using the Cox regression model with treatment and site as factors and age and height as covariates.

Use Table 14.2-2.1 shell for

Table 14.2-5.1: Analysis of Opioid-Free Subjects Through 72 hours - Efficacy Analysis Set

Use Table 14.2-2.2 shell for

Table 14.2-5.2: Summary of Opioid-Free Subjects Through 72 hours by Site - Efficacy Analysis Set

Use Table 14.2-3.1a and 3.1b shell for

Table 14.2-6.1a: Analysis of Summed Pain Intensity Scores (SPIS) Through 72 hours– Efficacy Analysis Set - Multiple Imputation Results

Replace "<=36" with "<=4.5" in Footnote 2.

Table 14.2-6.1b: Summary of Summed Pain Intensity Scores (SPIS) Through 72 hours by Site – Efficacy Analysis Set - Multiple Imputation Results

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Table 14.2-7a: Analysis of Integrated Rank Assessment Using SPIS at Rest and OMED of Rescue Medications Through 24, 48, and 72 hours - Efficacy Analysis Set

Time Period	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
0-72 hours	LS Mean [1]	xxx.x	xxx.x
	Standard Error of LS Mean [1]	xxx.xx	xxx.xx
	LSM Treatment Difference Difference [1][2]	xx.x	
	95% Confidence Interval [1][2]	(xx.x, xx.x)	
	P-value, 1-sided [1][2]	0.xxx	
0-48 hours	. . .		
0-24 hours	. . .		

LS = least squares;
VAS = 10 cm visual analog scale for pain, where 0 = no pain and 10 = worst possible pain;
[1] From an ANCOVA with main effects of treatment and site covariates of age and height.
[2] Test of Ha: LSM (EXPAREL 266 mg) < LSM (IR Bupivacaine).

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Table 14.2-7b: Summary of Integrated Rank Assessment Using SPIS at Rest and OMED of Rescue Medications Through 24, 48, and 72 hours - Efficacy Analysis Set

Time Period	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
0-72 hours	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
0-48 hours	. . .		
0-24 hours	. . .		

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Table 14.2-8a: Analysis of Overall Benefit of Analgesia Scale (OBAS) by Timepoint and Question - Efficacy Analysis Set

Timepoint Question	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
24 hours			
Total Score	LS Mean [1]	xxx.x	xxx.x
	Standard Error of LS Mean	xxx.xx	xxx.xx
	LSM Treatment Difference [1]	xx.x	
	95% Confidence Interval	(xx.x, xx.x)	
	P-value, 1-sided [2]	0.xxxx	
1. Current Pain	LS Mean [1]	xxx.x	xxx.x
	Standard Error of LS Mean	xxx.xx	xxx.xx
	LSM Treatment Difference [1]	xx.x	
	95% Confidence Interval	(xx.x, xx.x)	
	P-value, 1-sided [2]	0.xxxx	

Total score = sum of scores from questions 1 to 6 plus 4 minus question 7 score.
[1] From an ANCOVA with main effects of treatment and site and covariates of age and height.
[2] For Total and Questions 1 to 6 scores, Test of Ha: LSM (EXPAREL 266 mg) < LSM (IR Bupivacaine). For Question 7 score, Test of Ha: LSM (EXPAREL 266 mg) > LSM (IR Bupivacaine).

Note to programmer: *Timepoints to appear on this table, in order, are 24 and 72 hours and Day 10. Questions to appear on this table, in order, are 'Total Score', '1. Current Pain', '2. Vomiting', '3. Itching', '4. Sweating', '5. Freezing', '6. Dizziness', and '7. Satisfaction'. Do not split a question's statistics across pages. P-Values should only be generated for 'Total score'.*

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Table 14.2-8b: Summary of Overall Benefit of Analgesia Scale (OBAS) by Timepoint and Question - Efficacy Analysis Set

Timepoint Question	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
24 hours			
Total Score	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx	xx
	Min, Max	xx, xx	xx, xx
1. Current Pain	n	xx	xx
	Mean	xx.x	xx.x
	SD	xx.xx	xx.xx
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx

Total score = sum of scores from questions 1 to 6 plus 4 minus question 7 score.

Note to programmer: *Timepoints to appear on this table, in order, are 24 and 72 hours and Day 10. Questions to appear on this table, in order, are 'Total Score', '1. Current Pain', '2. Vomiting', '3. Itching', '4. Sweating', '5. Freezing', '6. Dizziness', and '7. Satisfaction'. Do not split a question's statistics across pages.*

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Table 14.2-9a: Analysis of Time Spent in Post-Anesthesia Care Unit (PACU) – Efficacy Analysis Set

Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
LS Mean [1]	xxx.x	xxx.x
Standard Error of LS Mean [1]	xxx.xx	xxx.xx
LSM Treatment Difference Difference [1][2]	xx.x	
95% Confidence Interval [1][2]	(xx.x, xx.x)	
P-value, 1-sided [1][2]	0.xxxx	

[1] From an ANCOVA with main effects of treatment and site and covariates of age and height on time spent in PACU.

[2] Test of Ha: LSM (EXPAREL 266 mg) < LSM (IR Bupivacaine).

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Table 14.2-9b: Summary of Time Spent in Post-Anesthesia Care Unit (PACU) – Efficacy Analysis Set

Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
N	xx	xx
Mean	xxx.x	xxx.x
SD	xxx.xx	xxx.xx
Median	xxx.x	xxx.x
Min, Max	xx, xx	xx, xx

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Table 14.2-10: Summary of Time to First Unassisted Ambulation - Efficacy Analysis Set

	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
Number of Subjects			
Achieved Unassisted Ambulation	n (%)	xx (xx.x)	xx (xx.x)
Did not Achieve Unassisted Ambulation	n (%)	xx (xx.x)	xx (xx.x)
Time to First Unassisted Ambulation			
Quartiles [1]			
First (25% Discharge Ready)	Estimate	xx.xx	xx.xx
	(95% CI)	(xx.xx,xx.xx)	(xx.xx,xx.xx)
Median (50% Discharge Ready)	Estimate	xx.xx	xx.xx
	(95% CI)	(xx.xx,xx.xx)	(xx.xx,xx.xx)
Third (75% Discharge Ready)	Estimate	xx.xx	xx.xx
	(95% CI)	(xx.xx,xx.xx)	(xx.xx,xx.xx)
Minimum	Observed	xx.xx	xx.xx
Maximum	Observed	xx.xx*	xx.xx
P-value, 2-sided [2]		0.xxxx	

* indicates censored observation CI = confidence interval

[1] Estimates from the adjusted survival curve with site, age, and height as confounders.

[2] P-value from the EXPAREL 266 mg to IR Bupivacaine comparison using the Cox regression model with treatment and site as factors and age and height as covariates.

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Table 14.2-11a: Analysis of Subjects Meeting Modified Post Anesthesia Discharge Scoring System (MPADSS) Criteria for Discharge Readiness at Each Assessed Timepoint - Efficacy Analysis Set

Time Point	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
24	Criterion Met [1] (%) [2]	xx.x	xx.x
	Criterion not Met (%)	xx.x	xx.x
	Odds Ratio [3]	xx.xx	
	95% CI for Odds Ratio	xx.xxx	
	P-value, 1-sided [4]	0.xxxx	
Etc.	Criterion Met (%)	xx.x	xx.x
	Criterion not Met (%)	xx.x	xx.x
	Odds Ratio	xx.xx	
	95% CI for Odds Ratio	xx.xxx	
	P-value, 1-sided	0.xxxx	

[1] Discharge-ready criterion is the MPADSS total score ≥9. Subjects who did not have assessment are considered "not ready".
[2] LS Means probability from the logistic regression with treatment, site, age, and height as explanatory variables.
[3] Ratio of EXPAREL 266 mg over IR Bupivacaine in the odds of having 0 phone call.
[4] Test of Ha: Odds Ratio >1

***Note to programmer: Repeat for all valid** Time periods for which data is available. Do not split a time period statistics across pages.*

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Table 14.2-11b: Summary of Subjects Meeting Modified Post Anesthesia Discharge Scoring System (MPADSS) Criteria for Discharge Readiness at Each Assessed Timepoint - Efficacy Analysis Set

Time Point	Statistic	EXPAREL 266 mg (N=XX) n (%)	IR Bupivacaine (N=XX) n (%)
24	Criterion Met [1] (%)	xx (xx.x)	xx (xx.x)
	Criterion not Met (%)	xx (xx.x)	xx (xx.x)
Etc.	Criterion Met (%)	xx (xx.x)	xx (xx.x)
	Criterion not Met (%)	xx (xx.x)	xx (xx.x)

[1] Discharge-ready criterion is the MPADSS total score ≥9. Subjects who did not have assessment are considered "not ready".

***Note to programmer: Repeat for all valid** Time periods for which data is available. Do not split a time period statistics across pages.*

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Table 14.2-12: Summary of Overall Assessment of Subject's Satisfaction with Postsurgical Pain Control at 72 hours After Surgery - Efficacy Analysis Set

Score	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
Summary	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
	P-value, 2-sided[1]	0.xxxx	
Score			
1: Extremely dissatisfied	n (%)	xx (xx.x)	xx (xx.x)
2: Dissatisfied	n (%)	xx (xx.x)	xx (xx.x)
3: Neither satisfied nor dissatisfied	n (%)	xx (xx.x)	xx (xx.x)
4: Satisfied	n (%)	xx (xx.x)	xx (xx.x)
5: Extremely Satisfied	n (%)	xx (xx.x)	xx (xx.x)

[1] P-value from CMH test performed using the "scores=modridit" option with site as stratification

Note to programmer: *include all subjects at 72 hours after surgery (or at hospital discharge if earlier than 72 hours).*

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Table 14.2-13a: Analysis of Quality of Recovery Questionnaire at 72 hours Postsurgery - Efficacy Analysis Set (Only Include Subjects who Completed the Correct QoR-15 Form)

	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
Overall Summary	LS Mean [1]	xxx.x	xxx.x
	Standard Error of LS Mean	xxx.xx	xxx.xx
	LSM Treatment Difference [1]	xx.x	
	95% Confidence Interval	(xx.x, xx.x)	
	P-value, 1-sided [2]	0.xxxx	
Question 3 (Feeling rested: 0=none, 10=all the time)	LS Mean [1]	xxx.x	xxx.x
	Standard Error of LS Mean	xxx.xx	xxx.xx
	LSM Treatment Difference [1]	xx.x	
	95% Confidence Interval	(xx.x, xx.x)	
	P-value, 1-sided [2]	0.xxxx	
Question 4 (Have had a good sleep: 0=none, 10=all the time)	LS Mean [1]	xxx.x	xxx.x
	Standard Error of LS Mean	xxx.xx	xxx.xx
	LSM Treatment Difference [1]	xx.x	
	95% Confidence Interval	(xx.x, xx.x)	
	P-value, 1-sided [2]	0.xxxx	
Question 14 (Feeling worried or anxious: 10=none, 0=all the time)	LS Mean [1]	xxx.x	xxx.x
	Standard Error of LS Mean	xxx.xx	xxx.xx
	LSM Treatment Difference [1]	xx.x	
	95% Confidence Interval	(xx.x, xx.x)	
	P-value, 1-sided [2]	0.xxxx	

Question 15 (Feeling sad or depressed: 10=none, 0=all the time)	LS Mean [1]	xxx.x	xxx.x
	Standard Error of LS Mean	xxx.xx	xxx.xx
	LSM Treatment Difference [1]	xx.x	
	95% Confidence Interval	(xx.x, xx.x)	
	P-value, 1-sided [2]	0.xxxx	

[1] From an ANCOVA with main effects of treatment and site and covariates of age and height.
[2] Test of Ha: LSM (EXPAREL 266 mg) < LSM (IR Bupivacaine).

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Table 14.2-13b: Summary of Quality of Recovery Questionnaire at 72 hours Postsurgery - Efficacy Analysis Set (Only Include Subjects who Completed the Correct QoR-15 Form)

	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
Overall Summary	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx	xx
	Min, Max	xx,xx	xx, xx
Question 3 (Feeling rested: 0=none, 10=all the time)	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx	xx
	Min, Max	xx,xx	xx, xx
Question 4 (Have had a good sleep: 0=none, 10=all the time)	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx	xx
	Min, Max	xx,xx	xx, xx
Question 14 (Feeling worried or anxious: 10=none, 0=all the time)	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx	xx
	Min, Max	xx,xx	xx, xx

	Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
Question 15 (Feeling sad or depressed: 10=none, 0=all the time)	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Median	xx	xx
	Min, Max	xx,xx	xx, xx

[1] P-value from CMH test performed using the "scores=modridit" option with site as stratification factors.

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Table 14.2-14a: Analysis of Subjects with Unscheduled Pain-Related Phone Calls - Efficacy Analysis Set

Statistic	EXPAREL 266 mg (N=XX)	IR Bupivacaine (N=XX)
0 (%) [1]	xx.x	xx.x
>=1 (%)	xx.x	xx.x
Odds Ratio [2]	xx.xx	
95% CI for Odds Ratio	xx.xxx	
P-value, 1-sided [3]	0.xxxx	

[1] LS Means probability from the logistic regression with treatment, site, age, and height as explanatory variables.
[2] Ratio of EXPAREL 266 mg over IR Bupivacaine in the odds of having 0 phone call.
[3] Test of Ha: Odds Ratio >1

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Table 14.2-14b: Summary of Number of Unscheduled Pain-Related Phone Calls - Efficacy Analysis Set

Number of Calls	EXPAREL 266 mg (N=XX) n (%)	IR Bupivacaine (N=XX) n (%)
0	xx (xx.x)	xx (xx.x)
1	xx (xx.x)	xx (xx.x)
2	xx (xx.x)	xx (xx.x)

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Table 14.3-1.1: Overview of Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set

Number of	EXPAREL 266 mg (N=XX) n (%)	IR Bupivacaine (N=XX) n (%)	Total (N=XX) n (%)
Subjects with Any TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Maximum Severity of Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)
Maximum Severity of Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)
Maximum Severity of Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)
At Least One Related	xx (xx.x)	xx (xx.x)	xx (xx.x)
At Least One Serious	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject with Any TEAESI	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects Discontinued due to TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Died on Study	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note to programmer: All categories on this table should appear, even if not present in the data.

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Table 14.3-1.2.1: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) by Preferred Term - Safety Analysis Set

Preferred Term	EXPAREL 266 mg (N=XX) n (%)	IR Bupivacaine (N=XX) n (%)	Total (N=XX) n (%)
Subjects with ≥1 TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT2	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT3	xx (xx.x)	xx (xx.x)	xx (xx.x)
...	xx (xx.x)	xx (xx.x)	xx (xx.x)

Adverse events coded using the Medical Dictionary for Regulatory Activities (MedDRA v21.1).
Sorted by descending order of Total incidence.
Subjects experiencing the same TEAE more than once are counted only once at each summary level.

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Table 14.3-1.2.2: Summary of Subject Incidence of Treatment-Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term - Safety Analysis Set

System Organ Class Preferred Term	EXPAREL 266 mg (N=XX) n (%)	IR Bupivacaine (N=XX) n (%)	Total (N=XX) n (%)
Subjects with ≥1 TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT1.1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT1.2	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC2	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT2.1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT2.2	xx (xx.x)	xx (xx.x)	xx (xx.x)
	xx (xx.x)	xx (xx.x)	xx (xx.x)
ETC.			

Adverse events coded using the Medical Dictionary for Regulatory Activities (MedDRA v21.1).
Sorted by system organ class and preferred term in alphabetical order.
Subjects experiencing the same TEAE more than once are counted only once at each summary level.

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Table 14.3-1.3: Summary of Subject Incidence of Treatment-Emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term, and Worst Severity - Safety Analysis Set

System Organ Class Preferred Term	Worst Severity	EXPAREL 266 mg (N=XX) n (%)	IR Bupivacaine (N=XX) n (%)	Total (N=XX) n (%)
Subjects with ≥1 TEAE	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC1	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT1.1	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT1.2	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)

...

Adverse events coded using the Medical Dictionary for Regulatory Activities (MedDRA v21.1).
Sorted by descending order of Total incidence by system organ class and preferred term.
Subjects experiencing the same TEAE more than once are counted only once at each summary level.

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Table 14.3-1.4: Summary of Subject Incidence of Treatment-Emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term, and Strongest Relationship to Study Drug - Safety Analysis Set

System Organ Class Preferred Term	Strongest Relation	EXPAREL 266 mg (N=XX) n (%)	IR Bupivacaine (N=XX) n (%)	Total (N=XX) n (%)
Subjects with ≥1 TEAE	Not Related	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Related	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC1	Not Related	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Related	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT1.1	Not Related	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Related	xx (xx.x)	xx (xx.x)	xx (xx.x)

Adverse events coded using the Medical Dictionary for Regulatory Activities (MedDRA v21.1).
Sorted by descending total incidence by system organ class and preferred term within system organ class.
Subjects experiencing the same TEAE more than once are counted only once at each summary level.
"Related" is "possible", "probable", or "definite" and "Not Related" is "unlikely" or "unrelated" by the investigator's assessment.

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Table 14.3-1.5: Summary of Subject Incidence of Treatment-Emergent Adverse Events of Special Interest (TEAESI) by Preferred Term - Safety Analysis Set

Group Preferred Term	EXPAREL 266 mg (N=XX) n (%)	IR Bupivacaine (N=XX) n (%)	Total (N=XX) n (%)
Subjects with ≥1 TEAESI	xx (xx.x)	xx (xx.x)	xx (xx.x)
	xx (xx.x)	xx (xx.x)	xx (xx.x)
FALL	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cardiac TEAESI	xx (xx.x)	xx (xx.x)	xx (xx.x)
Angina	xx (xx.x)	xx (xx.x)	xx (xx.x)
Myocardial infarction	xx (xx.x)	xx (xx.x)	xx (xx.x)
...			
Neurologic TEAESI	xx (xx.x)	xx (xx.x)	xx (xx.x)
Tinnitus	xx (xx.x)	xx (xx.x)	xx (xx.x)
Perioral numbness	xx (xx.x)	xx (xx.x)	xx (xx.x)
...			

Adverse events coded using the Medical Dictionary for Regulatory Activities (MedDRA 21.1).
Sorted by system organ class and preferred term in alphabetical order.
Subjects experiencing the same TEAE more than once are counted only once at each summary level.

Note to programmer: *see SAP the list of AESI*

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Table 14.3-2: Summary of Vital Signs by Timepoint – Safety Analysis Set

Heart Rate (bpm)

Timepoint	Value	Statistic	EXPAREL 266 mg (N=XXX)	IR Bupivacaine (N=XXX)	Total (N=XXX)
Baseline	Actual	n	xx	xx	xx
		Mean	xx.x	xx.x	xx.x
		SD	x.xx	x.xx	x.xx
		Minimum	xx	xx	xx
		Median	xx.x	xx.x	xx.x
		Maximum	xx	xx	xx
OR	Baseline [1]	n	xx	xx	xx
		Mean	xx.x	xx.x	xx.x
		SD	x.xx	x.xx	x.xx
		Minimum	xx	xx	xx
		Median	xx.x	xx.x	xx.x
		Maximum	xx	xx	xx
	Actual	n	xx	xx	xx
		Mean	xx.x	xx.x	xx.x
		SD	x.xx	x.xx	x.xx
		Minimum	xx	xx	xx
		Median	xx.x	xx.x	xx.x
		Maximum	xx	xx	xx
	Change	n	xx	xx	xx
		Mean	xx.x	xx.x	xx.x
		SD	x.xx	x.xx	x.xx
		Minimum	xx	xx	xx
		Median	xx.x	xx.x	xx.x
		Maximum	xx	xx	xx

[1] Baseline (prior to surgery) for subjects with data at the timepoint.

Note to programmer: *Vital signs are 'Resting Heart Rate (bpm)', 'Systolic Blood Pressure (mmHg)' and 'Diastolic Blood Pressure (mmHg)'. Timepoints to appear on this table are, in order of appearance, Baseline (prior to surgery), OR, PACU and Discharge. Do not split timepoint statistics across pages.*

Note to programmer: *Use mock-up 14.1-5.1 for tables:*

Table 14.3-3.1: Incidence of Prior Medications – Safety Analysis Set.

On this table change the footnote 'Intraoperatives medications are those indicated as such by the investigator' to read 'Prior medications are those stopped before start of study drug administration.'

Table 14.3-3.2: Incidence of Concomitant Medications – Safety Analysis Set.

On this table change the footnote 'Intraoperatives medications are those indicated as such by the investigator' to read 'Concomitant medications are those taken after the start of study drug administration and are not designated intraoperative medications.'

15. LIST OF LISTINGS

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Listing 16.2-1: Subject Disposition – All Randomized Subjects

TREATMENT: *treatment-name*

Subject	Date of Last Visit (Day)	End of Study Status	Specify
XXX-YYYY	DDMONYYYY (XX)		

Note to programmer: *End of study status for subject who early terminated from the study is the primary reason for termination. If subject discontinued due to an AE then the reason should read 'ADVERSE EVENT, AE # X'. If subject discontinued due to death the reason should read 'DEATH ON DDMONYYYY'. For those reasons that also collected a specify text, that text belongs in the specify column.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-2: Randomization and Analysis Sets – All Randomized Subjects

	Randomization			
Subject	Date and Time	Number	Safety	Efficacy
XXX-YYYY	DDMONYYYYTHH:MM	XXXXX	X	X

Note to programmer: *Analysis set will by 'Y' if subject in set, blank otherwise.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-3: Demographics – All Randomized Subjects

TREATMENT: *treatment-name*

Subject	Initials	Birth Date	Age(yrs)	Sex	Race	Ethnicity	ASA Class
XXX-YYYY	AMZ	DDMONYYYY	XX	XXXXXX	XXXXXXXXX	XXXXXXXXX	X

Note to programmer: *If race is 'other' then race should be 'Other: other-specify-text'.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-4: Height and Weight – All Randomized Subjects

TREATMENT: *treatment-name*

Subject	Collection Date (Day)	Height (cm)	Weight (kg)	Body Mass Index (kg/m^2)
XXX-YYYY	DDMONYYYYTHH:MM (-XX)	XXX.X	XXX.X	XX.X

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-5: Surgery – All Randomized Subjects

TREATMENT: *treatment-name*

Subject	Date (Day)	Start Time	Stop Time	Duration (hrs)	Location	Incision Length (cm)	IR Bupivacaine Admin Time	Anesthesia Type
XXX-YYYY	DDMONYYYY (XX)	HH:MM	HH:MM	X.X	XXXXX	XX.X	HH:MM	

Note to programmer: *If anesthesia type is 'other' then text should read 'other: specify-text'.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-6: Visual Analog Scale (VAS) – All Randomized Subjects

TREATMENT: *treatment-name*

Subject	Date Time (Day)	Time From Dose: Scheduled (hr)	Time From Dose: Actual (hr)	Time From Dose: Deviation (hrs)	VAS (cm)	Pain-Free (VAS ≤ 1.5cm)
XXX-YYYY	DDMONYYYYTHH:MM (X)	XX.XX	XX.XX	XXXX	XX.X	Y

VAS: 0=No pain to 10=Worst Pain Imaginable ND=Not Done NA=Not Applicable
* = out of window

Note to programmer: *Sort by VAS collection date and time. If VAS was taken due to rescue medication dosing, put RESCUE in scheduled column and hours from dose in actual column – leave deviation column blank. Do not split a subject's data across pages if it can be avoided. Pain-free will have Y if VAS ≤ 1.5 otherwise blank. An asterisk (*) will be placed next to the deviation if an assessment is out of window. See Table of Time and Events for windows.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-7.1: Postsurgical Total Opioid Dose (OMED mg) and Opioid-free Status – All Randomized Subjects

Subject	0 to ≤72 hrs	0 to ≤24 hrs	0 to ≤48 hrs	>24 to ≤48hrs	>48 to ≤72hrs	Opioid-Free
XXX-YYYY	XXXX.X	XXXX.X	XXXX.X	XXXX.X	XXXX.X	NO
XXX-YYYY	-	-	-	-	-	YES

Total dose is dose from end of surgery through timepoint.

Note to programmer: *If medication is 'Other', text should read 'Other: specify-text'. Sort by date and time within subject.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-7.2: Postsurgical Opioid Dosing – All Randomized Subjects

TREATMENT: *treatment-name*

Subject	Date and Time	Time to Dosing (hr)	Medication	Dose (units)	Conversion Factor	Dose (OMED mg)	Route
XXX-YYYY	DDMONYYYYTHH:MM	XXX.X	XXXXXXXXXXXX	(XXXXX)	X.XX	XXX.X	XXXXXXX
	DDMONYYYYTHH:MM	XXX.X	XXXXXXXXXXXX	(XXXXX)	X.XX	XXX.X	XXXXXXX
	DDMONYYYYTHH:MM	XXX.X	XXXXXXXXXXXX	(XXXXX)	X.XX	XXX.X	XXXXXXX
	DDMONYYYYTHH:MM	XXX.X	XXXXXXXXXXXX	(XXXXX)	X.XX	XXX.X	XXXXXXX

Time to rescue is time from end of surgery to rescue medication dose.

Note to programmer: *If medication is 'Other', text should read 'Other: specify-text'. Sort by date and time within subject.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411

Listing 16.2-8.1: Quality of Recovery (QoR-15) – Question Text

Question No.	Question Text
1	Able to breathe easily
2	Been able to enjoy food
3	Feeling rested
4	Have had a good sleep
5	Able to look after personal toilet and hygiene unaided
6	Able to communicate with family or friends
7	Getting support from hospital doctors and nurses
8	Able to return to work or usual home activities
9	Feeling comfortable and in control
10	Having a feeling of general well-being
11	Moderate pain
12	Severe pain
13	Nausea or vomiting
14	Feeling worried or anxious
15	Feeling sad or depresse

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-8.2: Quality of Recovery (QoR-15) – All Randomized Subjects

TREATMENT: *treatment-name*

	Assessment				Question														
Subject	Date and Time (Day)	Scheduled	Actual (hrs)	Deviation (hrs)	1	2	3	4	5	6	7	8	10	11	12	13	14	15	Total Score
XXX-YYYY	DDMONYYYYTHH:MM (XX)	72 hrs	XX.X	XX.X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	XX
	DDMONYYYYTHH:MM (XX)	Discharge	XX.X	XX.X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	XX

Note to programmer: *Sort by date and time within subject.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-9: Overall Benefit of Analgesia – All Randomized Subjects

TREATMENT: *treatment-name*

		Assessment			Question							
Subject	Date and Time (Day)	Schedule (hrs)	Actual (hrs)	Deviation (hrs)	1	2	3	4	5	6	7	Total Score
XXX-YYYY	DDMONYYYYTHH:MM (XX)	24	XX.X	XX.X	X	X	X	X	X	X	X	XX
	DDMONYYYYTHH:MM (XX)	72	XX.X	XX.X	X	X	X	X	X	X	X	XX
	DDMONYYYYTHH:MM (XX)	240 (D10)	XXX.X	XX.X	X	X	X	X	X	X	X	XX

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

Note to programmer: *Sort by date and time within subject.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411

Listing 16.2-10: Subject Satisfaction with Post-Surgical Pain Control at 72 hours – All Randomized Subjects

Treatment: *treatment-name*

Subject	Date and Time (Day)	Rating	Score
XXX-YYYY	DDMONYYYYTHH:MM (XX)	EXTREMELY DISSATISFIED	1
XXX-YYYY	DDMONYYYYTHH:MM (XX)	DISSATISFIED	2
XXX-YYYY	DDMONYYYYTHH:MM (XX)	NEITHER SATISFIED NOR DISSATISFIED	3
XXX-YYYY	DDMONYYYYTHH:MM (XX)	SATISFIED	4
XXX-YYYY	DDMONYYYYTHH:MM (XX)	EXTREMELY SATISIFIED	5
XXX-YYYY	DDMONYYYYTHH:MM (XX)	EXTREMELY SATISIFIED	5

Time to rescue is time from end of surgery to rescue medication dose.

Note to programmer: *Sort by date and time within subject.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411

Listing 16.2-11: Modified Post-Anesthesia Discharge Scoring System (MPADSS) - All Randomized Subjects

TREATMENT: *treatment-name*

	Assessment			Question					
Subject	Date and Time (Day)	Schedule (hrs)	Actual (hrs)	Deviation (hrs)	1	2	3	4	5	Total Score
XXX-YYYY	DDMONYYYYTHH:MM (XX)	24	XX.X	XX.X	X	X	X	X	X	XX
	DDMONYYYYTHH:MM (XX)	48	XX.X	XX.X	X	X	X	X	X	XX

*=out of window
Total score = sum of scores.
1) Vital signs: 2 = ≤ 20%; 1 = 20-40%; 0 = >40% of preoperative value.
2) Ambulation: 2 = steady gait/no dizziness; 1 = with assistance; 0 = none/dizziness
3) Nausea and Vomiting: 2 = minimal; 1 = moderate; 0 = severe
4) Pain: 2 = minimal; 1 = moderate; 0 = severe
5) Surgical bleeding: 2 = minimal; 1 = moderate; 0 = severe

Note to programmer: *Sort by date and time within subject.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-12: Day 14 Phone Call – All Randomized Subjects

TREATMENT: *treatment-name*

		Day 14 Phone Call			No. of Pain-Related Unscheduled				
Subject	Date	Schedule (days)	Actual (days)	Deviation (days)	Phone Calls	Visits	No. of ER Visit	No. of Hosp Readmission	AE Assessed
XXX-YYYY	DDMONYYYY	14	XX.X	XX.X	XX	XX	XXXX	XXXX	Y
XXX-YYYY	DDMONYYYY	14	XX.X	XX.X	XX	XX	XXXX	XXXX	Y
XXX-YYYY	DDMONYYYY	14	XX.X	XX.X	XX	XX	XXXX	XXXX	N

Note to programmer: *If the leading question "were there any …" is No, then "No. of …" is 0.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-13: Vital Signs Assessment – All Randomized Subjects

TREATMENT: *treatment-name*

		Assessment			Heart Rate (bpm)		Blood Pressure (mmHg) Systolic		Blood Pressure (mmHg) Diastolic	
Subject	Date and Time	Schedule (hrs)	Actual (hrs)	Dev. (hrs)	Actual	Change	Actual	Change	Actual	Change
XXX-YYYY	DDMONYYYYTHH:MM	Screening	-	-	XX	-	XXX	-	XX	-
	DDMONYYYYTHH:MM	Baseline	-	-	XX	-	XXX	-	XX	-
	DDMONYYYYTHH:MM	OR	-	-	XX	XX	XXX	-X	XX	X
	DDMONYYYYTHH:MM	PACU	XXX.XX	XXX	XX	-XX	XXX	X	XX	-X

*=out of window @=potentially clinically significant value
Change is change from baseline (Preop).

Note to programmer: *Sort by Date and time within subject. An asterisk (*) will be placed next to the deviation if an assessment is out of window. See Table of Time and Events for windows.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-14: Electrocardiogram Findings at Baseline – Investigator Assessment – All Randomized Subjects
Treatment: *treatment-name*

Subject	Date and Time	Actual (hrs)	Deviation (hrs)	Finding
XXX-YYYY	DDMONYYYYTHH:MM	-	-	Normal
	DDMONYYYYTHH:MM	-	-	Abnormal, clinically significant
	DDMONYYYYTHH:MM	-	-	Abnormal, not clinically significant
	DDMONYYYYTHH:MM	XXX.XX	XXX	Normal
	DDMONYYYYTHH:MM	XXX.XX	XXX	Normal

*=out of window

Note to programmer: *Sort by* Date and *date and time within subject. An asterisk (*) will be placed next to the deviation if an assessment is out of window. See Table of Time and Events for windows.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-15.1: All Adverse Events – All Randomized Subjects

Treatment: *treatment-name*

Subject	TEAE	Data Type		Data
XXX-YYYY	N	Start (Day)		DDMONYYYYTHH:MM (XX)
		Stop (Day)		DDMONYYYYTHH:MM (XX)
		AE Number		X
		System Organ Class		XXXXXXXXXXXXXXXXXX
		Preferred		XXXXXXXXXXXXXXXXXXXX
		Verbatim Severity		XXXXXXXXXXXXXXXXXXXXX
		Relationship		XXXXXXXX
		to Study	Drug	XXXXXXXX
		Action Taken		XXXXXXXXXXXXXXXXXXXX
		Outcome		XXXXXXXXXXXXX
		Serious		Yes/No
		Serious Cause(s)		Hospitalization
		AE of Special Interest		Yes/No

TEAE: Treatment-emergent AE (Y=TEAE/N=Not TEAE)

Note to programmer: *If AE is ongoing, put ONGOING in stop row. Do not split an AE across pages. Insert a page break between subjects. Use this mock-up for the following listings:*

Listing 16.2-15.2: Treatment-emergent Adverse Events – All Randomized Subjects
Listing 16.2-15.3: All Serious Adverse Events – All Randomized Subjects
Listing 16.2-15.4: Treatment-emergent Adverse Events of Special Interest – All Randomized Subjects

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-16.1: Prior Medications – All Randomized Subjects

Treatment: *treatment-name*

Subject	Category	Data Type	Data
XXX-YYYY		Start (Day)	DDMONYYYYTHH:MM (XX)
		Stop (Day)	DDMONYYYYTHH:MM (XX)
		Medication Number	X
		ATC Level 1	XXXXXXXXXXXXXXXXXX
		ATC Level 2	XXXXXXXXXXXXXXXXXXXX
		ATC Level 3	XXXXXXXXXXXXXXXXXXXXX
		ATC Level 4	XXXXXXXXXXXXXXXXXXX
		Preferred Name	XXXXXXXXXXXXXXXXXXXX
		Verbatim	XXXXXXXXXXXXXXXXXXXX
		Route	XXXXXXXX
		Frequency	XXXXXXXX
		Given for AE or MH?	XXXXXXXXXXXXXXXXXXXX AE # XX *(or MH # XX)*

ATC=Anatomical therapeutic class

Note to programmer: *If medication is ongoing, put ONGOING in stop row. Do not split a medication across pages. Insert a page break between subjects. Values for category column are: CONCOMITANT; SURGICAL/ANESTHESIA; NON-MEDICATION; PRIOR. Use this mock-up for the following listings:*

Listing 16.2-16.2: Concomitant Medications – All Randomized Subjects

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-17: Medical History – All Subjects

Treatment: *treatment-name*

Subject	Data Type	Data
XXX-YYYY	Start (Day)	DDMONYYYY (XX)
	Stop (Day)	DDMONYYYY (XX)
	System Organ Class	XXXXXXXXXXXXXXXXXX
	Preferred	XXXXXXXXXXXXXXXXXXXX
	History Verbatim	XXXXXXXXXXXXXXXXXXXXX
	Start (Day)	DDMONYYYY (XX)
	Stop (Day)	DDMONYYYY (XX)
	System Organ Class	XXXXXXXXXXXXXXXXXX
	Preferred	XXXXXXXXXXXXXXXXXXXX
	History Verbatim	XXXXXXXXXXXXXXXXXXXXX

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-18: Intraoperative Opioids – Randomized Subjects

TREATMENT: *treatment-name*

Subject	Administered	Name	Dose	Unit	Route
XXX-YYYY	YES	*OPIOID-NAME*	XXX.XX	(UNITS)	XXXX
XXX-YYYY	NO				

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-19: Study Drug Administration – Randomized Subjects

TREATMENT: *treatment-name*

Subject	Date	Start Time	Stop Time	Total Volume (mL)
XXX-YYYY	DDMONYYYY	HH:MM	HH:MM	XXX

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-20: Urine Drug Screen, Alcohol Blood Test and Pregnancy Test – All Subjects

TREATMENT: *treatment-name*

Subject	Visit	Urine Drug	Blood Alcohol	Pregnancy
XXX-YYYY	Screening	XXXXXXXX	XXXXXXXX	XXXXXXXX
	Day 0 (Preop)	XXXXXXXX	XXXXXXXX	XXXXXXXX
XXX-YYYY	Screening Day	XXXXXXXX	XXXXXXXX	XXXXXXXX
	0 (Preop)	XXXXXXXX	XXXXXXXX	XXXXXXXX
XXX-YYYY	Screening Day	XXXXXXXX	XXXXXXXX	XXXXXXXX
	0 (Preop)	XXXXXXXX	XXXXXXXX	XXXXXXXX
XXX-YYYY	Screening Day	XXXXXXXX	XXXXXXXX	XXXXXXXX
	0 (Preop)	XXXXXXXX	XXXXXXXX	XXXXXXXX

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Listing 16.2-21: Admission and Discharge – Randomized Subjects

TREATMENT: *treatment-name*

	Date and Time (Day)	
Subject	Admission	Discharge
XXX-YYYY	DDMONYYYYTHH:MM (XX)	DDMONYYYYTHH:MM (XX)
XXX-YYYY	DDMONYYYYTHH:MM (XX)	DDMONYYYYTHH:MM (XX)
XXX-YYYY	DDMONYYYYTHH:MM (XX)	DDMONYYYYTHH:MM (XX)

*=out of window
Total score = sum of scores.
1) Vital signs: 2 = ≤ 20%; 1 = 20-40%; 0 = >40% of preoperative value.
2) Ambulation: 2 = steady gait/no dizziness; 1 = with assistance; 0 = none/dizziness
3) Nausea and Vomiting: 2 = minimal; 1 = moderate; 0 = severe
4) Pain: 2 = minimal; 1 = moderate; 0 = severe
5) Surgical bleeding: 2 = minimal; 1 = moderate; 0 = severe

Listing 16.2-22: Important Protocol Deviations - Randomized Subjects

TREATMENT: *treatment-name*

Site	Subject	Date (day)	Epoch	Deviation Code	Description
XXX	XXX-YYYY	DDMONYYYY (XX)	XXX	***Mistakenly Unblinding***	XXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXX

Note to programmer: *Subjects may have multiple deviations. Sort deviations by subject and date.*
Select dvdecod "Mistakenly Unblinding", "Restricted Medications Taken", "Non-Compliance/Ultrasound", "Primary Efficacy Assessments", "Other Important Deviations", "Improper Informed Consent Procedure"

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-327
Listing 16.2-23: Unique Adverse Events Terms and Associated Coded Terms

MedDRA Terms SOC Preferred Term	Verbatim(s)
SOC1	XXXXXXXXXXXXXXXXXXXXXXXXXX
PT1.1	XXXXXXXXXXXXXXXXXXXXXXXXXX
	XXXXXXXXXXXXXXXXXXXXXXXXXX
	XXXXXXXXXXXXXXXXXXXXXXXXXX
PT1.2	XXXXXXXXXXXXXXXXXXXXXXXXXX
	XXXXXXXXXXXXXXXXXXXXXXXXXX
SOC2	
PT2.1	XXXXXXXXXXXXXXXXXXXXXXXXXX
	XXXXXXXXXXXXXXXXXXXXXXXXXX

Coded using MedDRA v21.1.

Note to programmer: *Sort by SOC and preferred term in alphabetical order*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-327
Listing 16.2-24: Unique Medication Terms and Associated Coded Terms

Who Drug Dictionary Terms ACT1 ACT2 ACT3 ACT4 Preferred name	Verbatim(s)
ATC1	
ATC1.2	
PN1.2.1	XXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXX
PN1.2.2	XXXXXXXXXXXXXXXXXXXXXXXXX
ATC2	
ATC2.2	
ATC2.3	
ATC2.4	
PN2.2.3.4.1	XXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXX

Coded using WHO Drug Dictionary September 2018.

Note to programmer: *Sort by ATC1, ATC2, ATC3, ATC4 and preferred name in alphabetical order*

16. LIST OF FIGURES

Use Figure mock-up xx for the following the x-axis should track through 76 hours:
Figure 1: Bar Chart of Total Postsurgery Opioid Consumption (MED) – Efficacy Analysis Set

Use Figure mock-up xx for the following (the x-axis should track through 76 hours):
Figure 2: Plot of Mean Pain Intensity Score (VAS) vs Time through 72 hours – Efficacy Analysis Set

Use Figure mock-up xx for the following (use actual hours since the end of surgery and not scheduled hours, include all VAS scores collected, the x-axis should track through 76 hours):
Figure 3: Plot of Time to First Opioid Rescue Medication – Efficacy Analysis Set

Use Figure mock-up xx for the following (use actual hours since the end of surgery and not scheduled hours, include all VAS scores collected, the x-axis should track through 100 hours):
Figure 4: Plot of % of Opioid-free Patients – Efficacy Analysis Set

17. Appendix

QoR-15 Patient Survey

Date: _ _ / _ _ / _ _ Study #: _____

Preoperative ☐ Postoperative ☐

PART A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1.	Able to breathe easily	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
2.	Been able to enjoy food	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
3.	Feeling rested	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
4.	Have had a good sleep	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
5.	Able to look after personal toilet and hygiene unaided	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
6.	Able to communicate with family or friends	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
7.	Getting support from hospital doctors and nurses	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
8.	Able to return to work or usual home activities	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
9.	Feeling comfortable and in control	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
10.	Having a feeling of general well-being	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time

PART B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11.	Moderate pain	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
12.	Severe pain	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
13.	Nausea or vomiting	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
14.	Feeling worried or anxious	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
15.	Feeling sad or depressed	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time