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STATISTICAL ANALYSIS PLAN

A Multicenter, Randomized, Double-Blind, Controlled Trial Comparing Local Infiltration Analgesia with EXPAREL to Local Infiltration Analgesia without EXPAREL to Manage Postsurgical Pain Following Total Knee Arthroplasty

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Study Drug:	EXPAREL (bupivacaine liposome injectable suspension)
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1. SIGNATURE PAGE

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2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse event
ANOVA	Analysis of variance
ATC	Anatomical therapeutic class
AUC	Area under the curve
BMI	Body mass index
bpm	Beats per minute
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CSR	Clinical study report
CV	Coefficient of Variation
d	Day
ECG	Electrocardiogram
EMA	European Medicines Agency
ER	Emergency Room
FDA	Food and Drug Administration
FNB	Femoral nerve block
hr/h	hour
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IV	Intravenous
LIA	Local infiltration analgesia
LS	Least square
MCMC	Markov-Chain Monte-Carlo method
MedDRA	Medical dictionary for regulatory affairs
MMRM	Mixed model repeated measures
MPADSS	Modified Postanesthesia Discharge Scoring System
min	minutes
MED	Morphine equivalent dose in mg
n	Number of subjects
OBAS	Overall benefit of analgesia score
OR	Operating Room
PACU	Postanesthesia care unit
PK	Pharmacokinetics
PO	Oral
Preop	Preoperative
PT	Physical Therapy
q8h	Every 8 hours
q12h	Every 12 hours
SAE	Serious adverse event
SAP	Statistical analysis plan
SCT	Stair climbing test
SD	Standard deviation
SE	Standard error
SPIS	Sum of Pain Intensity Scores
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

Abbreviation	Description
WHO-DD	World Health Organization – Drug Dictionary
WOCBP	Women of childbearing potential
wWOCF	Windowed worst observation carried forward

4. INTRODUCTION

This is a Phase 4, multicenter, randomized, double-blind, controlled trial in approximately 300 adult subjects undergoing primary unilateral TKA under spinal anesthesia with bupivacaine HCl (10-15 mg).

This study is intended to evaluate pain control and total opioid consumption following local infiltration analgesia (LIA) with EXPAREL to LIA without EXPAREL in adult subjects undergoing primary unilateral total knee arthroplasty (TKA).

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

The purposes of this SAP are to:

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

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or 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 were reviewed in preparation of this SAP:

- Original Protocol 402-C-331 issued on 16Nov2015.
- Amendment 1 of Protocol 402-C-331 issued on 22Feb2016.
- Amendment 2 of Protocol 402-C-331 issued on 28Jul2016.
- Case Report Form (CRF) version 1.0 issued on 23Feb2016.
- Physical therapy assessment manual version 1.0 issued on 11Dec2015
- 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 pain control and total opioid consumption following LIA with EXPAREL to LIA without EXPAREL in adult subjects undergoing primary unilateral total knee arthroplasty (TKA).

5.2. Secondary Objectives

The secondary objectives of this study are to compare additional efficacy, safety, and health economic outcomes following LIA with EXPAREL to LIA without EXPAREL in adult subjects undergoing primary unilateral TKA.

6. STUDY OVERVIEW

This is a Phase 4, multicenter, randomized, double-blind, controlled trial in approximately 300 adult subjects undergoing primary unilateral TKA under spinal anesthesia with bupivacaine HCl (10-15 mg).

Subjects will be screened within 30 days prior to study drug administration. During the screening visit, which must take place at least 1 day prior to surgery, subjects will be assessed for past or present neurologic, cardiac, and general medical conditions that in the opinion of the Investigator would preclude them from study participation. After the informed consent form (ICF) is signed, a medical history, surgical history, physical examination, physical therapy assessment, 12-lead electrocardiogram (ECG), vital sign measurements, urine drug screen, and urine pregnancy test for women of childbearing potential will be conducted.

On Day 0, all eligible subjects will receive the following medications within 4 hours prior to surgery:

- Acetaminophen/paracetamol 975-1000 mg, orally (PO).
- Celecoxib 200 mg, PO, if a subject has an allergy to celecoxib, they may use the following alternative drugs: naproxen 500 mg PO or meloxicam 7.5 mg PO.
- Pregabalin up to 300 mg, PO.
- Tranexamic acid up to 2 grams, intravenously (IV), at the beginning of surgery or intra-operatively.

Subjects will be randomized 1:1 to two treatment groups. Subjects in Group 1 will receive LIA with EXPAREL 266 mg (20 mL) admixed with 20 mL bupivacaine HCl 0.5% and expanded in volume with 80 mL normal saline (total volume of 120 mL). Subjects in Group 2 will receive LIA with 20 mL bupivacaine HCl 0.5% expanded in volume with 100 mL normal saline (total volume of 120 mL).

Use of tourniquets and drains, if used, will be recorded. The case is to be completed at a time that will allow for a postsurgical physical therapy assessment on Day 0.

After surgery all subjects will receive the following scheduled medications until hospital discharge:

- Acetaminophen/paracetamol 975-1000 mg PO every 8 hours (q8h). The total daily dose is not to exceed 3000 mg. (amendment 2 allowed for the dose range of 975 to 1000 mg, amendment 1 only allowed a 1000 mg dose).
- Celecoxib 200 mg PO every 12 hours (q12h), if a subject has an allergy to celecoxib, they may use the following alternative drugs: naproxen 500 mg PO or meloxicam 7.5 mg PO. (amendment 2 allowed for the celecoxib alternatives of naproxen or meloxicam).

Subjects will be required to remain at the hospital facility for a minimum of 48 hours after surgery. Subjects must still complete the 72-hour assessments if they are discharged from the hospital facility prior to 72 hours after surgery.

Postsurgical assessments include:

- Pain intensity (visual analog scale [VAS]);

- Postsurgical opioid consumption;
- Overall benefit of analgesia score (OBAS);
- Nurse's satisfaction with overall analgesia using a 5-point Likert scale;
- Subject's discharge ready as assessed by Modified Postanesthesia Discharge Scoring System (MPADSS);
- Unscheduled phone calls or office visits related to pain;
- Timed walk test (TWT);
- Timed up-and-go (TUG);
- Stair climbing test (SCT);
- Hospital length of stay;
- Hospital readmissions;
- Postsurgical physical therapy visits;
- Skill nursing facility use;
- Adverse events;
- Concomitant medications.

7. DEFINITIONS

Study Day

Study Day is calculated as the date of event minus the date of surgery plus one (1), if the date of event is on or after the date of surgery. 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.

This Study Day definition differs from the protocol defined Study Day. By this definition Day 1 is the day of the operation while the protocol defines this as Day 0. The definition assigning the operation to Day 1 aligns with the CDISC implementation guidance and FDA expectations.

Physical Therapy Timepoints

Physical therapy tests (TWT, TUG and SC) are to be performed twice daily. Since the data collection will only collect date and time of assessment, not study day or timepoint, the timepoint labels will be derived as follows:

Timepoint Label	Derivation Rule
Baseline	Last assessment performed prior to start of surgery.
Day 1-PM	Performed on the same day as but after surgery.
Day 2-AM	Performed before noon on the day after surgery
Day 2-PM	Performed after noon on the day after surgery
Day 3-AM	Performed before noon 2 days after surgery
Day 3-PM	Performed after noon 2 days after surgery
Day 4-AM	Performed before noon 3 days after surgery
Day 4-PM	Performed after noon 3 days after surgery

If multiple assessments fall within any of the above windows, use the assessment that is closest (before or after) to the protocol indicated assessment time of 8:00 am and 8:00 pm. Any assessments collected after Day 4-PM will not be summarized.

Treatment-Emergent Adverse Events

Treatment-Emergent adverse events (TEAEs) are those with onset on or after the start date and time of study drug administration and on or before the end of study (Study Day 30±3 days).

Time 0 (zero)

Time 0 is defined as the date and time of the start of study drug administration.

Time Periods

All schedule times have a window associated with them (see Time and Events Schedule for individual timepoint windows). Various time frames are used in the data analyses that are dependent on these windows. The table below defines the actual elapsed times with allowance for the windows that can be included in the window.

Defined time frame (hrs)	Acceptable elapsed times (hrs)
0-24	[0 to 25]
0-48	[0 to 50]
0-72	[0 to 76]

0-Day 14	[0 to 408]
12-24	[11 to 25]
12-48	[11 to 50]
12-72	[11 to 76]
24-48	[23 to 50]
48-72	[46 to 76]

If there are two or more data points that fit the time window the data point that occurs the latest in the window should be used. For example, when selecting the data point for the 48 hour timepoint, if a subject has data points collected at 47 and 49 hours then the 49 hour timepoint should be used. In this example the 49 hour timepoint record will be used as the end and start of all time intervals, thus the 0-48 hour interval will end using the 49 hour record and the 48-72 hour interval will start using the same 49 hour record.

Baseline

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

Sum of Pain Intensity Score (SPIS)

Sum of pain intensity scores (SPIS) are calculated by summing the imputed VAS scores for the timeframes of interest.

Duration of Surgery

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

Duration of Tourniquet Use

Duration of tourniquet (reported in minutes) use is calculated as the difference between the start of tourniquet inflation and removal.

Ready for Discharge

Ready for discharge is defined as a total score of 9 or more on the MPADSS. The total score is the sum of all scores. If there are missing data then the total score will not be calculated.

Time to Discharge Ready

Time to discharge ready is the time, in hours, from end of surgery to the first time when the MPADSS total score is 9 or more or Day 30 whichever is earlier. If Day 30 then the time to discharge ready will be censored.

Hospital Length of Stay

Hospital length of stay is defined as the time, in hours, from hospital admission to hospital discharge as collected on the CRF or Day 30 whichever is earlier. If Day 30 then the length of stay will be censored.

Region

This is a US only study, therefore region is the US.

8. ANALYSIS SETS

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

The efficacy analysis set will include all subjects in the safety analysis set who undergo the planned surgery. All analyses based on the efficacy analysis set will be by randomized treatment regardless of treatment actually received.

The per-protocol efficacy analysis set will include all subjects in the efficacy analysis set who do not have any important protocol deviations. Important protocol deviations include, but are not limited to, the following:

1) Deviation of inclusion or exclusion criteria;
2) Mis-randomization (ie, receiving study treatment other than that to which the subject was randomized);
3) Missing one or more of the scheduled VAS assessments;
4) At least one rescue medication dose without an VAS assessment within 15 minutes prior to or at the time of rescue medication dose;
5) Three or more doses of rescue medication within any 12 hour period during the primary efficacy endpoint period (ie, within 48 hours after surgery);
6) NSAIDs or other non-protocol allowed analgesic/anti-inflammatory medications within 48 hours after surgery;
7) Rescue medication received with a VAS pain intensity score immediately prior to rescue medication dose less than 4.
8) Failure to take at least 80% of the protocol prescribed postsurgery medications [acetaminophen/paracetamol 975-1000 mg every 8 hours (q8h); celecoxib 200 mg, naproxen 500 mg or meloxicam 7.5 mg every 12 hours (q12h)] as described in the protocol, including taking the incorrect dose or not taking medication on schedule (± 1 hour).

All analyses for the per-protocol efficacy analysis set will be by randomized treatment.

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 9.1 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 subjects. Unless otherwise noted, percentages will be based on the number of subjects in the treatment group within the population.

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

Unless otherwise stated summaries will present data across all sites (overall).

Unless otherwise noted, tabulations of categorical data will present only those categories appearing in the data.

On all figures, the comparator treatment will be represented in black with solid lines and filled squares; EXPAREL will be represented in red with solid lines and dots.

Plots of the VAS pain intensity scores will show both observed and imputed scores. A change in color and line type will differentiate the imputed VAS scores. Imputed values will be represented by blue and green symbols and dashed lines for the comparator and EXPAREL, respectively. VAS scores obtained immediately prior to rescue will be indicated by a change in symbol. For the comparator the symbol is a triangle, for EXPAREL the symbol is a star. The following table shows the SAS symbol statements:

Treatment	VAS Score	SAS Statement
Comparator	Observed	symbol font=marker interpol=j line=1 value=U color=black
	Imputed	symbol font=marker interpol=j line=3 value=C color=blue
EXPAREL	Observed	symbol font=marker interpol=j line=1 value=W color=red
	Imputed	symbol font=marker interpol=j line=3 value=V color=green

Note the symbol statement number will be dependent on the sort order of the treatment and VAS score group indicator variables.

Sites with fewer than 5 subjects per treatment arm will be pooled with other sites for analysis. US sites will be pooled with other small US sites based on the US Census Bureau geographic regions (see Table 1). Sites meeting the criteria for pooling will be pooled with other similar sites within their census division. If the resulting pooled site within a division still doesn't have enough subjects per treatment group, it will be pooled with the site within the division with the smallest enrollment that doesn't meet the pooling criteria. If all sites within a division are pooled and the resulting pooled site still meets the pooling criteria, the site will be pooled with other small sites within the region. If the pooled site with the region still meets the pooling criteria it will be pooled with the site with the smallest enrollment from the neighboring regions.

Table 1: US Census Regions and Divisions

Region	Division	State
Midwest	East North Central	Illinois, Indiana, Michigan, Ohio, Wisconsin
	West North Central	Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota
Northeast	Middle Atlantic	New Jersey, New York, Pennsylvania
	New England	Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont
South	East South Central	Alabama, Kentucky, Mississippi, Tennessee
	South Atlantic	Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia
	West South Central	Arkansas, Louisiana, Oklahoma, Texas
West	Mountain	Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming
	Pacific	Alaska, California, Hawaii, Oregon, Washington

Subjects who use opioid rescue medication will have the pain scores obtained after rescue replaced using pain scores obtained prior to rescue medication use. Pain scores obtained during the opioid medication window will be replaced. For this study the prescribed opioid rescue medication is oxycodone; however morphine or hydromorphone may be used. The durations of effect for various opioids are listed in Table 2.

Table 2: Opioid Windows

Medication	Route	Window Used to Impute VAS
Oxycodone	PO	6 hours
Morphine	IV	4 hours
Hydromorphone	IV	2 hours
Hydromorphone	PO	4 hours
Hydrocodone	PO	6 hours
Fentanyl	IV	2 hour
Tramadol (Ultram)	PO	6 hours

PO = oral; IV = intravenous; VAS = visual analog scale.
If other rescue medications are given then the window will be determined post-hoc. If a combination opioid product is given then the window will be determined by the opioid part of the medication. Opioids given post surgically with an indication such as 'anesthesia maintenance' will not be included for imputation purposes.

All non-efficacy tables will present with EXPAREL 266 mg, without EXAPREL and all treatments as separate columns.

Efficacy tables will present with EXPAREL 266 mg and without EXPAREL as separate columns.

If there are multiple VAS records with the same date/time, the record with the highest VAS score will be used for all endpoint derivations, summaries, and analyses.

9.1.1. Handling Missing Values

9.1.1.1. Area under the VAS-Time Curve

9.1.1.1.1. Multiple Imputation Method

Rubin's (1987)[4] 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. This multiple imputation method is being implemented per the advice provided in "The prevention and treatment of missing data in clinical trials."[5] For calculation of the area under the curve (AUC) of the VAS pain intensity scores, the windowed worst observation carried forward (wWOCF) multiple imputation procedure will be used in the following order:

a) 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 Table 2) will be replaced by the 'worst' observation. The worst observation will be the highest score from time 0 or end of previous rescue window to pain score immediately prior to rescue medication. The VAS score at rescue will be included in this calculation. Note that VAS scores in the window that are higher than the worst value prior to rescue medication will not be overwritten.

b) After the wWOCF imputation, described in Step a, subject data still missing with a non-monotone missing pattern (i.e., all pain scores between the last non-missing score and last timepoint) will have missing scores imputed using the Markov-Chain Monte-Carlo (MCMC) method (Schafer 1997)[6] within each treatment, which will be applied in the multiple imputation procedure for arbitrary missing patterns. This MCMC method will simulate 10 datasets with only monotone missing data. In order to achieve the stationary distribution and to avoid dependency within samples generated by the MCMC method, the number of iterations for the burn in period will be set to 2000 and the number of iterations between each sample will be set to 1000 (i.e., NBITER=2000 and NITER=1000.)

c) The resulting data from Step b will then have the remaining monotone missing pattern; hence a parametric regression method on pain (Rubin 1987) that assumes multivariate normality will be applied for this imputation procedure.

d) The AUC and SPIS at various time intervals will be derived from the imputed VAS scores resulting from Step c.

e) The endpoints derived in Step d will be analyzed as described in Section 9.6.1 for each imputation.

f) 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 created based on Rubin and Schenker method (1986)[7].

SAS pseudo-code for multiple imputations is provided in Section 13.

9.1.1.2. Surgery Date or Time

It is expected that all necessary information on surgery (start and stop date and time) and postsurgical rescue medication (start dates and times, doses, frequency) will be complete. Any such information that is missing and cannot be obtained through query resolution may be imputed, on a case-by-case basis, in a conservative manner that minimizes bias. For example, if

pain medication taken on Day 1 has no time of administration recorded, the imputed time will be the end of surgery.

9.1.1.3. Rescue Pain Medication

For calculation of the total rescue pain medication usage (morphine equivalent) through a time point, if a subject is discontinued early (e.g., dies, withdraws consent, is withdrawn from the study, or is lost to follow-up) before the end of the time interval (e.g., 24 hours after study drug administration), his or her total rescue pain medication usage through the time interval will be a projected amount. For example, if a subject discontinues early at 6 hours after surgery, the projected amounts through 24 hours will be actual amount + average amount (actual amount/6 hours) multiplied by the number of hours remaining in the time interval (18=24-6).

9.1.1.4. Adverse Event or Concomitant Medications Dates or Times

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

For partial start date/time:

- If the year is unknown, then the date will be assigned the date and time of first dose of study treatment.
- If the month is unknown, then:
  - i) If the year matches the year of the dose of study drug date, then the month and day of the dose of study drug date will be imputed.
  - ii) Otherwise, 'January' will be assigned.
- If the day is unknown, then:
  - i) If the month and year match the month and year of the dose of study drug date, then the day of the dose of study drug date will be imputed.
  - ii) Otherwise, '01' will be assigned.
- If the time is unknown, then:
  - i) If the date (day, month, and year) matches the date of the administration of study drug, then the time of the dose of study drug time will be imputed.
  - ii) Otherwise, '00:00' will be assigned.

For partial stop date/time:

- If the year is unknown, then the date will be assigned the date subject discontinued from study, time will be set to the last time of the day ('23:59').
- If the month is unknown, then month subject discontinued from study will be assigned.
- If the day is unknown, then the last day of the month will be assigned.
- If the time is unknown, then the last time of the day will be assigned ('23:59').

If after imputation the stop date/time is before the start date/time, set the start date/time to the stop date/time.

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'. 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. Multiplicity Adjustments

Significant testing will be at the 0.05 level for each of the co-primary endpoints in a hierarchal manner testing AUC first then, if significant, testing total opioid consumption both at the 0.05 level.

Secondary endpoints will be tested at the 0.05 level if both primary endpoints are significant. Secondary endpoints will be tested using the following hierarchy:

1. Percentage of opioid-free subjects through 48 hours;
2. Time to first rescue medication (opioid) dose through 48 hours;
3. Time to discharge ready;
4. Hospital length of stay;
5. Incidence of skilled nursing facility use;
6. Timed walk test;
7. Timed up-and-go;
8. Stair climb test;
9. Total time (days) spent in skilled nursing facility;
10. Incidence of hospital readmissions through Day 30;
11. Number of phone calls related to postsurgical pain;
12. Number of unscheduled visits related to postsurgical pain;
13. Number of postsurgical physical therapy visits;
14. Number of visits to the emergency department.

Tertiary efficacy endpoints will be summarized but not analyzed. No multiplicity adjustments need to be made for these endpoints.

9.1.3. By-Center Analyses

By-site summaries will present descriptive statistics only; no statistical analyses will be performed by individual sites. By-site summaries will be presented for disposition, demographics, primary and secondary efficacy endpoints and health outcome endpoints. By-site

summaries will present data by pooled and individual sites. Pooled site data will be presented first followed by data from the sites within that pool.

9.2. Subject Disposition

Subject disposition summaries will include the number of subjects that were:

- Screened,
  - Screen failure
  - Enrolled
- Randomized
  - Randomized not treated,
  - Randomized treated,
- In the safety analysis set,
- In the efficacy analysis set,
- In the per-protocol analysis set,
- 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 and for the safety, efficacy and PK analysis sets, completed study, discontinued from study and reasons for discontinuation with the number of subjects randomized as denominator. The percentages for the safety analysis set will use the number of subjects randomized and treated as denominator. The percentages for screen failure and enrolled will use the number of subjects screened as denominator.

Safety analysis set 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 and across treatment groups (Total). This summary table will present overall sites, pooled site(s) and sites within pooled site.

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. For partial birthdates, the first of the month will be imputed for missing day and January for missing month to calculate age. It is presumed that birth year is known.

The demographic summary will present the data for each treatment group and across treatment groups (Total). Summaries will be provided for all (safety, efficacy and per-protocol) analysis sets. This summary will present data for overall sites and for each site separately.

9.3.2. Baseline Characteristics

The summary of baseline characteristic data will present:

- American Society of Anesthesiologists (ASA) Classification – n (%)
- Baseline VAS scores
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)

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. Height in centimeters will be converted to meters using the conversion factor of 100 centimeters to 1 meter.

Descriptive statistics (n, mean, SD, median, minimum and maximum) will be provided for VAS scores, height, weight, BMI and vital signs.

Baseline characteristics summaries will present the data for each treatment group and across treatment groups (Total). Summaries will be provided for all (safety, efficacy and per-protocol) analysis sets. This summary table will present data by overall sites, pooled site(s) and sites within pooled site.

9.3.3. Surgery Characteristics

The summary of surgery characteristics will present:

- Location (left/right) – n (%),
- Duration of surgery – descriptive statistics,
- Total incision length (cm) – descriptive statistics,
- Tourniquet use (yes/no) – n (%),
- Duration of tourniquet inflation (minutes) – descriptive statistics,
- Maximum tourniquet inflation pressure (mmHg) – descriptive statistics
- Drain use (yes/no) – n (%)
- Duration of drain (hours) – descriptive statistics.

Descriptive statistics will be provided for the duration of surgery, tourniquet inflation and drain implant by treatment group and across all treatment groups. Location of surgery (left or right) and use of tourniquet and drains (yes/no) will be tabulated by treatment group and across all treatment groups. This summary table will present data by overall sites, pooled site(s) and sites within pooled site. Summaries will be provided for all (safety, efficacy and per-protocol) analysis sets.

9.4. Intraoperative, Prior, and Concomitant Medications

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

Intraoperative medications are defined as medications given as part of the surgical procedure as collected on the surgery page of the CRF (rather than concomitant medication page). These may include anesthesia, opioids or other medications.

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).

Intraoperative, prior and concomitant medications will be summarized separately using n (%) of subjects for each treatment group and across treatment groups by ATC class term and preferred name for the safety analysis set. This summary table will present overall sites, pooled site(s) and sites within pooled site. Intraoperative medications will also be summarized for the efficacy and per-protocol analysis sets. Subjects may have more than one medication per ATC category and preferred name. At each level of subject summarization, a subject will be counted once if one or more medications are reported by the subject at that level.

A listing mapping the ATC term and preferred name to verbatim term will be presented.

9.5. Measurements of Treatment Compliance

Study Treatment

Study treatment is administered by a party other than the subject; therefore, compliance is assured.

Protocol Prescribed Postsurgical Medications

Compliance with protocol prescribed postsurgical medications will be summarized. Compliance will be measured by dividing the total dose received by the total dose expected for the duration of the subjects stay in hospital. Each of the protocol prescribed medications, acetaminophen (975-1000mg PO q8h) and NSAID (celecoxib 200mg, naproxen 500mg, or meloxicam 7.5 mg PO q12h). The ratio of actual to expected dose will be derived for each drug and presented by drug classification, acetaminophen and NSAID. It is expected for the NSAID that each subject will use only one of the protocol prescribed NSAIDs, should a subject use more than one of the protocol prescribed NSAIDs treatment compliance for the NSAIDs is the sum of the ratios of the individual NSAIDs.

The expected dose of the protocol prescribed medications is derived using the following formulae:

Acetaminophen:

E_{A1} = 975 * INT(D/8), for 975 mg doses or E_{A2} = 1000 * INT(D/8), for 1000 mg doses.

Celecoxib:

$E_C = 200 * INT(D/12)$

Naproxen:

$E_P = 500 * INT(D/12)$

Meloxicam:

$E_M = 7.5 * INT(D/12)$

NSAID:

$E_N = E_C + E_P + E_M$

Overall Compliance:

$E_O = (E_{AX} + E_N)/2$, where AX=A1 or A2.

Where D is the time from end of surgery to hospital discharge and E_X is the expected dose for medicine X.

9.6. Efficacy Analysis

Primary and secondary efficacy endpoints will be summarized and analyzed using inferential statistics.

9.6.1. Efficacy Endpoints

9.6.1.1. Primary Efficacy

The co-primary efficacy endpoints are AUC of the VAS pain intensity scores from 12 through 48 hours [AUC(12-48)] and total postsurgical opioid consumption (mg) through 48 hours.

Since EXPAREL is admixed with bupivacaine HCl, the VAS AUC from time 0 through 12 hours is a mixture of EXPAREL and bupivacaine HCl efficacy. It is expected that the VAS AUC from 12 through 48 hours will reflect the EXPAREL efficacy.

9.6.1.2. Secondary Efficacy

The following secondary endpoints will be analyzed as described in Section 9.1.2:

- Percentage of opioid-free subjects through 48 hours.

- Time to first rescue medication (opioid) dose through 48 hours.

9.6.1.3. Health Economic Outcome Endpoints

- Time to discharge ready.
- Hospital length of stay.
- Incidence of hospital readmissions through Day 30.
- Incidence of skilled nursing facility.
- Total time (days) spent in skilled nursing facility.
- Number of postsurgical physical therapy visits.
- Number of phone calls related to postsurgical pain.
- Number of unscheduled visits related to postsurgical pain.
- Number of visits to the emergency department.

9.6.1.4. Other Efficacy Endpoints

9.6.1.5. The AUC of the VAS pain intensity scores from 12 through 24, 36, 60 and 72 hours.

- The AUC of the VAS pain intensity scores from PACU arrival through 24, 36, 48, 60 and 72 hours.
- The AUC of VAS pain intensity scores from PACU arrival -12, 24-48 and 48-72 hours.
- VAS pain intensity scores at each assessed timepoint.
- Proportion of subjects who are pain free (VAS $\leq$ 1.5 cm) at each assessed timepoint.
- SPIS from 12 through 24, 48 and 72 hours.
- SPIS from PACU arrival through 24, 48 and 72 hours.
- SPIS from PACU arrival -12, 24-48 and 48-72 hours.
- Total opioid consumption in IV morphine equivalents through 24 and 72 hours.
- Total opioid consumption in IV morphine equivalents from 24-48 and 48-72 hours.
- Percentage of subjects who are opioid-free through 24 and 72 hours or hospital discharge.
- Overall benefit of analgesia scale (OBAS) total score at 24, 48 and 72 hours or hospital discharge.
- Nurse's satisfaction with overall analgesia at 24, 48 and 72 hours or hospital discharge.
- Proportion of subjects ready for discharge (based on MPDASS) at each assessed timepoint.
- Time in postanesthesia care unit (PACU)

9.6.1.6. 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 wWOCF imputation (see Section 9.1.1.1). AUC will start with the first pain assessment obtained after surgery and use all

following pain assessments including those collected prior to rescue medication and unscheduled. Actual assessment times will be used in deriving AUC.

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

Where p_i is the VAS pain score at time i and t_i is the time, in hours, from end of surgery. Where k is the starting timepoint of the AUC interval (eg, k=7 for AUCs that start at the 12 hour timepoint).

9.6.1.7. Opioid Consumption

Opioids will be converted to IV morphine equivalent dose (MED in mg) using the appropriate conversion factor from Table 3 for all summaries. Total opioid dose is the sum of all opioids taken after surgery up to the timepoint of interest. Subjects with no opioid use during the period of interest will be assigned a dose of 0 for summaries and changed to the lesser of 1 or 0.5 of the smallest total amount observed in the study prior to being transformed for analysis.

Table 3: IV Morphine Equivalents

Medication	Unit	Route	Conversion (Multiplication) Factor
Oxycodone	mg	PO	0.5
Hydromorphone	mg	IV	6.7
Hydromorphone	mg	PO	1.3
Hydrocodone	mg	PO	0.33
Fentanyl	ug	IV	0.1
Tramadol (Ultram)	mg	PO	0.2
IV = Intravenous; PO = Oral			

9.6.1.8. Time to First Opioid Rescue Medication Use

Time to first opioid rescue medication use will be calculated as the time from end of surgery to time of event in hours.

9.6.1.9. Pain-free

Pain-free is defined as an observed VAS pain intensity score less than or equal to 1.5 cm with no prior rescue medication and all prior VAS pain intensity scores less than or equal to 1.5 cm.

9.6.1.10. Overall Benefit of Analgesia Score (OBAS)

The OBAS is derived as follows:

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

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

9.6.1.11. Hospital Length of Stay

Hospital length of stay is defined as the time from admission to date of discharge from hospital or Day 30 whichever is earlier.

9.6.1.12. Time to Discharge Ready

Time to discharge ready is defined as the time from end of surgery to discharge ready as assessed by the MPADSS or Day 30 whichever is earlier.

9.6.1.13. Time in PACU

Time in PACU is defined as the time from end of surgery to discharge from the PACU.

9.6.1.14. Total Time Spent in Skilled Nursing Facility

The total time spent in a skilled nursing facility is the number of days in the facility as reported on the CRF.

9.6.2. Methods of Analysis

9.6.2.1. Primary Efficacy Analysis

Primary Analysis

The primary efficacy variables are the AUC of VAS pain intensity scores through 48 hours [AUC(12-48)] using the multiple imputation method described in Section 9.6.1.6 and total opioid consumption through 48 hours as described in Section 9.6.1.7.

Tests for the treatment effect of treatment with versus without EXPAREL will be based on the following null hypotheses (H_0) and one-sided alternative hypotheses (H_a):

	VAS AUC(12-48)	Total Opioid Consumption
H_0:	$\mu_1 = \mu_2$	$\mu_1 < \mu_2$
H_a:	$\gamma_1 = \gamma_2$	$\gamma_1 < \gamma_2$

Where μ_1 and μ_2 are the AUC(12-48) means with and without EXPAREL, respectively and γ_1 and γ_2 are the total opioid consumption means with and without EXPAREL, respectively. A one-sided test will be performed at 0.025 level of significance comparing treatment with to treatment without EXPAREL. The treatment effect of EXPAREL will be considered significantly better than treatment without EXPAREL if the null hypothesis of no difference is rejected and the difference in means is in favor of treatment with EXPAREL (ie, mean with EXPAREL less than the mean without EXPAREL). AUC must be statistically significant before proceeding to test the total opioid consumption. Hypotheses will be tested at the one-sided 0.025 level which corresponds to a two-sided 0.05 level.

9.6.2.1.1. AUC Analysis

For AUC, treatment with EXPAREL will be compared to treatment without EXPAREL using analysis of variance (ANOVA) with treatment and site as main effects. Based on the model, the least squares (LS) means for each treatment group and the standard error (SE) of the LS mean, 95% two-sided confidence interval (CI) for the LS mean and p-value for the difference between

with and without EXPAREL treatment will be reported along with the descriptive statistics by treatment.

AUC will also be summarized within each site. No inferential statistical analyses will be performed within a site.

In addition, an ANOVA model with main effects of treatment and site and the treatment-by-site interaction terms will be reported to assess the effect of the interaction on the primary efficacy analysis. Additional analyses may be performed if the interaction term is significant (p-value < 0.1).

9.6.2.1.2. Total Opioid Consumption Analysis

Prior to analysis, the natural logarithm transformation will be applied to the total opioid consumption (in mg morphine equivalents) for each subject. When total consumption is 0, then the result will be changed to 1 in the study prior to being transformed with the natural logarithm. To test for significant differences between EXPAREL and No EXPAREL, an ANOVA with treatment and site as the main effects will be used. The LS means, LS mean difference between the two treatment groups, 95% two-sided CI for the LS mean difference between EXPAREL and No EXPAREL, and p-value will be reported. The LS means, LS mean differences and 95% CI will be back transformed for presentation (note the LS mean difference becomes the ratio when back-transformed) along with the descriptive statistics (untransformed), including geometric mean and coefficient of variation, by treatment.

Total opioid consumption will also be summarized within each site. No inferential statistical analyses will be performed within a site.

In addition, an ANOVA model with main effects of treatment and site and the treatment-by-site interaction terms will be reported to assess the effect of the interaction on the primary efficacy analysis. Additional analyses may be performed if the interaction term is significant (p-value < 0.1).

The number of times opioid (rescue) medication was used by a subject will be summarized and tabulated. The tabulation of the number of times opioid (rescue) medication used will include all values from 0 to the maximum number of uses reported by any subject, even if the value has zero subjects for all treatments.

9.6.2.2. Secondary Efficacy Analyses

9.6.2.2.1. Opioid-free

Percentage of opioid-free subjects through 24, 48 and 72 hours (or hospital discharge) will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by site. The p-value from the CMH analysis and mean treatment difference and 95% CI about the mean difference derived using the Newcombe[8] method (SAS pseudo-code below) will be presented. The tabulation of opioid-free subjects will be presented across all sites and for each site separately. No inferential statistics will be done for individual sites.

The number and percentage of subjects opioid-free will also be tabulated by timepoint.

Pseudo-code for Newcombe method:

```
PROC FREQ;
```

```
TABLE SITE*TREATMENT*RESPONSE / RISKDIFF(CL=NEWCOMBE COMMON);
RUN;
```

9.6.2.2.2. Time to First Rescue Medication

Time to first opioid rescue will be computed in hours as the date and time of the first opioid rescue minus the date and time of the end of surgery. If a subject is not administered an opioid, the time to first administration will be censored at 48 hours after surgery or at the time of last follow-up, whichever is earliest. Time of last follow-up will be defined as the latter of (1) the last pain assessment, (2) the start time of the last concomitant medication, or (3) the start time of the last AE.

Time to first opioid rescue will be analyzed by the Kaplan-Meier method. The n (%) of subjects administered an opioid as well as the n (%) of censored observations will be presented for each treatment group. In addition, Kaplan-Meier estimates in terms of the median and its 95% CI, and the 25th and 75th percentiles will be presented for each treatment. Gehan-Wilcoxon [SAS PROC LIFETEST STRATA option / TEST=(WILCOXON)] tests will be used to compare EXPAREL to No EXPAREL.

9.6.2.3. Health Economic Outcomes Analyses

9.6.2.3.1. Discharge Readiness

The time to discharge ready will be analyzed using ANOVA with fixed effects for treatment and site. Descriptive statistics and the LS mean, SE of the LS mean, LS estimate of the treatment difference and its 95% CI and p-value from the ANOVA will be presented. Analyses will be performed on the efficacy and per-protocol analysis sets.

Descriptive statistics for overall sites, pooled site(s) and site within pooled site will be presented. This summary will be provided for both the efficacy and per-protocol analysis set.

The number and percent of subjects meeting MPADSS criteria (total score of 9 or more) for discharge readiness at Day 1-PM, Day 2-AM, Day 2-PM, Day 3-AM, Day 3-PM and Day 4-AM will be summarized overall sites and by pooled site and site within pooled site. If a subject is discharge ready at an early timepoint, the subject will be considered discharge ready at all subsequent timepoints.

9.6.2.3.2. Hospital Length of Stay

Hospital length of stay will be analyzed using an ANOVA model with fixed effects for treatment and site. Descriptive statistics and the LS mean, SE of the LS mean, LS estimate of the treatment difference and its 95% CI and p-value from the ANOVA will be presented. Analyses will be performed on the efficacy and per-protocol analysis sets.

Descriptive statistics for overall sites, pooled site(s) and site within pooled site will be presented. This summary will be provided for both the efficacy and per-protocol analysis set.

9.6.2.3.3. Timed Walk Test

Subjects who did not perform the timed walk test will have a zero (0) imputed for distance walked in the analysis. The distance, in meters, covered during the timed walk test will be analyzed using a mixed model repeated measures (MMRM) analysis with fixed effects for treatment, site and time and a treatment-by-time interaction with subject within treatment as the

random effect. The LS mean, SE of the LS mean, LS treatment difference, 95% CI for the treatment difference and p-value will be reported as well as the treatment. Analyses will be performed on the efficacy and per-protocol analysis sets.

The MMRM will be fit with covariance matrices of UN (unstructured), CS (compound symmetry) and AR(1) (auto-regressive 1). The analysis with the lowest AIC criteria will be reported on the table. Other covariance matrix structures may be used if none of these converge.

The timed walk test summary will include tabulations of whether the test was performed and if not performed, reasons why not and the use of a walking aid (yes/no), level of physical assistance required and descriptive statistics for the distance covered. Statistics overall sites, pooled site(s) and site within pooled site will be presented. This summary will be provided for both the efficacy and per-protocol analysis set.

9.6.2.3.4. Timed Up-and-go Test (TUG)

Subjects who did not perform the timed walk test will have a zero (0) imputed for time in the analysis. The time, in seconds, to complete the TUG test will be analyzed using a mixed model repeated measures analysis with fixed effects for treatment, site and time and a treatment-by-time interaction with subject within treatment as the random effect. The LS mean, SE of the LS mean, LS treatment difference, 95% CI for the treatment difference and p-value will be reported as well as the treatment. Analyses will be performed on the efficacy and per-protocol analysis sets.

The MMRM will be fit with covariance matrices of UN, CS and AR(1). The analysis with the lowest Akaike's information criterion (AIC) criteria will be reported on the table. Other covariance matrix structures may be used if none of these converge.

The TUG test summary will include tabulations of whether the test was performed and if not performed, reasons why not and the use of a walking aid (yes/no), level of physical assistance required and descriptive statistics for the time to complete. Statistics for overall sites, pooled site(s) and site within pooled site will be presented. This summary will be provided for both the efficacy and per-protocol analysis set.

9.6.2.3.5. Stair Climb Test

The stair climb test will be analyzed using a general mixed effect model with the logit link function and fixed effects for treatment, site and time with treatment-by-time interaction and subject within treatment as the repeated effect. The odds ratio (EXPAREL / No EXPAREL) and its 95% CI and p-value will be reported as well as the odds ratio and its 95% CI at each testing timepoint as derived from the model. Analyses will be performed on the efficacy and per-protocol analysis sets.

The number of subjects not completing and completing the test will be tabulated at each testing timepoint. Tabulations for overall sites, pooled site(s) and site within pooled site will be presented. This tabulation will be provided for both the efficacy and per-protocol analysis set.

9.6.2.3.6. Skilled Nursing Facility

The incidence of skilled nursing facility use will be tabulated by treatment and site. The incidence will be analyzed using a CMH stratified by site. The p-value from the CMH analysis

and mean treatment difference and 95% CI about the mean difference using the Newcombe method (see Section 9.6.2.2.1) will be presented.

The number of days in a skilled nursing facility will be analyzed using an ANOVA model with fixed effects for treatment and site. Descriptive statistics and the LS mean, SE of the LS mean, LS estimate of the treatment difference and its 95% CI and p-value from the ANOVA will be presented. Analyses will be performed on the efficacy and per-protocol analysis sets.

Descriptive statistics overall sites, pooled site(s) and site within pooled site will be presented. This summary will be provided for both the efficacy and per-protocol analysis set.

9.6.2.3.7. Physical Therapy Visits

The number of physical therapy visits will be analyzed using an ANOVA model with fixed effects for treatment and site. Descriptive statistics and the LS mean, SE of the LS mean, LS estimate of the treatment difference and its 95% CI and p-value from the ANOVA will be presented. Analyses will be performed on the efficacy and per-protocol analysis sets.

Descriptive statistics overall sites, pooled site(s) and sites within pooled site will be presented as well as a tabulation (number and percentage of subjects) of the number of physical therapy visits reported. This summary will be provided for both the efficacy and per-protocol analysis set.

9.6.2.3.8. Emergency Room Visits

The number of emergency room visits will be analyzed using an ANOVA model with fixed effects for treatment and site. Descriptive statistics and the LS mean, SE of the LS mean, LS estimate of the treatment difference and its 95% CI and p-value from the ANOVA will be presented. Analyses will be performed on the efficacy and per-protocol analysis sets.

Descriptive statistics overall sites, pooled site(s) and site within pooled site will be presented as well as a tabulation (number and percentage of subjects) of the number of emergency room visits reported. This summary will be provided for both the efficacy and per-protocol analysis set.

9.6.2.3.9. Hospital Readmissions

The incidence of hospital readmissions will be tabulated by treatment and site. The incidence will be analyzed using a CMH stratified by site. This summary will be provided for both the efficacy and per-protocol analysis set. The p-value from the CMH analysis and mean treatment difference and 95% CI about the mean difference using the Newcombe method (see Section 9.6.2.2.1) will be presented.

9.6.2.4. Tertiary Efficacy Analyses

No inferential statistics will be performed on any tertiary endpoint.

9.6.2.4.1. Visual analog scale (VAS) AUC

Summary statistics will be presented by treatment for VAS AUC(0-12), VAS AUC(0-24), VAS AUC(0-48), VAS AUC(0-72), VAS AUC(12-24), VAS AUC(12-72), AUC(24-48) and AUC(48-72).

9.6.2.4.2. Visual analog scale

Summary statistics will be presented by treatment for VAS pain intensity scores at each assessment timepoint. This summary will be based on the observed VAS pain intensity scores.

9.6.2.4.3. Sum of Pain Intensity Scores (SPIS)

Summary statistics will be presented by treatment for SPIS(0-12), SPIS(0-24), SPIS(0-48), SPIS(0-72), SPIS(12-24) , SPIS(12-48), SPIS(12-72), SPIS(24-48) and SPIS(48-72).

9.6.2.4.4. Proportion of Pain-Free Subjects

The proportion of pain-free subjects will be tabulated by treatment. The number and proportion of subjects who are pain-free and not pain-free will be presented at each assessment timepoint.

9.6.2.4.5. Total Opioid Consumption through 24 and 72 hours

Total opioid consumption through 24 and 72 hours will be summarized by treatment group. The summaries will be calculated similar as the postsurgical opioid consumption through the 48 hour secondary endpoint (see Section 9.6.2.1.2). No inferential statistics will be reported for these endpoints.

9.6.2.4.6. Total Opioid Consumption during Specific Time Intervals

Total opioid consumption from 24-48 and 48-72 hours will be summarized by treatment group. The summaries will be calculated similar as the postsurgical opioid consumption through the 48 hour secondary endpoint (see Section 9.6.2.1.2). No inferential statistics will be reported for these endpoints.

9.6.2.4.7. Overall Benefit of Analgesia (OBAS)

The OBAS total score will be summarized by treatment and individual question responses tabulated at each assessment timepoint. The OBAS total score will be analyzed using a Kruskal-Wallis test.

9.6.2.4.8. Nurse's Satisfaction with Overall Analgesia

Nurse's satisfaction with overall analgesia (obtained using a 5-point Likert scale) will be summarized and individual responses tabulated by treatment for each assessment timepoint. The numeric value of the response will be presented using descriptive statistics. For each value of the scale the number and percentage of subjects selecting that value will also be presented.

9.6.2.4.9. Number of Pain-Related Visits/Phone Calls after Hospital Discharge

The number of pain-related unscheduled phone calls or office visits will be summarized (n, mean, SD, median, minimum and maximum) by treatment group. The number and percentage of subjects reporting for each number of pain-related unscheduled phone calls or visits (0, 1, 2, … maximum number observed) will be presented by treatment group.

9.6.2.4.10. Time in PACU

Descriptive statistics of PACU time will be presented for overall sites, pooled site(s) and site within pooled site will be presented.

9.6.2.4.11. Intensive Care Unit (ICU) Admissions

The incidence of ICU admissions will be tabulated by treatment and site.

9.7. Safety Analyses

Safety assessments in this study consist of AEs. Adverse events will be collected from the time of informed consent through Day 30.

No inferential statistics are planned for any safety assessment.

9.7.1. Adverse Events

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

An AE will be considered a TEAE if the onset date and time is on or after the start date and time of study drug administration and on or before the end of study (Day 30).

If an AE has a partial onset date and time the imputed start and stop dates and times will be used to determine treatment-emergence (e.g., stop date and time is before start date and time of study treatment). All AE summaries will present TEAEs only; AEs that are not treatment-emergent will be included in listings but not summarized.

The incidence of subjects reporting TEAEs will be tabulated by the number and percentage of subjects reporting the TEAE. Incidence is defined as a subject reporting at least one TEAE within the summary level. Summary levels are 'at least one TEAE', system organ class and preferred term. Subjects will be counted only once within each reporting level on the table. For example if a subject reports a TEAE of headache on two separate occasions, the subject will be counted only once in the headache row of the table. Similarly if a subject reports two separate TEAEs within the same system organ class the subject will only be counted once in the summary row for that system organ class. A summary of subjects reporting at least one TEAE during the study will also be presented.

The first row on every TEAE table will be the number and percentage of subjects reporting at least one TEAE. Subsequent rows will be presented in descending order of subject counts for the overall treatment group with the most common system organ class first, followed within each system organ class by the preferred terms in descending subject count order. For tables presenting the severity or relation to study treatment of AE, the sort order will be determined by the number and percentage of subjects reporting the preferred term, thus the sort order of rows will remain the same for the relation or severity tables as the tables by preferred term. .

The following summaries will be presented for the AEs reported by the subjects:

An overview of all TEAEs, serious TEAEs and TEAEs of special interest will present the number and percentage of subjects in the following categories:

- 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

Subjects will be counted once in each of the above categories except for maximum severity. Subjects will be counted only once at the highest severity reported. For example, if a subject has a mild and severe headache and a moderate rash, the subject will be counted under maximum severity of severe only.

Adverse event tables will present the data by treatment group and across all treatment groups. Incidence tables will be created for the following groups of TEAEs:

- All TEAEs
- Study treatment-related TEAEs
- TEAEs leading to study withdrawal
- Study treatment-related TEAEs leading to study withdrawal
- All TEAEs by severity
- All TEAEs by relationship to study treatment
- All serious TEAEs
- Study treatment-related serious TEAEs
- Serious TEAEs leading to study withdrawal
- Study treatment-related serious TEAEs leading to study withdrawal
- Serious TEAEs resulting in death
- Study treatment-related serious TEAEs resulting in death
- All TEAEs of special interest
- Study treatment-related TEAEs of special interest
- TEAEs of special interest leading to study withdrawal
- Study treatment-related TEAEs of special interest leading to study withdrawal
- TEAEs of special interest resulting in death

If there are no AEs to report on any of the above tables, the table should be created with the line 'no adverse events were reported' in the body of the table.

Adverse events will be considered related if the investigator assessment of relationship to study treatment is either 'possible', 'probable' or 'definite'.

All AE summaries based on related AEs will be produced based on the investigator assessment of relatedness. Below are the MedDRA terms for the AE of special interest:

Group	Protocol term	MedDRA Terms	
		Term Level	Term
Cardiac	Angina	Preferred term	Angina Pectoris
	Myocardial infarction	Preferred term	Myocardial Infarction
	Bradycardia	Preferred term	Bradycardia
	Tachycardia	Preferred term	Tachycardia
	Extrasystoles	Preferred term	Extrasystoles
	Shortness of breath requiring intervention	Preferred term	Dyspnoea
Neurologic	Altered mental status	Preferred term	Mental Status Changes
	Altered sensorium	Preferred term	Depressed level of consciousness
	Rigidity	Preferred term	Muscle Rigidity
	Dysarthria	Preferred term	Dysarthria
	Seizure	Preferred term	Seizure
	Tremors	Preferred term	Tremor
	Metallic taste	Preferred term	Dysgeusia
	Tinnitus	Preferred term	Tinnitus
	Perioral numbness	Preferred term	Hypoaesthesia Oral
	Visual disturbance	Preferred term	Visual Impairment
	Dizziness	Preferred term	Dizziness
	Hyperesthesia	Preferred term	Hyperaesthesia

	Muscular twitching*	Preferred term	Muscle Twitching
	Tingling*	Preferred term	Paresthesia
	Paresthesia*	Preferred term	Paresthesia
Other	Fall	Preferred term	Fall
* if event persists beyond or occurs after 72 hours after start of study treatment dose.			

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

9.8. Pharmacokinetic Analysis

Pharmacokinetic data were not collected in this study.

9.9. Interim Analysis

No interim analyses are planned for this study.

9.10. Study Stopping Rules

The study stopping rules, as described in the protocol, are designed to stop the study for safety reasons only. The study will not be stopped for efficacy or futility. The implementation of the study stopping rules are described in a separate document and not included here.

9.11. Deviations from Protocol Described Analyses

Sample size derivation

The protocol derived sample size using 90% power. The final study sample size was based on 80%.

A sample size of 80 subjects in each group is needed to have at least 80% power to detect a −0.3 unit difference in the geometric means for total opioid dose assuming the common standard deviation (SD) is 0.670 using a two group t-test with a 0.05 two-sided significance level. A sample size of 47 is needed in each group to have at least 80% power to detect a difference in AUC(12-48) of the VAS pain intensity score means of −40 assuming the common SD is 70 using a two group t-test with a 0.05 two-sided significance level. One hundred and sixty subjects (80 per treatment arm) are required to achieve at least 80% power.

10. SAMPLE SIZE CALCULATIONS

A sample size of 130 subjects in each group is needed to have at least 90% power to detect a −0.3 unit difference in the geometric means for total opioid dose assuming the common standard deviation (SD) is 0.670 using a two group t-test with a 0.025 two-sided significance level. A sample size of 78 is needed in each group to have at least 90% power to detect a difference in $AUC_{(12\text{-}48)}$ of the VAS pain intensity score means of −40 assuming the common SD is 70 using a two group t-test with a 0.025 two-sided significance level. Three hundred subjects (150 per treatment arm) will be randomized into this study in order to have 260 evaluable subjects.

11. REFERENCES

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[8] Newcombe RG, Interval estimation for the difference between independent proportions: Comparison of eleven methods. Statist. Med. 17, 873-890 (1998).

12. TIME AND EVENTS SCHEDULE OF STUDY PROCEDURES

Note that the study days defined in the table and footnotes start with surgery as Day 0; however, the SAP definitions start with surgery as Day 1. The SAP follows the CDISC convention to define study day. Thus in the SAP preoperative Day 0 is Day 1, Day 7 is Day 8, Day 10 is Day 11 and Day 29 is Day 30.

	Screen Visit**	D0 Preop	0 min	OR	PACU Arrival	4h	6h	8h	10h	12h	24h	28h	32h	36h	48h	52h	56h	60h	72h	D14 Visit	D29 Call
Time Window	**Within 30 days**					**±15 min**	**±30 min**	**±30 min**	**±1h**	**±1h**	**±1h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±4h**	**±3d**	**±3d**
Obtain signed ICF	X																				
Assess/confirm eligibility	X	X																			
Record medical and surgical history	X	X																			
Record demographics and baseline characteristics	X																				
Conduct pregnancy test for WOCBP	X	X																			
Conduct urine drug screen	X	X																			
Conduct alcohol breath test		X																			
Perform physical examination	X																			X	
Measure vital signs (heart rate and blood pressure)[1]	X	X																			
Perform 12-lead ECG	X																				
Perform PT assessment (at approximately 8:00 am and 8:00 pm ±2h); record date and time[2]	X						←												→	X	
Record VAS pain intensity score[3,4,5,6]		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Randomize subject, prepare study drug		X																			
Administer scheduled presurgical medications[7]		X																			
Administer study drug according to randomization schedule; record			X																		
Record intraoperative opioids administered and doses				X																	
Record start and end time of tourniquet use and maximum pressure (mmHg)				X																	
Record date and time of insertion of drain(s), if used				X																	
Record surgery start and stop times				X																	
Record date and time of removal of drain(s), if used						←													→		
Record times and doses of all analgesic medication administered					←																→
Administer scheduled postsurgical analgesics[3,8]					←														→		
Complete OBAS questionnaire[6]											X				X				X		
Nurse's satisfaction with postsurgical pain control[6]											X				X				X		
Assess discharge readiness q12h (at approximately 8:00 am and 8:00 pm ±2h); record date and time[3]						←													→		

	Screen Visit**	D0 Preop	0 min	OR	PACU Arrival	4h	6h	8h	10h	12h	24h	28h	32h	36h	48h	52h	56h	60h	72h	D14 Visit	D29 Call
Time Window	Within 30 days					±15 min	±30 min	±30 min	±1h	±1h	±1h	±2h	±2h	±2h	±2h	±2h	±2h	±2h	±4h	±3d	±3d
Record date and time of actual discharge											←	—	—	—	—	—	—	—	—	→	
Document any hospital readmissions																				X	X
Document post-surgical outpatient PT visits																				X	X
Document use of skilled nursing facility																				X	X
Document any unscheduled phone calls or office visits related to pain after discharge																				X	X
Document any unscheduled visits to the ER after discharge																					
Record prior and concomitant medications[9]	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	X
Record AEs (beginning at the time ICF is signed)[10]	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→	→

Abbreviations: AE = adverse event; d = day; D = day; ECG = electrocardiogram; ER = emergency room; h = hours; ICF = informed consent form; min = minutes; OBAS = overall benefit of analgesia score; OR = operating room; PACU = post-anesthesia care unit; Preop = preoperative; PT = physical therapy; q12h = every 12 hours; VAS = visual analog scale; WOCBP = women of childbearing potential.

* Postsurgical assessments will be conducted at the timepoints specified after the end of surgery. At timepoints when multiple assessments coincide, the VAS pain intensity assessment will be conducted first and the physical therapy assessment will be conducted last.

** The screening visit must take place at least 1 day prior to surgery.

1 Vital signs will be measured after the subject has rested in a supine position for at least 5 minutes.

2 Physical therapy assessments (timed up and go test, stair climbing test, and timed walk test) will be conducted once postsurgically on Day 0; q12h from postsurgical Day 1 through hospital discharge; and on postsurgical Day 14. Preemptive use of opioids or NSAIDs prior to the physical therapy assessment is not permitted.

3 Timepoints shown through 72 hours or until hospital discharge.

4 The preoperative pain intensity assessment should be conducted prior to administration of any premedication.

5 Also record VAS pain intensity scores immediately prior to each administration of rescue pain medication, and just prior to hospital discharge.

6 And just prior to hospital discharge.

7 Administer presurgical medications (i.e., acetaminophen/paracetamol 975-1000 mg orally (PO), celecoxib 200 mg PO (or in case of subject allergy, naproxen 500 mg PO or meloxicam 7.5 PO), and, pregabalin up to 300 mg PO, within 4 hours of surgery. Tranexamic acid up to 2 grams IV should be administrated at the beginning of surgery or intra-operatively.

8 Administer scheduled post-surgical analgesics (i.e., acetaminophen/paracetamol 975-1000 mg PO every 8 hours [maximum of 3000 mg per day] and celecoxib 200 mg PO q12h [or in case of subject allergy, naproxen 500 mg PO or meloxicam 7.5 PO]).

9 Instruct subject to discontinue prohibited medications. Record date and time of all medications starting at least 30 days prior to study drug administration until hospital discharge. Record medications administered for treatment of an AE through postsurgical Day 29.

10 If a cardiac AE, neurological AE, fall, or SAE occurs during the study, an unscheduled PK blood sample should be collected as close as possible to when the event occurs. For out-of-hospital events, the medical monitor should be contacted to determine need for a PK sample and ECG. In addition, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests should be conducted. Cardiac AEs of special interest include chest pain (angina, myocardial infarction), abnormal/irregular heart rate (bradycardia, tachycardia, extrasystoles), and shortness of breath requiring intervention. Neurologic AEs of special interest include altered mental status/altered sensorium, rigidity, dysarthria, seizure, tremors, metallic taste, tinnitus, perioral numbness, and visual disturbance. Additionally, the following events are of special interest if they persist or occur beyond 72-hours postdose: dizziness, hyperesthesia, muscular twitching, and tingling/paresthesia.

13. MULTIPLE IMPUTATION EXAMPLE PROGRAM CODE

```
** Note: INPUT_DATA is the dataset that contains the VAS data with the wWOCF imputation performed
for the rescue pain scores **;

** Step 1 use Markov-Chain Monte-Carlo (MCMC) method to create a monotonic missing pattern **;
** Note the value for the random seed should be fixed so that the results are reproducible **;
PROC MI DATA=INPUT_DATA SEED=M NIMPUTE=10 OUT=OUTPUT_STEP1;
        BY TREATMENT;
        MCMC IMPUTE=MONOTONE NBITER=2000 NITER=1000;
        VAR TIME_POINT_LIST;
RUN;

** Step 2 – use regression on output dataset from Step 1 to impute missing values **;
** T_i is the variable containing the pain score from time i **;
PROC MI DATA=OUTPUT_STEP1 OUT=OUTPUT_STEP2;
        BY _IMPUTATION_;
        CLASS TREATMENT;
        MONOTONE REG(T1 = TREATMENT / DETAILS);
        MONOTONE REG(T2 = TREATMENT T1 / DETAILS);
        ...
        MONOTONE REG(T(n-1) = TREAMENT T1 T2 T3 ... T(n-2) / DETAILS);
        MONOTONE REG(Tn = TREAMENT T1 T2 T3 ... T(n-1) / DETAILS);
        VAR TREATMENT T1 T2 T3 ... Tn
RUN;

** Dataset OUTPUT_STEP2 is as an ADaM dataset, include in DEFINE.XML and transfers **;

** Step 3 derive endpoint using appropriate techniques by variable _imputation_ **;
** Endpoints are: AUC(0.25-48), AUC(0.25-24), AUC(0.25-72), SPI(0.25-24), SPI(0.25-48), **;
** SPI(0.25-72) and integrated rank assessment at 24, 48 and 72 hours **;

** Step 4 get summary statistics **;
** Summary step 4a get the mean of all imputation endpoint values for each subject **;
PROC SUMMARY DATA=OUTPUT_STEP2;
        BY TREATMENT _IMPUTATION_;
        VAR endpoint_variable
        OUTPUT OUT=SMRYSTAT0 N=N MEAN=MEAN STDDEV=STDDEV STDERR=STDERR
MEDIAN=MED MIN=MIN MAX=MAX;
RUN;

PROC MIANALYZE DATA=SMRYSTAT0;
        BY TREATMENT;
        MODELEFFECTS MEAN;
        STDERR STDERR;
        ODS OUTPUT VARIANCEINFO=VARINFO PARAMETERESTIMATES=PARMEST
RUN;
```

```
PROC SUMMARY DATA=SMRYSTAT0;
        BY TREATMENT;
        VAR endpoint_variable
        OUTPUT OUT=SMRYSTAT1 MEDIAN=MED MIN=MIN MAX=MAX;
RUN;

*** use the mean (PARMEST dataset) and total variance ( VARINFO dataset to derive standard error as
the square root[variance/{ni-1}]) where ni is the sample size for the treatment arm (dataset SMRYSTAT0)
from PROC MIANALYZE output and use the minimum, median, maximum from dataset SMRYSTAT1 ***;

** Dataset SUMMARYSTATSA is as an ADaM dataset, include in DEFINE.XML and transfers      **;
** SUMMARYSTATSA also source for a data listing                                          **;

** Summary step 4b use subject imputation means to derive summary statistics           **;
PROC SUMMARY DATA=SUMMARYSTATSA;
        BY TREATMENT;
        VAR ENDPOINTMEAN;
        OUTPUT OUT=SUMMARYSTATSB N=N MEAN=MEAN STDDEV=STDDEV MEDIAN=MEDIAN
                MIN=MIN MAX=MAX;
RUN;

*** Step 5 analyze imputations                                                         **;
ODS OUTPUT ESTIMATES=MIXEDSTATSA;
PROC MIXED DATA= OUTPUT_STEP2 METHOD=TYPE3;
        BY _IMPUTATION_;
        CLASS TREATMENT SITE;
        MODEL ENDPOINT_VARIABLE = TREATMENT SITE;
        ESTIMATE 'EXPAREL - NO EXPAREL' TREATMENT 1 -1;
RUN;

ODS OUTPUT PARAMETERESTIMATES=MIXEDSTATSB;
PROC MIANALYZE DATA= MIXEDSTATSA ALPHA=0.05 THETA0=0;
        MODELEFFECTS ESTIMATE;
        STDERR STDERR;
RUN;

** Step 6 build report from SUMMARYSTATSB and MIXEDSTATSB                             **;
```

For combining site and other effects with more than 1 degree of freedom use the algorithm from the macro below from the Support.SAS.com (Wang, et al, paper 1543-2014: Combining Type-III Analyses from Multiple Imputations).

```
%macro type3_MI_mixed(type3table);
        *Identify Terms as Denominator*;
        data type3table;
                *length Denominator $50;
                set &type3table;
                Denominator = trim(scan(ErrorTerm,2,'()'));
        run;

        proc freq data=type3table noprint;
                where Denominator~=' ';
                table Denominator /out=Denominator_name;
        run;

        *Identify Terms as Numerators*;
        data error_set;
                set type3table;
                keep _imputation_ source df MS;
        run;

        proc sort data=error_set;
                by source;
        run;

        data Denominator_name;
                set Denominator_name;
                rename Denominator=source;
        run;

        proc sort data=Denominator_name;
                by source;
        run;

        *Merge Denominators to Each Error Source*;
        data error_set;
                merge error_set (in=in1) Denominator_name (in=in2);
                by source;
                if in2=1;
                rename source=denominator DF=de_DF MS=MSE;
                drop count percent;
        run;

        proc sort data=error_set;
                by _imputation_ Denominator;
        run;

        proc sort data=type3table;
                by _imputation_ Denominator;
        run;

        data type3table;
                merge type3table error_set;
```

```
            by _imputation_ Denominator;
            label MSE='Mean Squared Error';
        run;

        *Adjust F-statistics by Multiple Imputation*;
        data type3table;
            set type3table;
            An=1/MS;
            Bn=1/(MS**2 * DF);
            Ad=1/MSE;
            Bd=1/(MSE**2 * de_DF);
        run;

        proc means data=type3table noprint;
            class source;
            output out=MIanalyze
                mean(An Bn Ad Bd)=ave_An ave_Bn ave_Ad ave_Bd
                var(An Ad)=ave_Cn ave_Cd
                max(_Imputation_)=M;
        run;

        data MIanalyze;
            set MIanalyze;
            rn=2* ave_An**2 /( 2*ave_Bn+(M+1)*ave_Cn/M );
            rd=2* ave_Ad**2 /( 2*ave_Bd+(M+1)*ave_Cd/M );
            MI_F=ave_Ad/ave_An;
            p_value=1-PROBF(MI_F,rn,rd);
        run;

        data finaloutput;
            set MIanalyze;
            where Source~=' ' and p_value~=.;
            keep Source M rd rn MI_F p_value;
            label M='# of Imputation' rn=DF rd='Error DF' MI_F='MI adjusted F' p_value='p-value';
        run;

        proc sort data=finaloutput;
            by source;
        run;
        proc sort data=type3table;
            by source;
        run;

        data finaloutput;
            merge finaloutput type3table (where=(_imputation_=1) keep=_imputation_ source
            ErrorTerm);
            by source;
        run;

        proc print data= finaloutput label;
            where p_value~=.;
            var source M rn ErrorTerm rd MI_F p_value;
        run;

%mend;
```

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 templates 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 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 TLFs 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 AUC of VAS Pain Intensity Scores through 48
hours - Efficacy Analysis Set - Multiple Imputation Results
```

but should appear as follows on the final TLF:

```
                        Table 14.2-1.1.1
Analysis of AUC of VAS Pain Intensity Scores through 48 hours
                      Efficacy Analysis Set
                   Multiple Imputation Results
```

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

On all listings the treatments, in order of appearance, are: EXPAREL, NO EXPAREL and, if applicable, NOT RANDOMIZED. Always insert a page break between treatments.

All listings should be sorted within treatment by site then subject within site then assessment date and time within subject unless indicated otherwise.

The programmer's note 'break out by site' indicates that the output is to present the results by overall sites and by pooled site(s) and site within pooled site(s). The output should first present overall sites then present pooled sites and site within pool with page breaks after each block. The sites within a pooled site will be presented immediately following the pooled site summary; therefore the 'break out by site' outputs should appear in the following order:

1. Overall
   1.1. Pool 1
      1.1.1.Site XXX – *site within pooled site*
      1.1.2.Site XXX – *site within pooled site*
   1.2. Pool 2
      1.2.1.Site XXX – *site within pooled site*
      1.2.2.Site XXX – *site within pooled site*
   1.3. Site XXX – *unpooled site*

where each level in the list has an output (or page in output) generated.

Table, figure and listing shells follow.

14. TABLE OF CONTENTS FOR TABLE MOCK-UPS

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.1-1.1: Tabulation of Subject Disposition – All Screened Subjects

Site: Overall	EXPAREL [N=XX] n (%)	No EXPAREL [N=XX] n (%)	Total [N=XX] n (%)
Screened [1]			xx
Screen Failure [1]			xx (xx.x)
Enrolled [1]			xx (xx.x)
Randomized	xx	xx	xx
Not Treated	xx	xx	xx
Treated	xx	xx	xx
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)
Per-protocol Analysis Set [3]@	xx (xx.x)	xx (xx.x)	xx (xx.x)
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 but did not receive EXPAREL: *list subjects*
Subjects randomized to NO EXPAREL but received EXPAREL: *list subjects*
Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Note to programmer: *Break out by site. 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.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.1-1.2: Tabulation of Reasons Subjects were Excluded from Per-protocol Analysis Set - Per-protocol Analysis Set

Site	Reason for Exclusion	EXPAREL [N=XX] n (%)	No EXPAREL [N=XX] n (%)	Total [N=XX] n (%)
Overall	Deviation of inclusion or exclusion criteria	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Mis-randomization	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Missing one or more of the scheduled VAS assessments	xx (xx.x)	xx (xx.x)	xx (xx.x)
	1 or more rescue medication doses without an VAS assessment	xx (xx.x)	xx (xx.x)	xx (xx.x)
	3+ rescue medication doses within 12 hour period during first 48 hours after surgery	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Protocol disallowed analgesic/anti-inflammatory medications within 48 hours after surgery	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Rescue medication received with a VAS pain score < 4	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Failure to take the protocol postsurgery medications per protocol	xx (xx.x)	xx (xx.x)	xx (xx.x)
XXX	Deviation of inclusion or exclusion criteria	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Mis-randomization	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Missing one or more of the scheduled VAS assessments	xx (xx.x)	xx (xx.x)	xx (xx.x)
	1 or more rescue medication dose without an VAS assessment	xx (xx.x)	xx (xx.x)	xx (xx.x)
	3+ rescue medication doses within 12 hour period within 48 hours after surgery	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Protocol disallowed analgesic/anti-inflammatory medications during first 48 hours after surgery	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Rescue medication received with a VAS pain score < 4	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Failure to take the protocol postsurgery medications per protocol	xx (xx.x)	xx (xx.x)	xx (xx.x)

Percentages based on number randomized.
Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Note to programmer: *Break out by site. Do not split site across pages.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.1-2.1.1: Summary of Subject Demographics - Safety Analysis Set

Site: Overall	Statistic	EXPAREL [N=XX]	No EXPAREL [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
Age Category				
≤ 65 yrs	n (%)	xx(xx.x)	xx(xx.x)	xx(xx.x)
> 65 yrs	n (%)	xx(xx.x)	xx(xx.x)	xx(xx.x)
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)

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Note to programmer: *Break out by site. Only categories available in the data will appear on the table. For individual sites the label should be the site number. Use this template also for table:*

Table 14.1-2.1.2: Subject Demographics – Efficacy Analysis Set
Table 14.1-2.1.3: Subject Demographics – Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331

Table 14.1-2.2.1: Summary of Subject Baseline Characteristics - Safety Analysis Set

Site: Overall

	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]	Total [N=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)
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
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
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
Body Mass Index (kg/m^2)		xx	xx	xx
	n	xx.x	xx.x	xx.x
	Mean	x.xx	x.xx	x.xx
	SD	xx	xx	xx
	Minimum	xx.x	xx.x	xx.x
	Median	xx	xx	xx
	Maximum	xx	xx	xx

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Note to programmer: *Break out by site. For individual sites the label should be the site number. Use this template also for table:*

Table 14.1-2.2.2: Summary of Subject Baseline Characteristics – Efficacy Analysis Set
Table 14.1-2.2.3: Summary of Subject Baseline Characteristics – Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.1-3.1: Summary of Surgery Characteristics - Safety Analysis Set

Site: Overall Characteristic	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]	Total [N=XX]
Location				
Left	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Right	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
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
Total Incision Length (cm)	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

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.1-3.1: Summary of Surgery Characteristics - Safety Analysis Set

Site: Overall Characteristic	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]	Total [N=XX]
Tourniquet				
Used	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Used	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Duration (minutes)	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
Maximum Inflation Pressure (mmHg)	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	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not 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

Source: *list SAS datasets used to create table* DDMONYYYYTHH:MM
SAS X.Y program_name

Note to programmer: *Break out by site. Use this template also for table:*

Table 14.1-3.2: Summary of Surgery Characteristics - Efficacy Analysis Set
Table 14.1-3.3: Summary of Surgery Characteristics - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.1-4.1: Tabulation of Incidence of Intraoperative Medications - Safety Analysis Set

Site: Overall Anatomical Therapeutic Class (ATC) Preferred Name	EXPAREL [N=XX] n (%)	No EXPAREL [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)
ETC.	xx (xx.x)	xx (xx.x)	xx (xx.x)

Medications are coded using World Health Organization Drug Dictionary (WHO-DD) March 2015.
Sorted by descending total incidence by ATC and preferred name within ATC.
Intraoperative medications are those given during surgery.
Subjects using the same prior medication more than once are counted only once at each summary level.
Source: *list SAS datasets used to create table*
SAS X.Y
DDMONYYYYTHH:MM
program_name

Note to programmer: *Break out by site. Use this template also for tables:*

Table 14.1-4.2: Tabulation of Incidence of Intraoperative Medications - Efficacy Analysis Set
Table 14.1-4.3: Tabulation of Incidence of Intraoperative Medications - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.1-5.1: Summary of Protocol Prescribed Postsurgical Medications Compliance - Safety Analysis Set

Site: Overall Medication	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]	Total [N=XX]
Overall	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
Acetaminophen	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
NSAID	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

Source: *list SAS datasets used to create table*
SAS X.Y
DDMONYYYYTHH:MM
program_name

Note to programmer: *Break out by site. Use this template also for tables:*

Table 14.1-5.2: Summary of Protocol Prescribed Postsurgical Medications Compliance - Efficacy Analysis Set
Table 14.1-5.3: Summary of Protocol Prescribed Postsurgical Medications Compliance - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-1.1.1: Analysis of AUC(12-48) of VAS Pain Intensity Scores - Efficacy Analysis Set - Multiple Imputation Results

Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
N	xx	xx
Mean	xxx.x	xxx.x
SD	xxx.xx	xxx.xx
Median	xxx.x	xxx.x
Minimum	xx	xx
Maximum	xxx	xxx
LS Mean [1]	xxx.x	xxx.x
Standard Error of LS Mean [1]	xxx.xx	xxx.xx
LS Treatment Difference (EXPAREL - No EXPAREL) [1]	xx.x	
Treatment Difference 95% Confidence Interval [1]	(xx.x, xx.x)	
Treatment p-value [1]	0.xxx	

AUC = area under the curve calculated using the trapezoidal method; LS = least squares;
VAS = 10 cm visual analog scale for pain, where 0 = no pain and 10 = pain as bad as it could possibly be;
[1] From an ANOVA with main effects of treatment and site.

Source: *list SAS datasets used to create table*
SAS *X.Y*

DDMONYYYYTHH:MM
program_name

Note to programmer: *The raw SAS outputs from the procedures used to produce ALL 14.2-1.1.* & 14.2-1.2 series tables should be saved as a possible appendix to the clinical study report (CSR).*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-1.1.2: Analysis of Variance Model Results for AUC(12-48) of VAS Pain Intensity Scores - Efficacy Analysis Set - Multiple Imputation Results

Effect	Model 1 Main Effects	Model 2 Main Effects w/ Interaction
Treatment	0.xxxx	0.xxxx
Site	0.xxxx	0.xxxx
Treatment-by-Site Interaction	NA	0.xxxx

p-values from SAS macro %type3_MI_mixed (Wang, et al). These p-values may differ from those derived using SAS PROC MIANALYZE as presented on table 14.2-1.1.
Note: AUC = area under the curve calculated using the trapezoidal method;
VAS = 10 cm visual analog scale for pain, where 0 = no pain and 10 = pain as bad as it could possibly be;
Model 1: ANOVA with main effects of treatment and site.
Model 2: ANOVA with main effects of treatment and site and treatment-by-site interaction.

Source: *list SAS datasets used to create table* *DDMONYYYYTHH:MM*
SAS X.Y *program_name*

Note to programmer: *The raw SAS outputs from the procedures used to produce ALL 14.2-1.2 series tables should be saved as a possible appendix to the clinical study report (CSR).*

Mock-up 14.2-1.1.1:

Table 14.2-1.2.1: Analysis of AUC(12-48) of VAS Pain Intensity Scores - Per-protocol Analysis Set - Multiple Imputation Results

Mock-up 14.2-1.1.2:

Table 14.2-1.2.2: Analysis of Variance Model Results for AUC(12-48) of VAS Pain Intensity Scores - Per-protocol Analysis Set - Multiple Imputation Results

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-2.1.1: Analysis of Postsurgical Total Opioid Consumption (MED mg) through 48 hours - Efficacy Analysis Set

Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
N	xx	xx
Geometric Mean	xx.x	xx.x
%CV	x.xx	x.xx
Mean	xxx.x	xxx.x
SD	xxx.xx	xxx.xx
Median	xxx.x	xxx.x
Minimum	xx	xx
Maximum	xxx	xxx
Treatment LS Mean [1]	xxx.x	xxx.x
Treatment Standard Error of LS Mean [1]	xxx.xx	xxx.xx
Treatment LS Ratio [1][2]	xx.x	
Treatment Ratio 95% Confidence Interval [1][2]	(xx.x, xx.x)	
Treatment p-value [1][2]	0.xxx	

[1] From an ANOVA with main effects of treatment and site on log-transformed total opioid consumption. Subjects without any opioid use are set to 1 before transforming. Results are back-transformed.
[2] Treatment ratio is EXPAREL / No EXPAREL. Ratios less than 1 favor EXPAREL.

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-2.1.2: Summary of Total Opioid Consumption (MED mg) through 48 hours by Site - Efficacy Analysis Set

Site	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
XXX	n	xx	xx
	Geometric Mean	xx.x	xx.x
	%CV	x.xx	x.xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx
YYY	n	xx	xx
	Geometric Mean	xx.x	xx.x
	%CV	x.xx	x.xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx
ZZZ	n	xx	xx
	Geometric Mean	xx.x	xx.x
	%CV	x.xx	x.xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Note to programmer: *Break out by site. Do not split a site's statistics across pages.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-2.1.3: Summary of Total Opioid Consumption (MED mg) by Time Period - Efficacy Analysis Set

Site: Overall Time Period	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
0-24 hrs	n	xx	xx
	Geometric Mean	xx.x	xx.x
	%CV	x.xx	x.xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx
0-48 hrs	n	xx	xx
	Geometric Mean	xx.x	xx.x
	%CV	x.xx	x.xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Note to programmer: *Break out by site. Time periods to appear on this table, in order, are 0-24, 0-48, 24-48 and 48-72. Do not split a time period statistics across pages.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-2.1.4: Summary of the Number of Times Opioid (Rescue) Medication was used by Subject - Efficacy Analysis Set

	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
Count Summary	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Minimum	xx.x	xx.x
	Median	xx	xx
	Maximum	xx	xx
Count Distribution			
0	n (%)	xx (xx.x)	xx (xx.x)
1	n (%)	xx (xx.x)	xx (xx.x)
2	n (%)	xx (xx.x)	xx (xx.x)
3	n (%)	xx (xx.x)	xx (xx.x)
4	n (%)	xx (xx.x)	xx (xx.x)
5	n (%)	xx (xx.x)	xx (xx.x)
…	n (%)	xx (xx.x)	xx (xx.x)
U	n (%)	xx (xx.x)	xx (xx.x)

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Note to programmer: *Break out by site. Distribution should present all counts up to the highest number of visits in the data (U) on each page.*

Note to programmer: *Use the mock-ups indicated to for following tables:*

Mock-up 14.2.1.1:

Table 14.2-2.2.1: Analysis of Postsurgical Total Opioid Consumption (MED mg) through 48 hours - Per-protocol Analysis Set

Mock-up 14.2.1.2:

Table 14.2-2.2.2: Summary of Total Opioid Consumption (MED mg) through 48 hours by Site - Per-protocol Analysis Set

Mock-up 14.2.1.3:

Table 14.2-2.2.3: Summary of Total Opioid Consumption (MED mg) by Time Period - Per-protocol Analysis Set

Mock-up 14.2.1.4:

Table 14.2-2.2.4: Summary of the Number of Times Opioid (Rescue) Medication was used by Subject - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-3.1.1: Analysis of Opioid-Free Subjects through 48 hours - Efficacy Analysis Set

	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
No Opioid Use	n (%)	xx (xx.x)	xx (xx.x)
Opioid Used	n (%)	xx (xx.x)	xx (xx.x)
	Treatment Difference [1]	xx.x	
	95% CI for Difference [1]	(xx.x, xx.x)	
	p-value [2]	0.xxxx	

[1] Treatment difference (EXPAREL - No EXPAREL) and confidence intervals (CI) are based on the normal approximation to the binomial distribution using SAS PROC FREQ with RISKDIFFC option.
[2] From Cochran-Mantel-Haenszel (CMH) test stratified by site.

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-3.1.2: Tabulation of Opioid-Free Subjects through 48 hours by Site - Efficacy Analysis Set

Site	Opioid Use	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
Overall	No Opioid Use	n (%)	xx (xx.x)	xx (xx.x)
	Opioid Used	n (%)	xx (xx.x)	xx (xx.x)
XXX	No Opioid Use	n (%)	xx (xx.x)	xx (xx.x)
	Opioid Used	n (%)	xx (xx.x)	xx (xx.x)
XXX	No Opioid Use	n (%)	xx (xx.x)	xx (xx.x)
	Opioid Used	n (%)	xx (xx.x)	xx (xx.x)

Source: *list SAS datasets used to create table*
SAS X.Y
DDMONYYYYTHH:MM
program_name

Note to programmer: *Break out by site. Do not split a site's statistics across pages.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-3.1.3: Tabulation of Opioid-Free Subjects through 24 and 72 hours - Efficacy Analysis Set

Site	Through (hours)		Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
Overall	24	No Opioid Use	n (%)	xx (xx.x)	xx (xx.x)
		Opioid Used	n (%)	xx (xx.x)	xx (xx.x)
	72	No Opioid Use	n (%)	xx (xx.x)	xx (xx.x)
		Opioid Used	n (%)	xx (xx.x)	xx (xx.x)

Source: *list SAS datasets used to create table*
SAS X.Y
DDMONYYYYTHH:MM
program_name

Note to programmer: *Break out by site. Do not split a site's statistics across pages.*

Note to programmer: *Use the mock-ups indicated to for following tables:*

Mock-up 14.2-3.1.1:

Table 14.2-3.2.1: Analysis of Opioid-Free Subjects through 48 hours - Per-protocol Analysis Set

Mock-up 14.2-3.1.2:

Table 14.2-3.2.2: Tabulation of Opioid-Free Subjects through 48 hours by Site - Per-protocol Analysis Set

Mock-up 14.2-3.1.3:

Table 14.2-3.2.3: Tabulation of Opioid-Free Subjects at Assessment Timepoints - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-4.1: Analysis of Time to First Rescue Medication Use (hours) - Efficacy Analysis Set

Site: Overall	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
Number of Subjects Taking			
Rescue Medication (Opioid)	n (%)	xx (xx.x)	xx (xx.x)
No Rescue Medication (censored)	n (%)	xx (xx.x)	xx (xx.x)
Time to First 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]		0.xxxx	

* indicates censored observation
CI = confidence interval
[1] Estimates from Kaplan-Meier analysis.
[2] p-value from log-rank test with terms for treatment comparing EXPAREL to No EXPAREL.
Source: *list SAS datasets used to create table*
SAS X.Y
DDMONYYYYTHH:MM
program_name

Note to programmer: *Break out by site. Do not split a site's statistics across pages. Do not report the p-value for sites other than 'Overall'. Use this mock-ups indicated to for following table:*

Table 14.2-4.2: Analysis of Time to First Rescue Medication Use (hours) - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-5.1.1: Summary of VAS AUC at Various Time Intervals – Efficacy Analysis Set

Site	Parameter	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
Overall	AUC(0-12)	n	xx	xx
		Mean	xx.x	xx.x
		SD	x.xx	x.xx
		Minimum	xx	xx
		Median	xx.x	xx.x
		Maximum	xx	xx
	AUC(12-24)	n	xx	xx
		Mean	xx.x	xx.x
		SD	x.xx	x.xx
		Minimum	xx	xx
		Median	xx.x	xx.x
		Maximum	xx	xx
	Etc.	n	xx	xx
		Mean	xx.x	xx.x
		SD	x.xx	x.xx
		Minimum	xx	xx
		Median	xx.x	xx.x
		Maximum	xx	xx

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Note to programmer: *Break out by site. Do not split a site's or AUC's statistics across pages. VAS AUCs to be presented on this table are, in order, AUC(0-12), AUC(12-24), AUC(12-72), AUC(24-48) and AUC(48-72).*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-5.1.2: Summary of VAS at Assessment Timepoints - Efficacy Analysis Set

Timepoint	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
Baseline	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx
PACU	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx
Etc.	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx

PACU is Postanesthesia Care Unit
Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Note to programmer: *Timepoints to appear on this table are, in order, Baseline, PACU and 4, 6, 8, 10, 12, 24, 28, 32, 36, 48, 52, 56, 60 and 72 hours.*

Note to programmer: *Use the indicated mock-up for the following tables:*

Use mock-up 14.2-5.1.1:

Table 14.2-5.1.3: Summary of VAS SPIS at Various Time Intervals - Efficacy Analysis Set

VAS SPIS to be presented on Table 14.2-5.1.3 are, in order, SPIS(0-12), SPIS(0-24), SPIS(0-48), SPIS(0-72), SPIS(12-24), SPIS(12-48), SPIS(12-72), SPIS(24-48) and SPIS(48-72). Do not break an SPIS's statistics across pages.

Use mock-up 14.2-5.1.1:

Table 14.2-5.2.1: Summary of VAS AUC at Various Time Intervals - Per-protocol Analysis Set

Use mock-up 14.2-5.1.2:

Table 14.2-5.2.2: Summary of VAS at Assessment Timepoints - Per-protocol Analysis Set

Use mock-up 14.2-5.1.1:

Table 14.2-5.2.3: Summary of VAS SPIS at Various Time Intervals - Per-protocol Analysis Set

VAS SPIS to be presented on Table 14.2-5.2.3 are, in order, SPIS(0-12), SPIS(0-24), SPIS(0-48), SPIS(0-72),SPIS(12-24), SPIS(12-48), SPIS(12-72), SPIS(24-48) and SPIS(48-72). Do not break an SPIS's statistics across pages.

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-6.1: Tabulation of Pain-free Subjects at Assessment Timepoints - Efficacy Analysis Set

Timepoint Opioid Use	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
Baseline			
Pain-Free	n (%)	xx (xx.x)	xx (xx.x)
Pained	n (%)	xx (xx.x)	xx (xx.x)
PACU			
Pain-Free	n (%)	xx (xx.x)	xx (xx.x)
Pained	n (%)	xx (xx.x)	xx (xx.x)
Etc.			
Pain-Free	n (%)	xx (xx.x)	xx (xx.x)
Pained	n (%)	xx (xx.x)	xx (xx.x)

Pain-free = VAS score ≤ 1.5 and no prior rescue medication use and no prior VAS score > 1.5.
Source: *list SAS datasets used to create table*
SAS X.Y
DDMONYYYYTHH:MM
program_name

Note to programmer: *Timepoints to appear on this table are, in order, Baseline, PACU and 4, 6, 8, 10, 12, 24, 28, 32, 36, 48, 52, 56, 60, and 72 hours. Do not split a timepoint across pages. Use this mock-up for the following table:*

Table 14.2-6.2: Tabulation of Pain-free Subjects at Assessment Timepoints - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-7.1: Tabulation of Opioid-Free Subjects through 24 and 72 hours - Efficacy Analysis Set

Time Interval	Opioid Use	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
0-24	No	n (%)	xx (xx.x)	xx (xx.x)
	Yes	n (%)	xx (xx.x)	xx (xx.x)
0-72	No	n (%)	xx (xx.x)	xx (xx.x)
	Yes	n (%)	xx (xx.x)	xx (xx.x)

Source: *list SAS datasets used to create table*
SAS X.Y
DDMONYYYYTHH:MM
program_name

Note to programmer: *Use the indicated mock-up for the following tables:*

Use mock-up 14.2-7.1:

Table 14.2-7.2: Tabulation of Opioid-Free Subjects through 24 and 48 hours - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-8.1.1: Summary of Overall Benefit of Analgesia Total Score by Timepoint - Efficacy Analysis Set

Timepoint	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]	p-value [1]
24 hours	n	xx	xx	
	Mean	xx.x	xx.x	
	SD	x.xx	x.xx	
	Minimum	xx	xx	
	Median	xx.x	xx.x	0.xxx
	Maximum	xx	xx	
48 hours	n	xx	xx	
	Mean	xx.x	xx.x	
	SD	x.xx	x.xx	
	Minimum	xx	xx	
	Median	xx.x	xx.x	0.xxx
	Maximum	xx	Xx	
72 hours	n	xx	xx	
	Mean	xx.x	xx.x	
	SD	x.xx	x.xx	
	Minimum	xx	xx	
	Median	xx.x	xx.x	0.xxx
	Maximum	xx	xx	

Total score = sum of scores from questions 1 to 6 plus 4 minus question 7 score.
[1] p-value from Kruskal-Wallis test.
Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-8.1.2: Summary of Overall Benefit of Analgesia Score by Timepoint and Question - Efficacy Analysis Set

Timepoint / Question		Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
24 hours				
1. Current Pain	Summary	n	xx	xx
		Mean	xx.x	xx.x
		SD	x.xx	x.xx
		Minimum	xx	xx
		Median	xx.x	xx.x
		Maximum	xx	xx
	Score			
	0	n (%)	xx (xx.x)	xx (xx.x)
	1	n (%)	xx (xx.x)	xx (xx.x)
	2	n (%)	xx (xx.x)	xx (xx.x)
	3	n (%)	xx (xx.x)	xx (xx.x)
	4	n (%)	xx (xx.x)	xx (xx.x)
2. Vomiting	Summary	n	xx	xx
		Mean	xx.x	xx.x
		SD	x.xx	x.xx
		Minimum	xx	xx
		Median	xx.x	xx.x
		Maximum	xx	xx
	Score			
	0	n (%)	xx (xx.x)	xx (xx.x)
	1	n (%)	xx (xx.x)	xx (xx.x)
	2	n (%)	xx (xx.x)	xx (xx.x)
	3	n (%)	xx (xx.x)	xx (xx.x)
	4	n (%)	xx (xx.x)	xx (xx.x)

Source: *list SAS datasets used to create table*
SAS X.Y
DDMONYYYYTHH:MM
program_name

Note to programmer: *Timepoints to appear on this table, in order, are 24, 48 and 72 hours. Questions to appear on this table, in order, are '1. Current Pain', '2. Vomiting', '3. Itching', '4. Sweating', '5. Freezing', '6. Dizziness', '7. Satisfaction'. Do not split a question's statistics across pages.*

Note to programmer: *Use the indicated mock-up for the following tables:*

Use mock-up 14.2-8.1.1:

Table 14.2-8.2.1: Summary of Overall Benefit of Analgesia Total Score by Timepoint - Per-protocol Analysis Set

Use mock-up 14.2-8.1.2:

Table 14.2-8.2.2: Summary of Overall Benefit of Analgesia Score by Timepoint and Question - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-9.1: Summary of Nurse's Satisfaction with Postsurgical Pain Control Questionnaire Score by Timepoint - Efficacy Analysis Set

Timepoint	Score	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
24 hours	Summary	n	xx	xx
		Mean	xx.x	xx.x
		SD	x.xx	x.xx
		Minimum	xx	xx
		Median	xx.x	xx.x
		Maximum	xx	xx
	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)

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Note to programmer: *Timepoints to appear on this table are 24, 48 and 72 hours. Do not split timepoint across pages. Use this mock-up for the following table:*

Table 14.2-9.2: Summary of Satisfaction with Postsurgical Pain Control Questionnaire Score by Timepoint - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-10.1.1: Analysis of Distance Walked (meters) during Timed Walk Test - Efficacy Analysis Set

Timepoint	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
Overall	LS Mean	xxx.x	xxx.x
	Standard Error of LS Mean	xxx.xx	xxx.xx
	LS Treatment Difference (EXPAREL - No EXPAREL)	xx.x	
	Treatment Difference 95% Confidence Interval	(xx.x, xx.x)	
	Treatment Difference p-value	0.xxx	
At Day 1-PM	LS Treatment Difference (EXPAREL - No EXPAREL)	xx.x	
	Treatment Difference 95% Confidence Interval	(xx.x, xx.x)	
At Day 2-AM	LS Treatment Difference (EXPAREL - No EXPAREL)	xx.x	
	Treatment Difference 95% Confidence Interval	(xx.x, xx.x)	
At Day 2-PM	LS Treatment Difference (EXPAREL - No EXPAREL)	xx.x	
	Treatment Difference 95% Confidence Interval	(xx.x, xx.x)	
At Day 3-AM	LS Treatment Difference (EXPAREL - No EXPAREL)	xx.x	
	Treatment Difference 95% Confidence Interval	(xx.x, xx.x)	
At Day 3-PM	LS Treatment Difference (EXPAREL - No EXPAREL)	xx.x	
	Treatment Difference 95% Confidence Interval	(xx.x, xx.x)	
At Day 4-PM	LS Treatment Difference (EXPAREL - No EXPAREL)	xx.x	
	Treatment Difference 95% Confidence Interval	(xx.x, xx.x)	

[1] MMRM with fixed effects of treatment, site, time and treatment-by-time interaction and a random effect of subject within treatment with XXXX covariance structure.

Source: *list SAS datasets used to create table*
SAS *X.Y*

DDMONYYYYTHH:MM
program_name

Note to programmer: *Timepoints for this table are Day 1-PM, Day 2-AM, Day 2-PM, Day 3-AM, Day 3-PM, Day 4-AM, and Day 14. Use this mock-up for the following table:*

Table 14.2-10.1.2: Analysis of Distance Walked (meters) during Timed Walk Test - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-10.2.1: Summary of Timed Walk Test by Timepoint - Efficacy Analysis Set

Timepoint	Parameter	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
Day 1-PM	Not performed	n (%)	xx (xx.x)	xx (xx.x)
	Reasons not performed			
	Pain	n (%)	xx (xx.x)	xx (xx.x)
	Weakness	n (%)	xx (xx.x)	xx (xx.x)
	Nausea/Vomiting	n (%)	xx (xx.x)	xx (xx.x)
	Other	n (%)	xx (xx.x)	xx (xx.x)
	Walking Aid			
	No	n (%)	xx (xx.x)	xx (xx.x)
	Yes	n (%)	xx (xx.x)	xx (xx.x)
	Physical Assistance			
	Total Assistance	n (%)	xx (xx.x)	xx (xx.x)
	Maximal Assistance	n (%)	xx (xx.x)	xx (xx.x)
	Minimal Assistance	n (%)	xx (xx.x)	xx (xx.x)
	Supervision	n (%)	xx (xx.x)	xx (xx.x)
	Modified Independence	n (%)	xx (xx.x)	xx (xx.x)
	Complete Independence	n (%)	xx (xx.x)	xx (xx.x)
	Distance (meters)	N	xx	xx
		Mean	xxx.x	xxx.x
		SD	xxx.xx	xxx.xx
		Median	xxx.x	xxx.x
		Minimum	xx	xx
		Maximum	xxx	xxx

Source: *list SAS datasets used to create table*
SAS *X.Y*
DDMONYYYYTHH:MM
program_name

Note to programmer: *Break out by site. Timepoints for this table are Day 1-PM, Day 2-AM, Day 2-PM, Day 3-AM, Day 3-PM, Day 4-AM, and Day 14 with one timepoint per page. Use this mock-up for the following table:*

Table 14.2-10.2.1: Summary of Distance Walked (meters) during Timed Walk Test by Timepoint - Per-protocol Analysis Set

Note to programmer: *Timepoints for this table are Day 1-PM, Day 2-AM, Day 2-PM, Day 3-AM, Day 3-PM, Day 4-AM, and Day 14. Use mock-up 14.2-10.1.1 for the following tables:*

Table 14.2-11.1.1: Analysis of Timed Up-and-go Test Time (seconds) - Efficacy Analysis Set

Table 14.2-11.1.2: Analysis of Timed Up-and-go Test Time (seconds) - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-11.2.1: Summary Timed Up-and-go Test Time by Timepoint - Efficacy Analysis Set

Timepoint	Parameter	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
Day 1-PM	Not performed	n (%)	xx (xx.x)	xx (xx.x)
	Reasons not performed			
	Pain	n (%)	xx (xx.x)	xx (xx.x)
	Weakness	n (%)	xx (xx.x)	xx (xx.x)
	Nausea/Vomiting	n (%)	xx (xx.x)	xx (xx.x)
	Other	n (%)	xx (xx.x)	xx (xx.x)
	Walking Aid			
	No	n (%)	xx (xx.x)	xx (xx.x)
	Yes	n (%)	xx (xx.x)	xx (xx.x)
	Physical Assistance			
	Total Assistance	n (%)	xx (xx.x)	xx (xx.x)
	Maximal Assistance	n (%)	xx (xx.x)	xx (xx.x)
	Minimal Assistance	n (%)	xx (xx.x)	xx (xx.x)
	Supervision	n (%)	xx (xx.x)	xx (xx.x)
	Modified Independence	n (%)	xx (xx.x)	xx (xx.x)
	Complete Independence	n (%)	xx (xx.x)	xx (xx.x)
	Time (seconds)	N	xx	xx
		Mean	xxx.x	xxx.x
		SD	xxx.xx	xxx.xx
		Median	xxx.x	xxx.x
		Minimum	xx	xx
		Maximum	xxx	xxx

Source: *list SAS datasets used to create table*
SAS *X.Y*

DDMONYYYYTHH:MM
program_name

Note to programmer: *Break out by site. Timepoints for this table are Day 1-PM, Day 2-AM, Day 2-PM, Day 3-AM, Day 3-PM, Day 4-AM, and Day 14 with one timepoint per page. Use this mock-up for the following table:*

Table 14.2-11.2.1: Summary of Distance Walked (m) during Timed Walk Test by Timepoint - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-12.1.1: Analysis of Stair Climb Test - Efficacy Analysis Set

Timepoint	Statistic	Ratio of EXPAREL (N=XX) / No EXPAREL (N=XX)
Day 1-PM	Odds Ratio (EXPAREL n=XX / No EXPAREL n=XX) [1]	xxx.x
	Odds Ratio 95% Confidence Interval [1]	(xx.x, xx.x)
Day 2-AM	Odds Ratio (EXPAREL n=XX / No EXPAREL n=XX) [1]	xxx.x
	Odds Ratio 95% Confidence Interval [1]	(xx.x, xx.x)
Day 2-PM	Odds Ratio (EXPAREL n=XX / No EXPAREL n=XX) [1]	xxx.x
	Odds Ratio 95% Confidence Interval [1]	(xx.x, xx.x)
Day 3-AM	Odds Ratio (EXPAREL n=XX / No EXPAREL n=XX) [1]	xxx.x
	Odds Ratio 95% Confidence Interval [1]	(xx.x, xx.x)
Day 3-PM	Odds Ratio (EXPAREL n=XX / No EXPAREL n=XX) [1]	xxx.x
	Odds Ratio 95% Confidence Interval [1]	(xx.x, xx.x)
Day 4-AM	Odds Ratio (EXPAREL n=XX / No EXPAREL n=XX) [1]	xxx.x
	Odds Ratio 95% Confidence Interval [1]	(xx.x, xx.x)
Day 14	Odds Ratio (EXPAREL n=XX / No EXPAREL n=XX) [1]	xxx.x
	Odds Ratio 95% Confidence Interval [1]	(xx.x, xx.x)

[1] Generalized mixed effect model with logit linking function and fixed effects of treatment, site, time and treatment-by-time interaction and a repeated effect of subject within treatment.

Source: *list SAS datasets used to create table*
SAS *X.Y*

DDMONYYYYTHH:MM
program_name

Note to programmer: *Timepoints for this table are Day 1-PM, Day 2-AM, Day 2-PM, Day 3-AM, Day 3-PM, Day 4-AM, and Day 14. Use this mock-up for the following table:*

Table 14.2-12.1.2: Analysis of Stair Climb Test - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-12.2.1: Tabulation of Stair Climb Test - Efficacy Analysis Set

Timepoint	Completed Test?	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
Day 1-PM	No	n (%)	XXX (XXX.X)	XXX (XXX.X)
	Yes	n (%)	XXX (XXX.X)	XXX (XXX.X)
Day 2-AM	No	n (%)	XXX (XXX.X)	XXX (XXX.X)
	Yes	n (%)	XXX (XXX.X)	XXX (XXX.X)
Day 2-PM	No	n (%)	XXX (XXX.X)	XXX (XXX.X)
	Yes	n (%)	XXX (XXX.X)	XXX (XXX.X)
Day 3-AM	No	n (%)	XXX (XXX.X)	XXX (XXX.X)
	Yes	n (%)	XXX (XXX.X)	XXX (XXX.X)
Day 3-PM	No	n (%)	XXX (XXX.X)	XXX (XXX.X)
	Yes	n (%)	XXX (XXX.X)	XXX (XXX.X)
Day 4-AM	No	n (%)	XXX (XXX.X)	XXX (XXX.X)
	Yes	n (%)	XXX (XXX.X)	XXX (XXX.X)
Day 14	No	n (%)	XXX (XXX.X)	XXX (XXX.X)
	Yes	n (%)	XXX (XXX.X)	XXX (XXX.X)

Source: *list SAS datasets used to create table*
SAS *X.Y*

DDMONYYYYTHH:MM
program_name

Note to programmer: *Break out by site. Timepoints for this table are Day 1-PM, Day 2-AM, Day 2-PM, Day 3-AM, Day 3-PM, Day 4-AM, and Day 14. Use this mock-up for the following table:*

Table 14.2-12.2.2: Tabulation of Stair Climb Test - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-13.1.1: Analysis of Time to Discharge Ready (days) - Efficacy Analysis Set

Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
N	xx	xx
Mean	xxx.x	xxx.x
SD	xxx.xx	xxx.xx
Median	xxx.x	xxx.x
Minimum	xx	xx
Maximum	xxx	xxx
LS Mean [1]	xxx.x	xxx.x
Standard Error of LS Mean [1]	xxx.xx	xxx.xx
LS Treatment Difference (EXPAREL - No EXPAREL) [1]	xx.x	
Treatment Difference 95% Confidence Interval [1]	(xx.x, xx.x)	
Treatment Difference p-value [1]	0.xxx	

[1] From an ANOVA with main effects of treatment and site.

Source: list SAS datasets used to create table
SAS X.Y

DDMONYYYYTHH:MM
program_name

Note to programmer: *Use this mock-up for the following table:*

Table 14.2-13.1.2: Analysis of Time to Discharge Ready (days) - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-13.2.1: Summary of Discharge Ready at Assessment - Efficacy Analysis Set

Assessment Time	Discharge Ready	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
Day 1-PM (12 hr)	No	n (%)	xx (xx.x)	xx (xx.x)
	Yes	n (%)	xx (xx.x)	xx (xx.x)
Day 2-AM (24 hr)	No	n (%)	xx (xx.x)	xx (xx.x)
	Yes	n (%)	xx (xx.x)	xx (xx.x)
Day 2-PM (36 hr)	No	n (%)	xx (xx.x)	xx (xx.x)
	Yes	n (%)	xx (xx.x)	xx (xx.x)
Day 3-AM (48 hr)	No	n (%)	xx (xx.x)	xx (xx.x)
	Yes	n (%)	xx (xx.x)	xx (xx.x)
Day 3-PM (60 hr)	No	n (%)	xx (xx.x)	xx (xx.x)
	Yes	n (%)	xx (xx.x)	xx (xx.x)
Day 4-AM (72 hr)	No	n (%)	xx (xx.x)	xx (xx.x)
	Yes	n (%)	xx (xx.x)	xx (xx.x)

Source: *list SAS datasets used to create table*
SAS X.Y
DDMONYYYYTHH:MM
program_name

Note to programmer: *Do not split timepoint across pages. Use this mock-up for the following table:*

Table 14.2-13.2.2: Summary of Discharge Ready at Assessment - Per-protocol Analysis Set

Note to programmer: *Use mock-up 14.2-13.1.1 for the following tables:*

Table 14.2-14.1.1: Analysis of Hospital Length of Stay (days) - Efficacy Analysis Set
Table 14.2-14.1.2: Analysis of Hospital Length of Stay (days) - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-14.2.1: Summary of Hospital Length of Stay (days) Overall and by Site - Efficacy Analysis Set

Site	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
Overall	N	xx	xx
	Mean	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Minimum	xx	xx
	Maximum	xxx	xxx
XXX	N	xx	xx
	Mean	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Minimum	xx	xx
	Maximum	xxx	xxx
XXX	N	xx	xx
	Mean	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Minimum	xx	xx
	Maximum	xxx	xxx

Length of Stay is the time from hospital admission to discharge.

Source: *list SAS datasets used to create table*
SAS *X.Y*

DDMONYYYYTHH:MM
program_name

Note to programmer: *Break out by site. Use this mock-up for the following table:*

Table 14.2-14.2.2: Summary of Hospital Length of Stay (days) Overall and by Site - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-15.1.1.1: Analysis of Incidence of Skilled Nursing Facility (SNF) Use - Efficacy Analysis Set

	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
No SNF	n (%)	xx (xx.x)	xx (xx.x)
SNF	n (%)	xx (xx.x)	xx (xx.x)
	Treatment Difference [1]	xx.x	
	95% CI for Difference [1]	(xx.x, xx.x)	
	p-value [2]	0.xxxx	

[1] Treatment difference (EXPAREL - No EXPAREL) and confidence intervals (CI) are based on the normal approximation to the binomial distribution using SAS PROC FREQ with RISKDIFFC option.
[2] From Cochran-Mantel-Haenszel (CMH) test stratified by site.

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Note to programmer:

Use mock-up 14.2-15.1.1 for the following table:

Table 14.2-15.1.1.2: Analysis of Incidence of Skilled Nursing Facility Use - Per-protocol Analysis Set

Note to programmer:

Use mock-up 14.2-13.1.1 for the following tables:

Table 14.2-15.2.1.1: Analysis of Days in Skilled Nursing Facility - Efficacy Analysis Set
Table 14.2-15.2.1.2: Analysis of Days in Skilled Nursing Facility - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-15.3.1: Incidence of Skilled Nursing Facility Use Overall and by Site - Efficacy Analysis Set

Site	Skilled Nursing Facility Use	EXPAREL [N=XX]	No EXPAREL [N=XX]
Overall	No	xxx (xx.x)	xxx (xx.x)
	Yes	xxx (xx.x)	xxx (xx.x)
Pool1	No	xxx (xx.x)	xxx (xx.x)
	Yes	xxx (xx.x)	xxx (xx.x)
XXX	No	xxx (xx.x)	xxx (xx.x)
	Yes	xxx (xx.x)	xxx (xx.x)
XXX	No	xxx (xx.x)	xxx (xx.x)
	Yes	xxx (xx.x)	xxx (xx.x)
XXX	No	xxx (xx.x)	xxx (xx.x)
	Yes	xxx (xx.x)	xxx (xx.x)
XXX	No	xxx (xx.x)	xxx (xx.x)
	Yes	xxx (xx.x)	xxx (xx.x)
XXX	No	xxx (xx.x)	xxx (xx.x)
	Yes	xxx (xx.x)	xxx (xx.x)

Source: *list SAS datasets used to create table*
SAS *X.Y*

DDMONYYYYTHH:MM
program_name

Note to programmer: *Break out by site. Use this mock-up for the following table:*

Table 14.2-15.3.2: Incidence of Skilled Nursing Facility Overall and by Site - Per-protocol Analysis Set

Note to programmer: *Use mock-up 14.2-13.1.1 for the following tables:*

Table 14.2-16.1.1: Analysis of Number of Physical Therapy Visits - Efficacy Analysis Set
Table 14.2-16.1.2: Analysis of Number of Physical Therapy Visits - Per-protocol Analysis Set

Use mock-up 14.2-2.1.4 for the following tables:

Table 14.2-16.2.1: Summary of Number Physical Therapy Visits Overall and by Site - Efficacy Analysis Set
Table 14.2-16.2.2: Summary of Number Physical Therapy Visits Overall and by Site - Per-protocol Analysis Set

Use mock-up 14.2-13.1.1 for the following tables:

Table 14.2-17.1.1: Analysis of Number of Emergency Room Visits - Efficacy Analysis Set
Table 14.2-17.1.2: Analysis of Number of Emergency Room Visits - Per-protocol Analysis Set

Use mock-up 14.2-2.1.4 for the following tables:

Table 14.2-17.2.1: Summary of Number Emergency Room Visits - Efficacy Analysis Set
Table 14.2-17.2.2: Summary of Number Emergency Room Visits - Per-protocol Analysis Set

Use mock-up 14.2-13.1.1 for the following tables:

Table 14.2-18.1.1: Analysis of Number of Phone Calls Related to Pain - Efficacy Analysis Set
Table 14.2-18.1.2: Analysis of Number of Phone Calls Related to Pain - Per-protocol Analysis Set

Use mock-up 14.2-2.1.4 for the following tables:

Table 14.2-18.2.1: Summary of Number of Phone Calls Related to Pain - Efficacy Analysis Set
Table 14.2-18.2.2: Summary of Number of Phone Calls Related to Pain - Per-protocol Analysis Set

Use mock-up 14.2-13.1.1 for the following tables:

Table 14.2-19.1.1: Analysis of Number of Unscheduled Office Visits Related to Pain - Efficacy Analysis Set
Table 14.2-19.1.2: Analysis of Number of Unscheduled Office Visits Related to Pain - Per-protocol Analysis Set

Use mock-up 14.2-2.1.4 for the following tables:

Table 14.2-19.2.1: Summary of Number of Unscheduled Office Visits Related to Pain - Efficacy Analysis Set

Table 14.2-19.2.2: Summary of Number of Unscheduled Office Visits Related to Pain - Per-protocol Analysis Set

Use mock-up 14.2-15.1.1.1 for the following tables, replace 'No SNF' with 'No Readmission' and 'SNF' with 'Readmission':

Table 14.2-20.1: Analysis of Incidence of Hospital Readmissions - Efficacy Analysis Set
Table 14.2-20.2: Analysis of Incidence of Hospital Readmissions - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.2-21.1: Incidence of Intensive Care Admissions (ICU) and Summary of Time in Postanesthesia Care Unit (hours) - Efficacy Analysis Set

	Statistic	EXPAREL [N=XX]	No EXPAREL [N=XX]
No ICU Admission	n (%)	xx (xx.x)	xx (xx.x)
ICU Admission	n (%)	xx (xx.x)	xx (xx.x)
Time in PACU (hours)	N	xx	xx
	Mean	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Minimum	xx	xx
	Maximum	xxx	xxx

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Note to programmer:

Use mock-up 14.2-21.1 for the following table:

Table 14.2-21.2: Incidence of Intensive Care Admissions (ICU) and Summary of Time in Postanesthesia Care Unit (hours) - Per-protocol Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.3-1.1.1: Overview of Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set

Number of	EXPAREL [N=XX] n (%)	No EXPAREL [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)
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)

Source: *list SAS datasets used to create table*
SAS X.Y
DDMONYYYYTHH:MM
program_name

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.3-1.1.2: Tabulation of Incidence of Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set

System Organ Class Preferred Term	EXPAREL [N=XX] n (%)	No EXPAREL [N=XX] n (%)	Total [N=XX] n (%)
Subjects with at least one 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)
ETC.	xx (xx.x)	xx (xx.x)	xx (xx.x)

Adverse events coded using the Medical Dictionary for Regulatory Activities (MedDRA TBD).
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.
Source: *list SAS datasets used to create table*
SAS X.Y
DDMONYYYYTHH:MM
program_name

Note to programmer: *Only present overall sites. Use mock-up Table 14.3-2.1.2 for the following tables:*

Table 14.3-1.1.3: Summary of Incidence of Study Drug-Related Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set
Table 14.3-1.1.4: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) Leading to Study Withdrawal - Safety Analysis Set
Table 14.3-1.1.5: Summary of Incidence of Study Drug-Related Treatment-Emergent Adverse Events (TEAEs) Leading to Study Withdrawal - Safety Analysis Set

For related tables add the following footnote to the table:
Related TEAEs are those AEs indicated as 'possible', 'probable' or 'definite' related by the investigator on the AE CRF.

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.3-1.1.6: Tabulation of Incidence of Treatment-Emergent Adverse Events (TEAEs) by Severity - Safety Analysis Set

System Organ Class Preferred Term	Severity	EXPAREL [N=XX] n (%)	No EXPAREL [N=XX] n (%)	Total [N=XX] n (%)
Subjects with at least one 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)

Adverse events coded using the Medical Dictionary for Regulatory Activities (MedDRA TBD).
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.
Source: *list SAS datasets used to create table*
SAS X.Y
DDMONYYYYTHH:MM
program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Table 14.3-1.1.7: Tabulation of Incidence of Treatment-Emergent Adverse Events (TEAEs) by Relationship to Study Drug - Safety Analysis Set

System Organ Class Preferred Term	Relation	EXPAREL [N=XX] n (%)	No EXPAREL [N=XX] n (%)	Total [N=XX] n (%)
Subjects with at least one TEAE	Unlikely	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Possible	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Probable	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Definite	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC1	Unlikely	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Possible	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Probable	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Definite	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT1.1	Unlikely	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Possible	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Probable	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Definite	xx (xx.x)	xx (xx.x)	xx (xx.x)

Adverse events coded using the Medical Dictionary for Regulatory Activities (MedDRA TBD).
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.
Source: *list SAS datasets used to create table*
SAS X.Y
DDMONYYYYTHH:MM
program_name

Note to programmer: *Only present overall sites. Use indicated mock-up for the following tables:*

Serious adverse event tables:

Use mock-up Table 14.3-1.1.1
Table 14.3-1.2.1: Overview of Serious Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set

Use mock-up Table 14.3-1.1.2
Table 14.3-1.2.2: Tabulation of Incidence of Serious Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set

Use mock-up Table 14.3-2.1.2
Table 14.3-1.2.3: Tabulation of Incidence of Study Drug-Related Serious Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set

Use mock-up Table 14.3-2.1.2
Table 14.3-1.2.4: Tabulation of Incidence of Serious Treatment-Emergent Adverse Events (TEAEs) Leading to Study Withdrawal - Safety Analysis Set

Use mock-up Table 14.3-2.1.2
Table 14.3-1.2.5: Tabulation of Incidence of Study Drug-Related Serious Treatment-Emergent Adverse Events (TEAEs) Leading to Study Withdrawal - Safety Analysis Set

Use mock-up Table 14.3-2.1.2
Table 14.3-1.2.6: Tabulation of Incidence of Serious Treatment-Emergent Adverse Events (TEAEs) Resulting in Death - Safety Analysis Set

Use mock-up Table 14.3-2.1.7
Table 14.3-1.2.7: Tabulation of Incidence of Study Drug-Related Serious Treatment-Emergent Adverse Events (TEAEs) Resulting in Death - Safety Analysis Set

Adverse events of special interest tables:

Use mock-up Table 14.3-1.1.1
Table 14.3-1.3.1: Overview of Treatment-Emergent Adverse Events (TEAEs) of Special Interest - Safety Analysis Set

Use mock-up Table 14.3-1.1.2
Table 14.3-1.3.2: Tabulation of Incidence of Treatment-Emergent Adverse Events (TEAEs) of Special Interest - Safety Analysis Set

Use mock-up Table 14.3-2.1.2
Table 14.3-1.3.3: Tabulation of Incidence of Study Drug-Related Treatment-Emergent Adverse Events (TEAEs) of Special Interest - Safety Analysis Set

Use mock-up Table 14.3-2.1.2
Table 14.3-1.3.4: Tabulation of Incidence of Treatment-Emergent Adverse Events (TEAEs) of Special Interest Leading to Study Withdrawal - Safety Analysis Set

Use mock-up Table 14.3-2.1.2
Table 14.3-1.3.5: Tabulation of Incidence of Study Drug-Related Treatment-Emergent Adverse Events (TEAEs) of Special Interest Leading to Study Withdrawal - Safety Analysis Set

Use mock-up Table 14.3-2.1.2
Table 14.3-1.3.6: Tabulation of Incidence of Treatment-Emergent Adverse Events (TEAEs) of Special Interest Resulting in Death - Safety Analysis Set

Use mock-up Table 14.3-1.1.7
Table 14.3-1.3.7: Tabulation of Incidence of Study Drug-Related Treatment-Emergent Adverse Events (TEAEs) of Special Interest Resulting in Death - Safety Analysis Set

Non-serious adverse events tables - needed for ClinTrials.GOV posting. For these tables only present non-serious (ie, AESER=NO) TEAEs:

Use mock-up Table 14.3-1.1.2
Table 14.3-1.4.1.1: Tabulation of Incidence of Non-Serious Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set

Use mock-up Table 14.3-1.1.2
Table 14.3-1.4.1.2: Tabulation of Incidence of Study Drug-Related Non-Serious Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set

Use mock-up Table 14.3-1.1.2
Table 14.3-1.4.1.3: Tabulation of Incidence of Non-Serious Treatment-Emergent Adverse Events (TEAEs) Leading to Study Withdrawal - Safety Analysis Set

Use mock-up Table 14.3-1.1.2
Table 14.3-1.4.1.4: Tabulation of Incidence of Study Drug-Related Non-Serious Treatment-Emergent Adverse Events (TEAEs) Leading to Study Withdrawal - Safety Analysis Set

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Use mock-up Table 14.3-1.1.2
Table 14.3-1.4.2.1: Tabulation of Incidence of Non-Serious Treatment-Emergent Adverse Events (TEAEs) of Special Interest - Safety Analysis Set

Use mock-up Table 14.3-1.1.2
Table 14.3-1.4.2.2: Tabulation of Incidence of Study Drug-Related Non-Serious Treatment-Emergent Adverse Events (TEAEs) of Special Interest - Safety Analysis Set

Use mock-up Table 14.3-1.1.2
Table 14.3-1.2.3: Tabulation of Incidence of Non-Serious Treatment-Emergent Adverse Events (TEAEs) of Special Interest Leading to Study Withdrawal - Safety Analysis Set

Use mock-up Table 14.3-1.1.7
Table 14.3-1.2.4: Tabulation of Incidence of Study Drug-Related Non-Serious Treatment-Emergent Adverse Events (TEAEs) of Special Interest Leading to Study Withdrawal - Safety Analysis Set

Note to programmer: *Use mock-up 14.1-4.1 for the following tables:*

Table 14.3-2.1: Tabulation of Incidence of Prior Medications - Safety Analysis Set

On this table change the footnote 'Intraoperative medications are those given during surgery.
' to '*Prior medications are those stopped before end of surgery.*'

Table 14.3-2.2: Incidence of Concomitant Medications - Safety Analysis Set.

*On this table change the footnote 'Intraoperative medications are those given during surgery.
' to 'Concomitant medications are those taken between the end of surgery and discharge from study.'*

15. TABLE OF CONTENTS FOR LISTING MOCK-UPS

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-1: Subject Disposition - All Subjects
TREATMENT: *treatment-name*

Site	Subject	Date of Last Visit	End of Study Status	Specify
XXX	XXX-YYYY	DDMONYYYY		

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

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-331
Listing 16.2-2: Randomization and Analysis Sets - Randomized Subjects
TREATMENT: *treatment-name*

Site	Subject	Region	Pooled Site Number	Randomization		Analysis Set		
				Date and Time	Number	Safety	Efficacy	Per-protocol
XXX	XXX-YYYY	XXX	XXXXX	DDMONYYYYTHH:MM	XXXXX	X	X	X

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Note to programmer: *Analysis set will by 'Y' if subject in set, blank otherwise. If a site is not pooled, then the pooled site number is the site number.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-3: Demographics - All Subjects
TREATMENT: *treatment-name*

Site	Subject	Subject Init.	Informed Consent Date	Birth Date	Age (yrs)	Sex	Race	Ethnicity	ASA Class	Country
XXX	XXX-YYYY	AMZ	DDMONYYYY	DDMONYYYY	XX	XXXXXX	XXXXXXXXXXXXXXXXXX	XXXXXXXXX	X	XXXXXXX

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-4: Height and Weight - All Subjects
TREATMENT: *treatment-name*

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

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-5.1: Surgery Characteristics (Part 1 of 2) - Randomized Subjects
TREATMENT: *treatment-name*

Site	Subject	Date	Start Time	Stop Time	Duration (hrs)	Location	Total Incision Length (cm)	Bupivacaine HCl Administration Time	Anesthesia Type
XXX	XXX-YYYY	DDMONYYYY	HH:MM	HH:MM	X.X	XXXXX	XX.X	HH:MM	XXXXXXXXXXXXXXXXXXXX

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-5.2: Surgery Characteristics (Part 1 of 2) - Randomized Subjects
TREATMENT: *treatment-name*

		Tourniquet					Drain			
Site	Subject	Used?	Start Time	Stop Time	Duration (hrs)	Maximum Pressure (mmHg)	Used?	Start Time	Stop Time	Duration (hrs)
XXX	XXX-YYYY	XXX	HH:MM	HH:MM	X.X	XXX	XXX	HH:MM	HH:MM	XXX.X

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-6: Visual Analog Scale (VAS) - Randomized Subjects
TREATMENT: *treatment-name*

Site	Subject	Date Time	Time From Dose: Scheduled (hr)	Time From Dose: Actual (hr)	Time From Dose: Deviation (hrs)	VAS Score (cm)	Pain-Free[1]
XXX	XXX-YYYY	DDMONYYYYTHH:MM	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
[1] pain free is VAS pain intensity score ≤ 1.5 cm with no prior rescue medication use and no prior VAS pain intensity score > 1.5 cm.
Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

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 pain free 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-331
Listing 16.2-7.1: Opioid Rescue Medication Total Dose (MED mg) and Opioid-Free Status - Randomized Subjects
TREATMENT: *treatment-name*

Site	Subject	24 hrs	48 hrs	72 hrs	24-48hrs	48-72hrs	Opioid-Free through 24 hrs	Opioid-Free through 48 hrs	Opioid-Free through 72 hrs
XXX	XXX-YYYY	XXXX.X	XXXX.X	XXXX.X	XXXX.X	XXXX.X	NO	NO	NO
XXX	XXX-YYYY	-	XXXX.X	XXXX.X	XXXX.X	XXXX.X	YES	NO	NO
XXX	XXX-YYYY	-	-	-	-	-	YES	YES	YES

Total dose is dose from end of surgery through timepoint.
Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-7.2: Opioid Rescue Medication - Randomized Subjects
TREATMENT: *treatment-name*

Site	Subject	Date and Time	Time to Rescue (hr)	Medication	Dose (units)	Conversion Factor	Dose (MED mg)	Route
XXX	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.
Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-8: Timed Walk Test - Randomized Subjects
TREATMENT: *treatment-name*

Site	Subject	Timepoint	Date and Time	Done?	Reason not done	Distance (m)	Walking Aid?	Physical Assistance
XXX	XXX-YYYY	Day 1-PM	DDMONYYYYTHH:MM	Y		XX	XXX	X
		Day 2-AM	DDMONYYYYTHH:MM	N	XXXXXXXXXXXXXXX			
		Day 2-PM	DDMONYYYYTHH:MM	Y		XX	XX	X
		Day 3-AM	DDMONYYYYTHH:MM	Y		XX	XX	X
		Day 3-PM	DDMONYYYYTHH:MM	Y		XX	XX	X
		Day 4-AM	DDMONYYYYTHH:MM	Y		XX	XX	X
		Day 4-PM	DDMONYYYYTHH:MM	Y		XX	XX	X
		Day 14	DDMONYYYYTHH:MM	Y		XX	XX	X

Physical Assistance: 1=Total Assistance 2=Maximal Assistance 3=Moderate Assistance
4=Minimal Assistance 5=Supervision 6=Modified Independence 7=Complete Independence
Source: *list SAS datasets used to create table*
SAS X.Y
DDMONYYYYTHH:MM
program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-9: Timed Up-and-go Test - Randomized Subjects
TREATMENT: *treatment-name*

Site	Subject	Timepoint	Date and Time	Done?	Reason not done	Duration of Test (seconds)	Aid Used?	Physical Assistance
XXX	XXX-YYYY	Day 1-PM	DDMONYYYYTHH:MM	Y				
		Day 2-AM	DDMONYYYYTHH:MM	N	XXXXXXXXXXXXXXX	XXX	XXX	
		Day 2-PM	DDMONYYYYTHH:MM	Y				
		Day 3-AM	DDMONYYYYTHH:MM	Y				
		Day 3-PM	DDMONYYYYTHH:MM	Y				
		Day 4-AM	DDMONYYYYTHH:MM	Y				
		Day 4-PM	DDMONYYYYTHH:MM	Y				
		Day 14	DDMONYYYYTHH:MM	Y				

Physical Assistance: 1=Total Assistance 2=Maximal Assistance 3=Moderate Assistance
4=Minimal Assistance 5=Supervision 6=Modified Independence 7=Complete Independence
Source: *list SAS datasets used to create table*
SAS X.Y DDMONYYYYTHH:MM
program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-10: Stair Climbing Test - Randomized Subjects
TREATMENT: *treatment-name*

Site	Subject	Timepoint	Date and Time	Done?	Reason not done	Successfully Completed
XXX	XXX-YYYY	Day 1-PM	DDMONYYYYTHH:MM	Y		
		Day 2-AM	DDMONYYYYTHH:MM	N	XXXXXXXXXXXXXXX	XXX
		Day 2-PM	DDMONYYYYTHH:MM	Y		
		Day 3-AM	DDMONYYYYTHH:MM	Y		
		Day 3-PM	DDMONYYYYTHH:MM	Y		
		Day 4-AM	DDMONYYYYTHH:MM	Y		
		Day 4-PM	DDMONYYYYTHH:MM	Y		
		Day 14	DDMONYYYYTHH:MM	Y		

Physical Assistance: 1=Total Assistance 2=Maximal Assistance 3=Moderate Assistance
4=Minimal Assistance 5=Supervision 6=Modified Independence 7=Complete Independence
Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-11: Overall Benefit of Analgesia - Randomized Subjects
TREATMENT: *treatment-name*

		Assessment				Question							
Site	Subject	Date and Time	Schedule (hrs)	Actual (hrs)	Deviation (hrs)	1	2	3	4	5	6	7	Total Score
XXX	XXX-YYYY	DDMONYYYYTHH:MM	24	XX.X	XX.X	X	X	X	X	X	X	X	XX
		DDMONYYYYTHH:MM	48	XX.X	XX.X	X	X	X	X	X	X	X	XX
		DDMONYYYYTHH:MM	72	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 the past 24 h (0=not at all to 4=very much)
Source: *list SAS datasets used to create table* DDMONYYYYTHH:MM
SAS X.Y program_name

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-12: Nurse's Satisfaction with Post-Surgical Pain Control - Randomized Subjects

TREATMENT: *treatment-name*

Site	Subject	Assessment	Date and Time	Rating	Score
XXX	XXX-YYYY	24 hr	DDMONYYYYTHH:MM	EXTREMELY DISSATISFIED	1
		48 hr	DDMONYYYYTHH:MM	DISSATISFIED	2
		72 hr	DDMONYYYYTHH:MM	NEITHER SATISFIED NOR DISSATISFIED	3
XXX	XXX-YYYY	24 hr	DDMONYYYYTHH:MM	SATISFIED	4
		48 hr	DDMONYYYYTHH:MM	EXTREMELY SATISIFIED	5
		72 hr	DDMONYYYYTHH:MM	EXTREMELY SATISIFIED	5

Etc.

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-13: Modified Post-Anesthesia Discharge Scoring System (MPADSS) - Randomized Subjects
TREATMENT: *treatment-name*

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

Total score = sum of scores.
*=out of window
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
Source: list SAS datasets used to create table
SAS X.Y

DDMONYYYYTHH:MM
program_name

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-14: Day 30 Phone Call - Randomized Subjects
TREATMENT: *treatment-name*

Site	Subject	Date and Time	Schedule (days)	Actual (days)	Deviation (days)	Number of pain-related Phone Calls	Number of pain-related Office Visits	ER Visits	PT Visits	Days in SNF
XXX	XXX-YYYY	DDMONYYYYTHH:MM	29	XX	XX.X	XX	XX	XX	XX	XX
XXX	XXX-YYYY	DDMONYYYYTHH:MM	29	XX	XX.X	XX	XX	XX	XX	XX
XXX	XXX-YYYY	DDMONYYYYTHH:MM	29	XX	XX.X	XX	XX	XX	XX	XX

ER=Emergency Room PT=Physical Therapy SNF=Skilled Nursing Facility
Source: *list SAS datasets used to create table*
SAS X.Y
DDMONYYYYTHH:MM
program_name

Note to programmer: *Sort by date and time within subject. If subject had no phone call, office, ER or PT visits or no days in SNF put '0' in column.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-15: Vital Signs Assessment - All Subjects
TREATMENT: *treatment-name*

Site	Subject	Date and Time	Visit	Heart Rate (bpm)	Blood Pressure (mmHg)	
					Systolic	Diastolic
XXX	XXX-YYYY	DDMONYYYYTHH:MM	Screening	XX	XXX	XX
		DDMONYYYYTHH:MM	Day 0	XX	XXX	XX
	XXX-YYYY	DDMONYYYYTHH:MM	Screening	XX	XXX	XX
		DDMONYYYYTHH:MM	Day 0	XX	XXX	XX
	XXX-YYYY	DDMONYYYYTHH:MM	Screening	XX	XXX	XX
		DDMONYYYYTHH:MM	Day 0	XX	XXX	XX
	XXX-YYYY	DDMONYYYYTHH:MM	Screening	XX	XXX	XX
		DDMONYYYYTHH:MM	Day 0	XX	XXX	XX

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-16: Electrocardiogram Findings - Investigator Assessment - All Subjects
TREATMENT: *treatment-name*

		Assessment		
Site	Subject	Date and Time	Schedule (hrs)	Finding
XXX	XXX-YYYY	DDMONYYYYTHH:MM	Screening	Normal
	XXX-YYYY	DDMONYYYYTHH:MM	Screening	Normal
	XXX-YYYY	DDMONYYYYTHH:MM	Screening	Normal
	XXX-YYYY	DDMONYYYYTHH:MM	Screening	Normal
	XXX-YYYY	DDMONYYYYTHH:MM	Screening	Normal
	XXX-YYYY	DDMONYYYYTHH:MM	Screening	Normal
	XXX-YYYY	DDMONYYYYTHH:MM	Screening	Normal

*=out of window

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-17.1: All Adverse Events - All Subjects
Treatment: *treatment-name*

Site	Subject	TEAE	Data Type	Data
XXX	XXX-YYYY	N	Start	DDMONYYYYTHH:MM
			Stop	DDMONYYYYTHH:MM
			AE Number	X
			System Organ Class	XXXXXXXXXXXXXXXXX
			Preferred	XXXXXXXXXXXXXXXXXXXX
			Verbatim	XXXXXXXXXXXXXXXXXXXXXX
			Severity	XXXXXXXX
			Relationship to Study Drug	XXXXXXXX
			Action Taken	XXXXXXXXXXXXXXXXXXXX
			Outcome	XXXXXXXXXXXXX
			Serious	XXX
			Serious Cause(s)	XXXXXXXXXXXX
				XXXXXXXXXXXXXXXXXXXXX

TEAE: Treatment-Emergent AE (Y=TEAE/N=Not TEAE)
Source: *list SAS datasets used to create listing*
SAS *X.Y*

DDMONYYYYTHH:MM
program_name

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 template for the following listings:*

Listing 16.2-17.2.1: Treatment-Emergent Adverse Events - Randomized Subjects
Listing 16.2-17.2.2: Treatment-Emergent Study Drug-Related Adverse Events - Randomized Subjects
Listing 16.2-17.3: All Serious Adverse Events - All Subjects
Listing 16.2-17.4.1: Treatment-Emergent Serious Adverse Events - Randomized Subjects
Listing 16.2-17.4.2: Treatment-Emergent Study Drug-Related Serious Adverse Events - Randomized Subjects
Listing 16.2-17.5.1: Treatment-Emergent Adverse Events of Special Interest - Randomized Subjects
Listing 16.2-17.5.2: Treatment-Emergent Study Drug-Related Adverse Events of Special Interest - Randomized Subjects

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-18.1: All Prior and Concomitant Medications - All Subjects
Treatment: *treatment-name*

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

ATC=Anatomical therapeutic class
Source: *list SAS datasets used to create listing*
SAS *X.Y*

DDMONYYYYTHH:MM
program_name

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 template for the following listings:*

Listing 16.2-18.2: Prior Medications - Randomized Subjects
Listing 16.2-18.3: Concomitant Medications - Randomized Subjects

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-19: Medical History - All Subjects
Treatment: *treatment-name*

Site	Subject	Data Type	Data
XXX	XXX-YYYY	Start	DDMONYYYY
		Stop	DDMONYYYY
		System Organ Class	XXXXXXXXXXXXXXXXXX
		Preferred	XXXXXXXXXXXXXXXXXXXX
		History Verbatim	XXXXXXXXXXXXXXXXXXXXXX
		Start	DDMONYYYY
		Stop	DDMONYYYY
		System Organ Class	XXXXXXXXXXXXXXXXXX
		Preferred	XXXXXXXXXXXXXXXXXXXX
		History Verbatim	XXXXXXXXXXXXXXXXXXXXXX

Source: list SAS datasets used to create listing
SAS X.Y

DDMONYYYYTHH:MM
program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-20: Intraoperative Opioids - Randomized Subjects
TREATMENT: *treatment-name*

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

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-21.1: Protocol Prescribed Postsurgical Medications Compliance – Randomized Subjects
TREATMENT: *treatment-name*

Site	Subject	Acetaminophen	NSAID	Celocoxib	Naproxen	Meloxicam
XXX	XXX-YYYY	XXX.X	XXX.X	XXX.X	XXX.X	XXX.X
XXX	XXX-YYYY	XXX.X	XXX.X	XXX.X	XXX.X	XXX.X

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-21.2: Protocol Prescribed Postsurgical Medications - Randomized Subjects

TREATMENT: *treatment-name*

Site	Subject	Medication	Dose Date Time	Dose	Unit	Route
XXX	XXX-YYYY	*MEDICATION-NAME*	DDMONYYYY HH:MM	XXX.XX	(UNITS)	XXXX
XXX	XXX-YYYY					

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Note programmer: List all acetominaphen, celecoxib, naproxen, and meloxicam taken by subject after surgery and on or before hospital discharge.

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-22: Study Drug Administration - Randomized Subjects
TREATMENT: *treatment-name*

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

Source: *list SAS datasets used to create table*
SAS X.Y

DDMONYYYYTHH:MM
program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331

Listing 16.2-23: Drug Screen, Alcohol Blood Test and Pregnancy Test - All Subjects

TREATMENT: *treatment-name*

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

Source: list SAS datasets used to create table
SAS X.Y

DDMONYYYYTHH:MM
program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-24: Admission and Discharge to Hospital and PACU - Randomized Subjects
TREATMENT: *treatment-name*

Site	Subject	Hospital			PACU		
		Admission	Discharge	LOS (hours)	End of Surgery	Discharge	LOS (hours)
XXX	XXX-YYYY	DDMONYYYYTHH:MM	DDMONYYYYTHH:MM	XXX.XX	DDMONYYYYTHH:MM	DDMONYYYYTHH:MM	XXX.XX
	XXX-YYYY	DDMONYYYYTHH:MM	DDMONYYYYTHH:MM	XXX.XX	DDMONYYYYTHH:MM	DDMONYYYYTHH:MM	XXX.XX

LOS = Length of Stay
Source: list SAS datasets used to create table
SAS X.Y

DDMONYYYYTHH:MM
program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-326
Listing 16.2-25: Bupivacaine Plasma Concentrations - Randomized Subjects
TREATMENT: *treatment-name*

Site	Subject	Date and Time	Concentration (ng/mL)
XXX	XXX-YYYY	DDMONYYYYTHH:MM	XXXX.X
	XXX-YYYY	DDMONYYYYTHH:MM	XXXX.X
	XXX-YYYY	DDMONYYYYTHH:MM	XXXX.X

Source: *list SAS datasets used to create table*
SAS X.Y program_name DDMONYYYYTHH:MM

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-26: Unique Adverse Events Terms and Associated Coded Terms

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

Coded using MedDRA
Source: *list SAS datasets used to create listing*
SAS X.Y

DDMONYYYYTHH:MM
program_name

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-27: 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	XXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXX
PN1.2.2	XXXXXXXXXXXXXXXXXXXXXXXXXX
ATC2	
ATC2.2	
ATC2.3	
ATC2.4	
PN2.2.3.4.1	XXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXX

Coded using Who Drug Dictionary
Source: *list SAS datasets used to create listing*
SAS X.Y

DDMONYYYYTHH:MM
program_name

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-331
Listing 16.2-28: Protocol Deviations

TREATMENT: *treatment-name*

Site	Subject	Date and Time	Deviation
XXX	XXX-YYYY	DDMONYYYYTHH:MM	XXXXXXXXXXXXXXXXXXXXXXXXXX
		DDMONYYYYTHH:MM	XXXXXXXXXXXXXXXXXXXXXXXXXX

Source: *list SAS datasets used to create listing*
SAS X.Y

DDMONYYYYTHH:MM
program_name

16. TABLE OF CONTENTS FOR FIGURE MOCK-UPS

Figure Mock-up 1

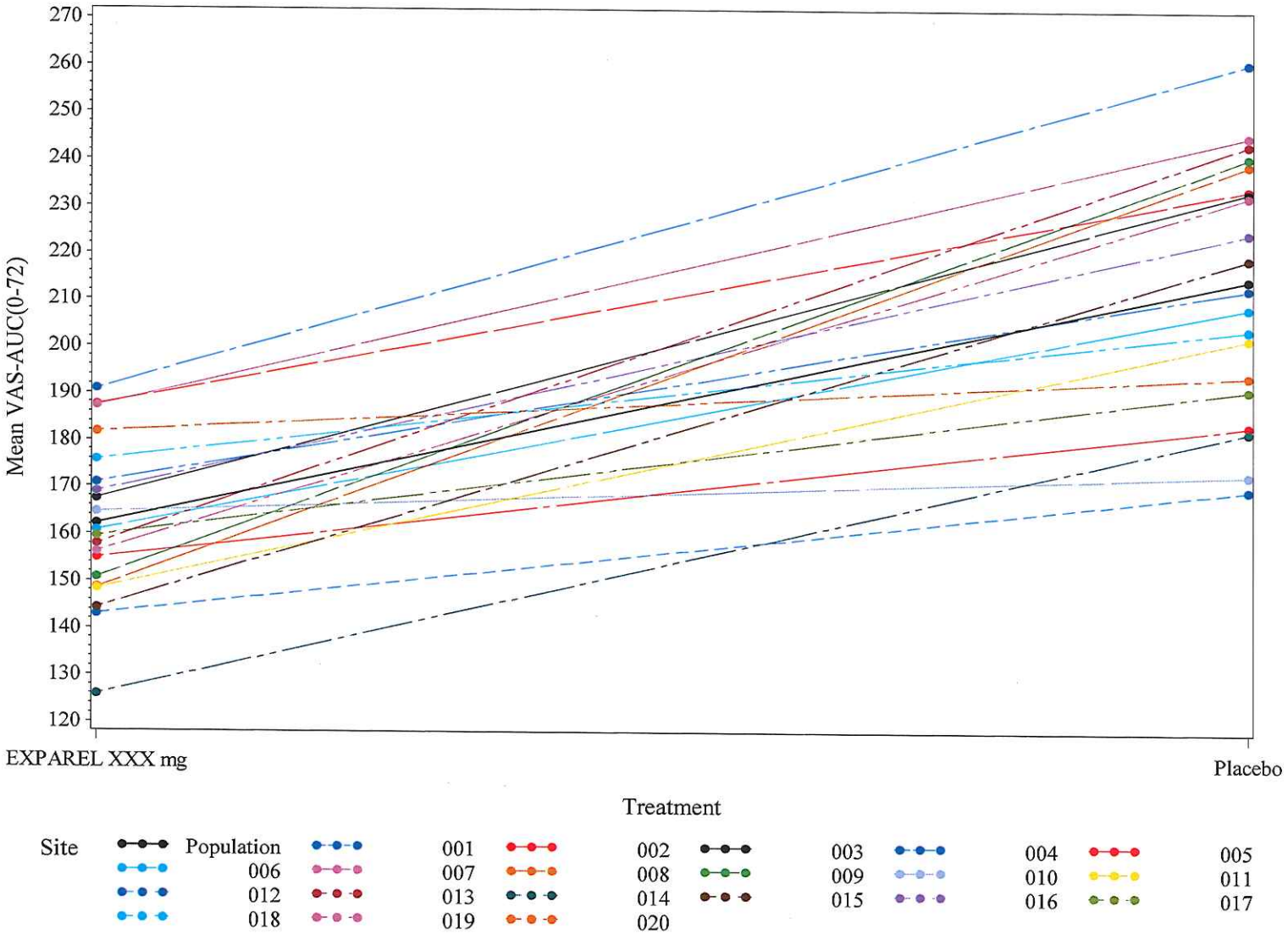
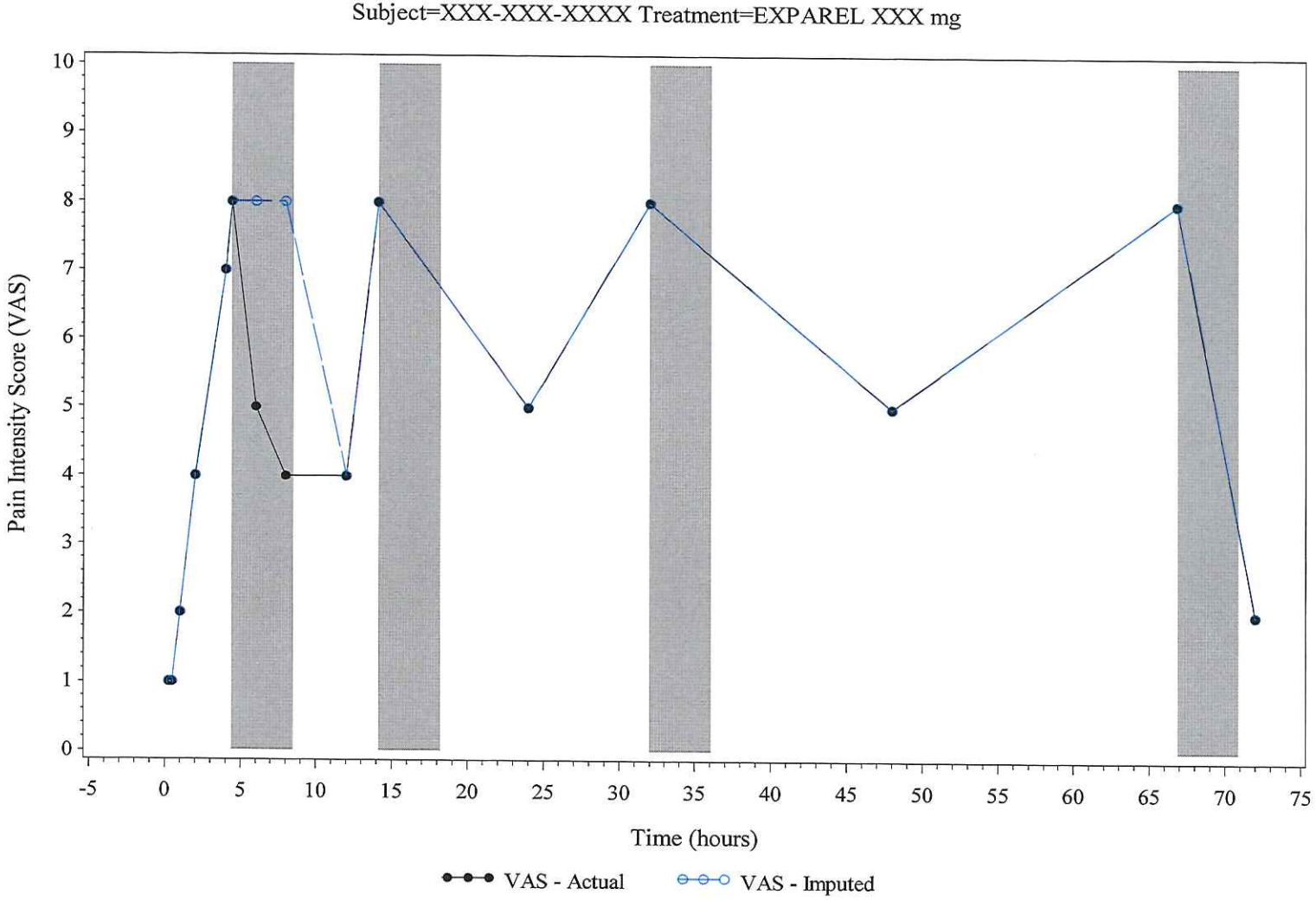


Figure Mock-up 2



Gray bars indicate rescue medication windows

Note to programmers: *In figure mock-up 2 the gray bars highlight the rescue medication windows for that subject; the time axes are set to ensure the entire period is captured and doesn't end at the limits of the figure.*

Use Figure mock-up 1 for the following:
Figure 1.1: Plot of Mean VAS-AUC(0-72) by Treatment and Site (Overall and Individual) - Efficacy Analysis Set
Figure 1.2: Plot of Mean VAS-AUC(0-72) by Treatment and Site (Overall and Individual) - Per-protocol Analysis Set

Use Figure mock-up 2 for the following (note no gray bars or actual scores on these figures):
Figure 2.1: Plot of Mean Pain Intensity Score (VAS) vs Time through 72 hours - Efficacy Analysis Set
Figure 2.2: Plot of Mean Pain Intensity Score (VAS) vs Time through 72 hours - Per-protocol Analysis Set

Use Figure mock-up 2 for the following:
Figure 3: Plot of Individual Subject Pain Intensity Score (VAS) vs Time through 72 hours - Efficacy Analysis Set