Pacira Pharmaceuticals, Inc.
EXPAREL

Document:	Statistical Analysis Plan
Official Title:	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Local Administration of EXPAREL for Prolonged Postsurgical Analgesia in Subjects Undergoing Third Molar Extraction
NCT Number:	NCT02517905
Document Date:	Original: November 12, 2015 Addendum: February 29, 2016

STATISTICAL ANALYSIS PLAN

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Local Administration of EXPAREL for Prolonged Postsurgical Analgesia in Subjects Undergoing Third Molar Extraction

Protocol No.: 402-C-329

IND No.: 69,198

Study Phase: 3

Study Drug: EXPAREL (bupivacaine liposome injectable suspension)

Date/Version: 12 November 2015, Final 1.0

Prepared by: James Nezamis, MS
Senior Director, Biostatistics
Pacira Pharmaceuticals

Sponsor: Pacira Pharmaceuticals, Inc.
5 Sylvan Way
Parsippany, NJ 07054
Tel: 973-254-3560

SIGNATURE PAGE

Wei Sun, MD Senior Medical Director, Clinical Research	12 Nov 2015 Date
James Jones, MD Chief Medical Officer	12 Nov 2015 Date
George M. Wagner Vice President, Regulatory Affairs and Pharmacovigilance	16 Nov 2015 Date
James Nezamis, MS Senior Director, Biostatistics	12 Nov 2015 Date

TABLE OF CONTENTS

TABLE OF CONTENTS 3
1.LIST OF ABBREVIATIONS 4
2.INTRODUCTION 5
3.STUDY OBJECTIVES 6
4.STUDY OVERVIEW 7
5.DEFINITIONS 9
6.ANALYSIS SETS 11
7.STATISTICAL METHODS OF ANALYSIS 12
7.1.GENERAL PRINCIPLES 12
7.2.SUBJECT DISPOSITION 17
7.3.DESCRIPTION OF DEMOGRAPHICS 17
7.4.PRIOR AND CONCOMITANT MEDICATIONS 18
7.5.MEASUREMENTS OF TREATMENT COMPLIANCE 18
7.6.EFFICACY ANALYSIS 18
7.7.SAFETY ANALYSES 25
7.8.PHARMACOKINETIC ANALYSIS 28
7.9.INTERIM ANALYSIS 29
8.SAMPLE SIZE CALCUALTIONS 31
9.REFERENCEs 32
10.TIME AND EVENTS SCHEDULED OF STUDY PROCEDURES 33
11.LAYOUT OF TABLES, LISTINGS AND FIGURES 35
11.1.TABLE OF CONTENTS FOR TABLE MOCK-UPS 36
11.2.TABLE OF CONTENTS FOR LISTING MOCK-UPS 86
11.3. LIST OF FIGURES 123
12.MULTIPLE IMPUTATION EXAMPLE PROGRAM CODE 124

1. LIST OF ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
C-Section	Cesarean Section
CRF	Case Report Form
CSR	Clinical Study Report
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IV	Intravenous
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MED	Morphine Equivalent Dose
n	Sample Size
NRS	Numerical Rating Scale
PACU	Post-Anesthesia Care Unit
PK	Pharmacokinetics
PO	Per Oral (by mouth)
PoSSe	Postoperative symptom severity questionnaire
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
TEAE	Treatment-Emergent Adverse Event
TLFs	Tables, Listings, Figures
WHO-DD	World Health Organization Drug Dictionary
wWOCF	Windowed Worst Observation Carried Forward

2. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analysis and reporting of the clinical study 402-C-329 titled "A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Local Administration of EXPAREL for Prolonged Postsurgical Analgesia in Subjects Undergoing Third Molar Extraction".

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

The purposes of this SAP are to:

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

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

The following documents related to clinical study Protocol 402-C-329 were reviewed in preparation of this SAP:

- Protocol Amendment 1 issued 27 July 2015.
- Protocol Amendment 2 issued 2 September 2015.
- Case report forms (CRFs).
- ICH Guidance on Statistical Principles for Clinical Trials (E9).
- FDA protocol feedback received 18 August 2015.

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.

3. STUDY OBJECTIVES

The primary objective of this study is to demonstrate the analgesic efficacy of single-dose local administration of EXPAREL® (bupivacaine liposome injectable suspension)) compared with placebo in subjects following bilateral third molar extraction.

The secondary objectives of this study are to assess additional efficacy parameters, characterize the pharmacokinetic (PK) profile in this surgical model, and further assess the safety profile of EXPAREL.

4. STUDY OVERVIEW

This is a Phase 3, randomized, double-blind, placebo-controlled study in subjects scheduled to undergo elective bilateral third molar extraction (i.e., extraction of all four third molars) under local anesthesia. At least one lower mandibular third molar must involve full or partial bony impaction confirmed by visual or radiographic evidence.

Approximately 175 subjects (at least 100 in the EXPAREL group and 50 in the placebo group) are planned for enrollment. Subjects enrolled under Amendment 1 were randomized in a 1:1 ratio. Due to FDA feedback Amendment 2 changed the randomization ratio to 2:1 (EXPAREL: placebo), thus subjects enrolled under Amendment 2 will be randomized in a 2:1 ratio to receive local administration of a single dose of either EXPAREL (133 mg/10 mL) or placebo (normal saline, 10 mL).

The timing of all assessments is in the Time and Events Schedule of study procedures (Section 10) and further described in the protocol.

Screening

Subjects will be screened within 30 days prior to surgery. During the screening visit, subjects will be assessed for any past or present medical conditions that in the opinion of the Investigator would preclude them from study participation.

Day 1 (Day of Surgery)

On Day 1 prior to surgery, any AEs or changes in concomitant medications since screening will be recorded, vital signs will be measured, a urine drug screen will be conducted for all subjects, and a urine pregnancy test will be conducted for women of childbearing potential. A pre-dose PK sample will be collected from all subjects eligible for randomization. Randomized subjects will receive a dental nerve block with lidocaine 2% with epinephrine 1:100,000 before undergoing bilateral third molar extraction under local anesthesia

At the end of surgery, and at least 20 minutes after the lidocaine administration, a total of 10 mL of study drug will be infiltrated [4 mL (2 mL per side) into the maxilla and 6 mL (3 mL per side) into the mandible].

Subjects will be required to remain in the research facility for 96 hours after study drug administration.

Postsurgical Safety and Efficacy Assessments

Postsurgical assessments will include pain intensity scores using the 0-10 point numeric rating scale (NRS, note that NRS assessments for this study are at rest) at scheduled timepoints and prior to each request for rescue medication; use of supplemental opioid rescue medication; vital signs; subject's satisfaction with postsurgical pain control; and the postoperative symptom severity (PoSSe) scale questionnaire (Ruta 2000).

All subjects will return for a follow-up visit on Days 7 and 10. A phone call will be made to each subject on Day 30 for an AE assessment and to inquire as to whether the subject made any unscheduled phone calls or office visits related to pain.

Adverse events will be recorded from the time the ICF is signed through Day 30. If a cardiac or neurological event occurs during the study, an unscheduled PK blood sample and ECG should be obtained within 2 hours of the time the event is noted. If there is a scheduled PK blood draw within 2 hours before or after the event, an additional draw is not needed.

Postsurgical Analgesia

Subjects should only receive rescue pain medication (oral [PO] oxycodone 10 mg) upon request for breakthrough pain, as needed. No other analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs) are allowed during the 96 hour observation period. All postsurgical opioid analgesics administered must be documented through 96 hours.

Pharmacokinetic Assessment

Blood samples for PK analysis will be obtained at baseline (prior to study drug administration); 15 minutes, 30 minutes, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 84, and 96 hours after the beginning of study drug administration; and on Days 7 and 10. Blood samples will be collected from all subjects in order to maintain the treatment double-blind. However, blood samples from subjects randomized to the placebo group will not be analyzed.

5. 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, thus day of surgery is Day 1. Study Day is based on the calendar dates, thus days before the date of surgery have negative values while those on or after the date of surgery are positive. However for those events that have times associated with them, if the event occurs on the day of surgery but before time 0, Study Day will be -1; Study Day will be 1 for those events occurring on the day of surgery but start after time 0.

Treatment-emergent Adverse Event

Treatment-emergent adverse events (TEAEs) are those with onset between the start datetime of study drug administration and end of study (Study Day 30±3 days).

Time 0 (zero)

Time 0 is defined as the date and time of the end of surgery for all end points except AEs and bupivacaine plasma concentrations. For AEs and PK sampling times 0 is defined as the date and time of the start of study drug administration.

Pain-free

Pain-free is defined as a NRS score of 0 or 1 with no rescue medication use prior to that assessment.

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 which 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]
0-96	[0 to 100]
0-Day 10	[0 to 264]
24-48	[23 to 50]
48-96	[46 to 100]

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.

Topline Result Tables

Topline result tables are to be expedited for Pacira review after database lock. The topline tables for this study are:

- 14.1-1: Summary of Subject Disposition
- 14.2-1.1.1: Analysis of AUC of NRS Pain Intensity Scores through 48 hours – Primary Efficacy Analysis Set - Multiple Imputation Results
- 14.2-1.1.2: Sensitivity Analysis of AUC of NRS Pain Intensity Scores through 48 hours – Secondary Efficacy Analysis Set - Multiple Imputation Results
- 14.2-1.1.3: Sensitivity Analysis of AUC of NRS Pain Intensity Scores through 48 hours – Primary Efficacy Analysis Set – Mixed Model Repeated Measures Results
- 14.2-2.1: Analysis of AUC of NRS Pain Intensity Scores through 24 hours - Primary Efficacy Analysis Set - Multiple Imputation Results
- 14.2-2.2: Summary of AUC of NRS Pain Intensity Scores through 24 hours - Primary Efficacy Analysis Set - Analysis of Variance Model Results - Multiple Imputation Results
- 14.2-3.1: Analysis of AUC of NRS Pain Intensity Scores through 72 hours - Primary Efficacy Analysis Set - Multiple Imputation Results
- 14.2-3.2: Summary of AUC of NRS Pain Intensity Scores through 72 hours - Primary Efficacy Analysis Set - Analysis of Variance Model Results - Multiple Imputation Results
- 14.2-5.1: Analysis of Opioid-Free Subjects through 24 hours - Primary Efficacy Analysis Set
- 14.2-5.2: Analysis of Opioid Free Subjects through 48 hours - Primary Efficacy Analysis Set
- 14.2-5.3: Analysis of Opioid Free Subjects through 72 hours - Primary Efficacy Analysis Set
- 14.3-2.2: Summary of Potentially Clinically Meaningful Abnormal Electrocardiogram Results – Central Read - Safety Analysis Set
- 14.3-3.2: Summary of Potentially Clinically Significant Abnormal Vital Signs – Safety Analysis Set
- 14.3-4.1.2: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set
- 14.3-4.2.2: Summary of Incidence of Serious Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set

6. ANALYSIS SETS

Safety Analysis Set

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

Efficacy Analysis Sets

Under the protocol, the efficacy analysis set will include all subjects in the safety analysis set who undergo the planned surgery and will be based on the randomized treatment, regardless of actual treatment received. However Amendment 2 changee the pain score collection around rescue medication use, thus subjects enrolled under Amendment 1 and Amendment 2 have differences in efficacy data collection. Subjects enrolled under Amendment 1 collected pain scores only before the first use of rescue medication while those enrolled under Amendment 2 collected pain scores prior to each use of rescue medication. This has direct impact on the derivation of the primary efficacy endpoint. Under Amendment 2 the sample size was increased to accommodate the FDA request of at least 100 subjects on EXPAREL and to ensure an adequate number of subjects in both treatment groups to enable an efficacy analyses based solely on those subjects enrolled under Amendment 2. Thus two efficacy analysis sets are defined for this study, primary and secondary efficacy analysis sets.

The primary efficacy analysis set will include all subjects enrolled under Amendent 2 in the safety analysis set who undergo the planned surgery. This will be the analysis set used for the decision on efficacy.

The secondary efficacy analysis set will include all subjects enrolled under either amendment in the safety analysis set who undergo the planned surgery. This analyses set will be used for a sensitivity analysis to ensure that the protocol amendment did not change the efficacy results. When adjusting pain scores for rescue medication use, subjects enrolled under Amendment 1 will use the highest score prior to the first rescue medication request to impute pain scores obtained in the rescue medication window.

In both efficacy analyses sets subjects will be analyzed as randomized, regardless of treatment recieved.

Pharmacokinetic Analysis Set

The PK analysis set will include all subjects in the safety analysis set who receive EXPAREL, provide sufficient samples to allow for calculation of PK parameters required for analysis, and do not have significant protocol deviations that may invalidate or bias the results.

7. STATISTICAL METHODS OF ANALYSIS

7.1. General Principles

The statistical analyses will be reported using summary tables, and figures. 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).

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

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

Treatment	NRS 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 NRS score group indicator variables.

Sites with fewer than 5 subjects per treatment arm will be pooled with other sites for analysis. Sites will be pooled with other small sites based on the US Census Bureau geogrpahic 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 meeting the pooling criteria, the site will be pooled with other small sites within the region. 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

Table 1: US Census Regions and Divisions

Region	Division	State
	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

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 window when the opioid medication is effect will be replaced. For this study the prescribed opioid rescue medication is oxycodone. The duration of effect for various opioid are listed in Table 2.

Table 2: Opioid Windows

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

PO = oral; IV = intravenous

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 postsurgically with an indication like 'anesthesia maintenance' will not be included for imputation purposes.

7.1.1. Handling Missing Values

7.1.1.1. Area Under the NRS-Time Curve

7.1.1.1.1. 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 area under the curve (AUC) of NRS pain intensity scores, the windowed worst observation carried forward (wWOCF) multiple imputation procedure will be used in the following order:

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

For sujects who take a rescue medication, their NRS scores recorded within the window of controlled type of rescue medication (see Table 2Table 2: Opioid Windows**Error! Reference source not found.**) will be replaced by the 'worst' observation. The worst observation will be the highest score from time 0.25 or end of previous rescue window, to pain score immediately prior to rescue medication for those subjects with pain score prior to each rescue medication (Amendment 2) or, for those subjects with pains scores only prior to first rescue medication use (Amendment 1) in the time interval from time 0.25 to up to the time of rescue medication. The NRS score at rescue will be included in this

calculation. Note that NRS scores in the window that are higher than the worst value prior to rescue medication will not be overwritten.

b) After the wWOCF imputation, described in Step a, subject data still missing with a non-monotone missing pattern (ie, 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], which will be applied in the multiple imputation procedure for arbitrary missing patterns. This MCMC method will use 1000 imputation datasets with NBITER=2000 and NITER=1000.

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

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

e) The endpoints derived in Step d will be analyzed as described in Section 7.6.2.1 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].

For summary statisitics based on multiple imputations, the mean value from each imputation will be derived for each subject. These mean values will then be summarized to obtain the summary statistics for reporting.

SAS pseudo-code for multiple imputations is provided in Section 12

7.1.1.1.2. Single Imputation Method

The single imputation method was the method used for previously submitted studies. It is being provided in this study as a bridge to the older studies.

For calculation of area under the curve (AUC) of NRS pain intensity scores, the windowed worst observation carried forward (wWOCF) and last observation carried forward (LOCF) imputation procedure will be used in the following order:

a) Windowed worst observation carried forward for rescue medications

For subjects who take a rescue medication, their NRS scores recorded within the window of controlled type of rescue medication (see Table 2) will be replaced by the 'worst' observation. The worst observation will be the highest score in the time interval from time 0 up to the time of first rescue medication. The NRS score at the first rescue will be included in this calculation. Note that NRS scores in the window that are higher than the worst value prior to rescue medication will not be overwritten. If no NRS score is available prior to the first rescue the worst observation from all available NRS scores for that subject will be used instead.

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

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

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

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

f) The AUC and SPIS at various time intervals will be derived from the imputed NRS scores resulting from Step e.

7.1.1.2. Integrated Rank Assessment

No imputation of missing data will be performed for the integrated rank assessment calculation. Subjects will missing NRS scores at the timepoints of interest will not be included in the summaries.

7.1.1.3. 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.

7.1.1.4. Rescue Pain Medication

For calculation of the total rescue pain medication usage (in morphine dose 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).

7.1.1.5. 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.
  - i) 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:
  - iii) 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.
  - iv) Otherwise, '00:00' will be assigned.

For partial stop date/time:

- If the year is unknown, then the date assigned will be 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').

7.1.1.6. 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

7.1.1.7. Time to Event

For calculating time to an event when only the hour is reported, the minutes will be set to zero. If only date is reported, the time will be set to midnight (00:00).

7.1.2. Multiplicity Adjustments

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

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

There are five secondary efficacy endpoints that will be analyzed using a hierarchical fixed-sequence stepwise testing procedure (See Section 7.6.1.2). The five secondary efficacy endpoints will only be analyzed if the prmary efficacy endpoint is statistically significant at the two-sided 0.05 significance level. To protect the Type 1 error rate, the testing will be performed sequentially rejecting secondary endpoints at the two-sided 0.05 significance. The prior secondary endpoint must be rejected before before proceeding to the next. The five secondary endpoints will be tested in the following order:

1. AUC(0.25-24)
2. AUC(0.25-72)

3. Percentage of opioid-free subjects from end of surgery through 24 hours
4. Percentage of opioid-free subjects from end of surgery through 48 hours
5. Percentage of opioid-free subjects from end of surgery through 72 hours

Tertiary efficacy endpoints will be summarized but not be analyzed.

7.1.3. By-Site Analyses

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

7.2. Subject Disposition

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

- Screened,
- Randomized
  - Randomized Not treated,
  - Randomized Treated,
- In the safety analysis set,
- In the primary efficacy analysis set,
- In the secondary efficacy analysis set
- In the PK analysis set,
- Completed the study as planned,
- Discontinued from the study, and
- Reasons for discontinuation from the study.

Percentages will be reported for the safety, efficacy and PK analysis sets, completed study, discontinued from study and reasons for discontinuation. The denominator for all percentages will be the number of subjects randomized.

Safety and PK analysis sets will be presented as treated. This may result in percentages greater than 100%. All other data will be presented as randomized.

Summaries will present the data for each treatment group (EXPAREL, Placebo) and across treatment groups (Total). This summary table will show summaries across all sites and for each site separately.

7.3. Description of Demographics

The summary of demographics will present:

- Age (years) – descriptive statistics
- Sex – n (%)
- Ethnicity – n (%)
- Race – n (%)
- Height (cm) – descriptive statistics
- Weight (kg) – descriptive statistics
- Body Mass Index (BMI) (kg/m^2) – descriptive statistics

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

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.

Summaries will present the data for each treatment group (EXPAREL, Placebo) and across treatment groups (Total). Summaries will be provided for all (safety, efficacy and PK) analysis sets. This summary table will show summaries across all sites and for each site separately.

7.4. Prior and Concomitant Medications

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

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

Prior and concomitant medications will be summarized 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. 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.

7.5. Measurements of Treatment Compliance

Study treatment is administered by a party other than the subject, therefore compliance is assured. Duration of surgery will be summarized by treatment and across treatments.

7.6. Efficacy Analysis

Primary and secondary efficacy endpoints will be summarized and analyzed using inferential statistics. Tertiary efficacy endpoints will be summarized, no statistical tests will be performed on these endpoints.

7.6.1. Efficacy Endpoints

7.6.1.1. Primary Efficacy

The primary endpoint is the AUC of the NRS pain intensity scores through 48 hours [AUC(0.25-48)].

7.6.1.2. Secondary Efficacy

The following secondary endpoints will be analyzed in the following order using a hierarchical fixed-sequence stepwise testing procedure:

1. The AUC of the NRS pain intensity scores through 24 hours [AUC(0.25-24)].
2. The AUC of the NRS pain intensity scores through 72 hours [AUC(0.25-72)].
3. Percentage of opioid-free subjects from end of surgery through 24 hours.
4. Percentage of opioid-free subjects from end of surgery through 48 hours.
5. Percentage of opioid-free subjects from end of surgery through 72 hours.

7.6.1.3. Tertiary Efficacy

- The AUC of the NRS pain intensity scores through 96 hours.
- Sum of pain intensity scores (SPIS) through 24, 48, 72, and 96 hours.
- The NRS pain intensity scores at each assessed timepoint and immediately prior to each request for rescue pain medication.
- The AUC of the NRS pain intensity scores from 24-48 and 48-72 hours.
- Percentage of pain-free subjects at each assessed timepoint using the NRS pain intensity score.
- Percentage of opioid-free subjects through 96 hours.
- Time to first opioid rescue medication.
- Integrated rank assessment using the NRS pain intensity score at 48 hours and the total amount of postsurgical opioids consumed through 48 hours (Silverman 1993)[8].
- Overall assessment of the subject's satisfaction with postsurgical pain control (using a 5-point Likert scale) at 24, 48, 72, and 96 hours, and on Day 10.
- PoSSe scale mean total score at 72 hours and on Day 7.
- Number of unscheduled phone calls or office visits related to pain through Day 30.

7.6.1.4. Opioid Consumption

Opioids will be converted to IV Morphine Equivalent Dose (MED) using the appropriate conversion factor from Table 3 for all summaries. Total opioid dose (MED) is the sum of all opioids taken after surgery up to the timepoint of interest. Subjects with no opioid use during the period in question will be assigned a dose of 0 for analysis.

Table 3: IV Morphine Equivalents

Medication	Unit	Route	Conversion (Multiplication) Factor
Oxycodone	mg	PO	0.5
Opioids taken during the study not on table will be reviewed and conversion facter determined.			

7.6.1.5. Area Under the Curve

Area under the pain-time curve is derived using the trapezoidal rule on the pain scores adjusted for rescue medication use using the wWOCF imputation methods (see Section 7.1.1.1). Actual

assessment times will be used in deriving AUC. AUC of pain scores will be calculated from the first timepoint after surgery to the timepoint of interest.

7.6.1.6. Sum of Pain Intensity Scores

The sum of pain intensity scores (SPIS) is the sum of the pain scores from the first timepoint after surgery to the timepoint of interest. The pain scores obtained after wWOCF imputation method will be used to derive SPI. SPIs will be derived for 24, 48, 72 and 96 hours.

7.6.1.7. Integrated Rank Assessment

Integrated rank assessment is a single score that takes pain rating and rescue medication use into account. Positive values for the integrated rank assessment score indicate less pain or opioid use and negative numbers indicate more pain or opioid use. The score is derived as:

$$\left[\frac{2r - p_i - m_i}{r}\right] * 100$$

Where:

- *i* indicates subject;
- p_i is the rank of the subject's pain score in the pool of all subjects to be analyzed;
- m_i is the rank of the subject's total opioid use (in MED) through the time period in question in the pool of all subjects to be analyzed;
- *r* is the mean rank defined as $(\mathrm{N} + 1)/2$;
- *N* is the total number of subjects to be analyzed.

Subjects with no opioid use will be assigned a dose of 0 for analysis.

Integrated rank assessment will be calculated at 24, 48 and 72 hour timepoints. Missing NRS scores at timepoints of interest will not be imputed. Subjects with missing NRS values at the timepoint of interest will be excluded from the summary. If the timepoint of interest falls within a rescue medication window, the wWOCF value will be used to derive the integrated rank assessment.

7.6.1.8. Postoperative Symptom Severity (PoSSe) Questionnaire

The PoSSe score is the total score of the weighted responses for each question. If a response is missing to any question in the PoSSe, the total score will not be calculated.

7.6.1.9. 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. Missing NRS scores at timepoints of interest will not be imputed. Subjects with missing NRS values at the timepoint of interest will be excluded from the summary.

7.6.1.10. Pain-free

Pain free is defined as an NRS score of 0 or 1 with no rescue medication use prior to that assessment.

7.6.2. Methods of Analysis

7.6.2.1. Primary Efficacy Analysis

The primary effiacacy analyses will be conducted for both the primary and secondary efficacy analysis sets. Results from the primary efficacy analysis set will be primary efficacy result; the the analyses based on the secondary efficacy analysis set are a sensitivity analysis.

The primary efficacy variable is the AUC of NRS scores from first postsurgery assessment (0.25 hours) through 48 hours [AUC(0.25-48)] using the wWOCF to adjust for rescue medication use and multiple imputation method to account for missing data described in Section7.1.1.1.1.

Tests for the treatment effect of EXPAREL versus placebo will be based on the following null hypothesis (H_o) and two-sided alternative hypothesis (H_a):

H_o: $\mu_s = \mu_p$ versus H_a: $\mu_s \neq \mu_p$

where μ_s and μ_p are the mean of AUC(0.25-48) for EXPAREL and the mean of AUC(0.25-48) for placebo, respectively. A two-sided test will be performed at 5% level of significance. The treatment effect of EXPAREL will be considered significantly better than that of placebo if the null hypothesis of no difference is rejected and a difference in mean of AUC(0.25-48) in favor of EXPAREL (mean for EXPAREL < mean for placebo) is observed.

For the primary efficacy variable of AUC(0.25-48), EXPAREL will be compared to placebo using analysis of variance (ANOVA) with treatment and site as main effects. Based on the model, the least squares (LS) means, LS mean difference between the two treatment groups, 95% confidence interval (CI) for the LS mean difference between the two treatment groups, and p-value will be reported.

Descriptive statistics of the primary efficacy variable will also be shown by site but no statistical analyses will be performed by site.

In addition, an ANOVA model with main effects of treatment and site and the treatment by site interaction will be reported to assess the interaction on the primary efficacy analysis. Additional analyses may be performed if the interaction effect is significant (p-value <0.05).

Sensitivity Analyses

Mixed Model Repeated Measures

A mixed model repeated measures analysis will be performed using only the data imputed using wWOCF but not imputing any missing values outside of the rescue medication windows. The MMRM model will have fixed effects for treatment and time. The initial model will be fit with the treatment-by-time interaction. If this interaction is not significant (p-value > 0.05) the final model will include the main effects only. If the interaction is significant (p-value ≤ 0.05) the interaction will be investigated to determine if it is qualitative or quantitative. If the interaction is quantitative, the final model will include the interaction term. If the interaction is qualitative, additional analyses may be required. The treatment effect at 48 hours will be estimated from the final model.

Tipping Point

A tipping point analysis will be performed using similar imputation technique as the primary AUC calculations (see section 7.1.1.1.1) but adding shift values to the imputation until the primary analysis results change direction (SAS pseudo-code below).

```
PROC MI DATA=OUTDATA_STEPB OUT=OUTDATA_TIP;
        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);

        MNAR ADJUST(T1 / SHIFT=Q ADJUSTOBS=(TREATMENT='EXPAREL'));
        MNAR ADJUST(T2 / SHIFT=Q ADJUSTOBS=(TREATMENT='EXPAREL'));
        …
        MNAR ADJUST(T(n-1) / SHIFT=Q ADJUSTOBS=(TREATMENT='EXPAREL'));
        MNAR ADJUST(Tn / SHIFT=Q ADJUSTOBS=(TREATMENT='EXPAREL'));

        VAR TREATMENT T1 T2 T3 … Tn
RUN;
where Q is the value to shift the results.
```

If the result from the primary efficacy analysis is statistically significant, the above code will be run iteratively for integer values of Q from 1 to 10 analyzing each step of the way until the result "tips" from statistically significant to not statistically significant. If the primary efficacy analysis result is not statistically significant, the above code will be run iteratively for integer values from -1 to -10 until the result "tips" from not clinically significant to clinically significant. The value of Q that results in the change in significance will be reported along with the analysis results.

Original Imputation Method

The AUC of NRS scores from first postsurgery assessment (0.25 hours) through 48 hours [AUCo(0.25-48)] will also be derived using the methodology used in previous submission, wWOCF + LOCF as described in Section 7.1.1.1.2. AUC(0.25-48) will be analyzed for the primary and secondary analysis sets using an analysis of variance with fixed effect of treatment reporting the the least squares (LS) means, LS mean difference between the two treatment groups, 95% confidence interval (CI) for the LS mean difference between the two treatment groups, and p-value along with descriptive statistics.

7.6.2.2. Secondary Efficacy Analyses

Secondary endpoints AUC(0.25-24) and AUC(0.25-72) will be analyzed in same manner as the primary endpoint for the primary efficacy analysis set.

The secondary endpoints of percentage of opioid-free subjects through 24, 48 and 72 hours will be independently analyzed using a Chi-square test stratified on site for the primary efficacy analysis set. Treatment differences and 95% CIs will be derived using the normal approximation to the binomial.

7.6.2.3. Tertiary Efficacy Analyses

Tertiary endpoints will be summarized as appropriate (eg, descriptive statistics or tabulations). No statistical tests will be performed on these endpoints.

7.6.2.3.1. AUC(0.25-96)

The NRS AUC(0.25-96) will be summarized (n, mean, SD, median, minimum and maximum) by treatment group. The summary will be based on the data obtained using multiple imputations.

7.6.2.3.2. SPI(0.25-24), SPI(0.25-48), SPI(0.25-72) and SPI(0.25-96)

The NRS SPI(0.25-24), SPI(0.25-48), SPI(0.25-72) and SPI(0.25-96) will be summarized (n, mean, SD, median, minimum and maximum) by treatment group. The summary will be based on the data obtained using multiple imputations.

7.6.2.3.3. Numeric Rating Scale Pain Intensity Scores by Assessment Timepoint

The NRS pain intensity scores will be summarized (n, mean, SD, median, minimum and maximum) at each scheduled assessment timepoint for each treatment group. The summaries and figures will be based on the data obtained using multiple imputations.

The NRS pain intensity scores will also be summarized (n, mean, SD, median, minimum and maximum) prior to each rescue medication. The summary will also include the median, minimum and maximum time to rescue for those subjects using rescue medication. Rescue medication will be presented in order of the request for rescue medication, e.g., first request, second request and so on. The time to request for rescue medication may differ widely from subject to subject. Only subject with NRS pain scores prior to rescue will be presented in this summary.

Plots of NRS pain intensity scores over time from baseline to last assessment will be presented for the mean (± SD) and individual subjects. The mean plot will be presented for both the observed and imputed mean values. The mean plot will be based only on the scheduled NRS assessment scores. The subject plots will be show both the scheduled and immediately prior to rescue NRS assessment scores. On the subject plots, scores obtained prior to rescue medication use will be differentiated from the scheduled scores. The subject plots will present the observed and imputed scores separately. The scores will be connected using straightlines.

7.6.2.3.4. Numeric Rating Scale Pain Intensity Scores Partial Area Under the Curve

The NRS AUC(24-48) and AUC(48-72) will be summarized (n, mean, SD, median, minimum and maximum) by treatment group. The summary will be based on the data obtained using multiple imputations.

7.6.2.3.5. Percentage of Pain-free Subjects by Assessment Timepoint

The number and percentage of subjects ever and never using opioids from end of surgery through each NRS assessment timepoint will be tabulated by treatment. Missing NRS values will not be imputed for this summary. Subjects will be excluded from the summaries where they are missing NRS values.

A bar chart presenting the percentage of pain-free subjects at each assessment timepoint will be provided.

7.6.2.3.6. Percentage of Opioid-free Subjects Through 96 hours

The number and percentage of subjects ever and never using opioids from end of surgery through 96 hours will be tabulated by treatment.

A bar chart presenting the percentage of opioid-free subjects at 24, 48 and 96 hours will be provided.

7.6.2.3.7. Time to First Opioid Rescue Medication

The number and percentage of subjects ever and never using opioids after surgery through 72 hours will be presented by treatment. Subjects who did not take opioids will be censored at the time of discharge from the clinic or from the time of withdrawal, whichever is sooner. The 25th (first quartile), 50th (median – second quartile) and 75th (third quartile) percentiles, minimum and maximum time to first use of opioid rescue medication will be estimated using Kaplan-Meier methods. The quartile and the 95% confidence limits for each quartile will be presented by treatment. This summary will be presented overall and for each site.

A Kaplan-Meier plot of the time to first rescue medication use will be presented.

7.6.2.3.8. Integrated Rank Assessment

The integrated rank assessment will be derived through 24, 48 and 72 hours. Each of these integrated rank assessments will be summarized (n, mean, SD, median, minimum and maximum) by treatment group.

7.6.2.3.9. Subject Satisfaction with Postsurgical Pain Control

The numeric value for the response to the subject satisfaction with postsurgical pain control will be summarized (n, mean, SD, median, minimum and maximum) by treatment group. The responses ‘extremely dissatisfied’, ‘dissatisfied’, ‘neither satisfied nor dissatisfied’, ‘satisfied’, ‘extremely satisfied’will be scored 1 through 5 respectively. The data will also be summarized by presenting the number and percentage of subjects by treatment group for each of the five categories (i.e., ‘extremely dissatisfied’, ‘dissatisfied’, ‘neither satisfied nor dissatisfied’, ‘satisfied’, ‘extremely satisfied’) available in the subject satisfaction with postsurgical pain control questionnaire.

A bar chart of the percentage of subjects in each category at each assessment timepoint will be presented.

7.6.2.3.10. Postsurgical Symptom Severity (PoSSe) Scale Questionnaire

The total PoSSE score at 72 hours and Day 7 will be summarized (n, mean, SD, median, minimum and maximum) by treatment group. Individual question scores will be summarized (n, mean, SD, median, minimum and maximum) by treatment group at each of the assessment timepoints as well.

The total score is the sum of the individual question values (see Listing 16.2-11.2 for values). The total score will be derived only if all questions are answered.

7.6.2.3.11. Number of Pain-Related Unscheduled Phone Calls or Office Visits

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.

7.6.2.3.12. Postsurgical Opioid Consumption (Rescue)

Postsurgical opioid consumption (MED) will be summarized (n, mean, SD, median, minimum and maximum) by treatment group for the total dose consumed over the 72 hours after the end of surgery. The number and percentages of the types of opioids used will be presented by treatment group. The number and percentage of subjects using any opioid will be presented by treatment for 24, 48 and 72 hours after dosing. This summary table will show summaries across all sites and for each site separately.

The number of times each subject used rescue medication thru 24, 48 and 72 hours will be tabulated across all sites and for each site separately.

7.7. Safety Analyses

Safety assessments in this study consist of neurological, ECGs, vital signs and AEs. Vital signs will be collected at screening, baseline (prior to surgery) and 1, 2, 4 and 96 hours after surgery. Adverse events will be collected from the time of informed consent through Day 30.

7.7.1. Neurological Assessment

Neurological assessments include orientation (orientated, disoriented, not assessable), numbness (of lips, tongue, or around mouth), metallic taste, hearing problems, vision problems and muscle twitching. The number and percentage of subjects will be tabulated for each neurological assessment by treatment group at each assessment timepoint.

7.7.2. Electrocardiograms

Investigator Read

Investigator's interpretation of ECGs will be tabulated by treatment presenting the number and percentage of subjects in all of the reported interpretations.

Central Read

Electrocardiogram intervals (RR, PR, QRS, QT, QTcB, and QTcF) and heart rate will be summarized by treatment at each assessment timepoint. Electrocardiogram interval derivations and morphological analysis will be done by a central reader.

Summaries will present both actual and change-from-baseline results for all ECG parameters. Baseline statistics will be presented at each assessment timepoint for those subjects reporting data at that timepoint. The summary will highlight the timepoint closest the median PK Tmax observed during the study.

The ECG data will be assessed for potentially clinically meaningful values (see Table 4). The number and percentage of subjects satisfying the potentially clinically significant abnormal criteria at any time during the study and at each assessment timepoint will be tabulated. The table will present the number and percentage of subjects meeting the individual criteria (critical value, critical change) as well as the composite criteria (critical value and critical change). To satisfy the composite criteria the subject must satisfy both within the same ECG read.

Table 4: Criteria for Potentially Clinically Meaningful ECG Results

ECG Parameter	Unit	Critical Value	Critical Change[1]

Heart rate	Bpm	> 100 < 50	Increase of at least 25 Decrease of at least 25
PR Interval	millisecond	> 200	Increase of at least 25
QRS Interval	millisecond	> 100	Increase of at least 25
QT Interval	millisecond	> 500	Baseline ≤ 500
QTcF	millisecond	> 500 >480 >450	Baseline ≤ 500 Baseline ≤ 480 Baseline ≤ 450 >30-60 >60
QTcB	millisecond	> 500 >480 >450	Baseline ≤ 500 Baseline ≤ 480 Baseline ≤ 450 >30-60 >60

[1]Change criteria not applicable at baseline or screening.

Tabulations of the number and percent of subjects with each of the ECG morphologies identified by the central reader will be presented by treatment at each assessment timepoint.

7.7.3. Vital Signs

Vital signs (resting heart rate and blood pressure) will be summarized by treatment at each assessment timepoint. Summaries will present both actual and change from baseline values.

Vital signs will also be assessed for potentially clinically significant abnormal values (see Table 5). The number and percentage of subjects satisifying the potentially clinically significant abnormal criteria will be tabulated by treatment group. The table will present the number and percentage of subjects meeting the individual criteria (critical value, critical change) as well as the composite criteria (critical value and critical change). To satisfy the composite criteria the subject must satisfy both within the same vital signs collection.

Table 5: Criteria for Potentially Clinically Significant Abnormal Vital Signs

Vital Sign	Unit	Critical Value	Critical Change[1]
Resting Heart Rate	beats/minute (bpm)	High: ≥ 120 Low: ≤ 50	Increase of at least 15 Decrease of at least 15
Systolic Blood Pressure	mmHg	High: ≥ 180 Low: ≤ 90	Increase of at least 20 Decrease of at least 20
Diastolic Blood Pressure	mmHg	High: ≥ 105 Low: ≤ 50	Increase of at least 15 Decrease of at least 15

[1]Change criteria not applicable at baseline or screening.

7.7.4. Adverse Events

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

Subjects' AEs will be considered TEAEs if the onset datetime is between the start datetime of study treatment and Day 30.

If an AE has a partial onset datetime the imputed start and stop dates and times will be used to determine treatment-emergence (e.g., stop datetime of AE is before start datetime of study

treatment then this is not a TEAE). 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 overall severity or relation to study treatment subject count (i.e., do not consider severity or relation to study treatment in the sort order).

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

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

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

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 drug-related TEAEs
- TEAEs leading to study withdrawal
- Study drug-related TEAEs leading to study withdrawal
- All TEAEs by severity
- All TEAEs by relationship to study drug
- All serious TEAEs
- Study drug-related serious TEAEs
- Serious TEAEs leading to study withdrawal
- Study drug-related serious TEAEs leading to study withdrawal
- Serious TEAEs resulting in death
- Study drug-related serious TEAEs 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 relationship to study treatment is either 'possible', 'probable' or 'definite'.

Relation of AE to study treatment will also be assessed by the sponsor. All AE summaries based on related AEs will be produced based on the investigator and sponsor assessment of relatedness independently. A shift table presenting the investigator versus the sponsor assessment of relatedness will be presented. The shift table will display the shift in relatedness assessments for at least one AE reported at maximum relatedness across all AEs and for each SOC at the maximum relatedness across all AEs within SOC and for each AE preferred term. Relatedness categories from least to most related are 'Unlikely', 'Possible', 'Probable' and 'Definite'.

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

7.7.5. Laboratory Parameters

Not collected in this study.

7.8. Pharmacokinetic Analysis

7.8.1. Pharmacokinetic Parameter Calculation Methods

Pharmacokinetic parameters will be calculated by noncompartmental analysis method from concentration-time data following these guidelines:

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

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

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

Pharmacokinetic parameters will be estimated according to the following guidelines:

- The maximum observed plasma concentration (C_{max}) will be obtained directly from the concentration-time data.
- Time to maximum concentration (T_{max}) is the time at which C_{max} is observed.
- The apparent terminal elimination rate constant (λ_Z) will be estimated at terminal phase by linear regression after log-transformation of the concentrations:
    - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression.

- A minimum number of three data points in the terminal phase will be used in calculating λ_z with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope) and including C_{last}, t_{last}.
- The adjusted correlation coefficient (R^2 adjusted) in general should be greater than 0.90. Any value less than 0.90 may be used at the pharmacokineticist's best knowledge and judgment.
- An appropriate number of decimal places should be used for λ_z to enable the reported value of half-life ($t_{½}$) to be calculated.

- Half-life ($t_{1/2}$) will be calculated as $\ln(2)/\lambda_Z$.
- AUC will be calculated as follows:
  - The linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.
  - $AUC_{(0\text{-}t)} = \int_0^t C(t)dt$
  - $AUC_{(0\text{-}inf)} = \int_0^t C(t)dt + \int_t^\infty C(t)dt = AUC_{(0\text{-}t)} + C_t/\lambda_z$
  - $C_{(t)}$ is last observed quantifiable concentration.

7.8.2. Pharmacokinetic Concentrations and Variables

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

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

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

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

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

7.9. Interim Analysis

7.9.1. Pharmacokinetic Review

After the first 30 subjects have completed the study through Day 10, the plasma samples from the subjects who received EXPAREL will be reviewed by an unblinded pharmacokineticist not involved in the conduct of the study to determine the median time to the observed maximum plasma concentration. The pharmacokineticist will make a recommendation on the PK sampling

times so that subsequent assessment and endpoints are collected through the median time to maximum plasma concentration (T_{max}) plus at least 24 hours. This recommendation may indicate additional, fewer or no change to the PK sample times. The study team may, based on the pharmacokineticists findings, decide to amended the protocol.

8. SAMPLE SIZE CALCUALTIONS

In previous wound infiltrations studies in hemorrhoidectomy and bunionectomy, the difference between treatment groups in mean AUC(0-48 hours) or NRS pain intensity scores varied from 20 to 103. The standard deviations varied from 100 to 128. A sample size of 50 in each group will have 90% power to detect a difference in means of 66 assuming that the common SD is 100 using a two group t-test with a 0.05 two-sided significance level. A sample size of 50 in each group will have 90% power to detect a difference in means of 86 assuming that the common SD is 130 using a two group t-test with a 0.05 two-sided significance level.

9. REFERENCES

[1] US Federal Register. International Conference on Harmonisation; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. 16 September 1998.

[2] American Statistical Association. Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, 07 August 1999. http://www.amstat.org/profession/ ethicalstatistics.html

[3] Royal Statistical Society. The Royal Statistical Society: Code of Conduct, August 1993. http://www.rss.org.uk/about/conduct.html.

[4] Rubin, D. B. (1987). Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons.

[5] The National Academies Press. The Prevention and Treatment of Missing Data in Clinical Trials, prepared by the Panel on Handling Missing Data in Clinical Trials and Committee on National Statistics, 2010.

[6] Schafer, J. L. (1997). Analysis of Incomplete Multivariate Data. New York: Chapman & Hall.

7 Rubin DB, Schenker N. Multiple imputation for interval estimation from simple random samples with ignorable nonresponse. J Am Stat Assoc 1986;81:366-374.

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

10. TIME AND EVENTS SCHEDULED OF STUDY PROCEDURES

	Screen Visit	Day 1	15 min	30 min	1h	2h	4h	6h	8h	12h	18h	24h	30h	36h	42h	48h	54h	60h	66h	72h	84h	96h	D7	D10	D30
Time Window	Within 30 days		±5 min	±5 min	±5 min	±15 min	±15 min	±30 min	±30 min	±30 min	±30 min	±1h	±1h	±1h	±1h	±2h	±2h	±2h	±2h	±4h	±4h	±4h	±1d	±1d	±4d
Obtain signed informed consent	X																								
Perform dental examination[1]	X																								
Assess/confirm eligibility	X	X[2]																							
Medical/surgical history	X	X[2]																							
Demographics and baseline characteristics	X																								
Physical examination including height and weight	X																								
Urine pregnancy test for women of childbearing potential	X	X[2]																							
Urine drug screen	X	X[2]																							
Vital signs[3]	X	X[2]			X	X	X															X			
Neurological assessment		X[2]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
12-lead electrocardiogram	X	X[2]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Randomize subject and prepare study drug		X[2]																							
Perform dental nerve block with lidocaine 2% with epinephrine 1:100,000		X[2]																							
Administer study drug; record start and stop time		X																							
Conduct NRS pain intensity assessment[4]			X	X	X	X	X	X	X	X		X				X				X		X			
Record times and amounts of opioid rescue medication administered[5]		←---	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	---→			
Subject satisfaction with postsurgical pain control												X				X				X		X		X	
Complete PoSSe scale questionnaire																				X			X		
Collect scheduled PK blood sample		X[2]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Document any unscheduled phone calls or office visits related to pain after hospital discharge																							X	X	X
Phone call																									X
Record concomitant medications	←---	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	---→
Record AEs (starting at signing of ICF)[6]	←---	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	---→

Abbreviations: AE = adverse event; ICF = informed consent form; NRS = numeric rating scale; PK = pharmacokinetic; PoSSe = postoperative symptom severity.

* Postsurgical efficacy assessments will be conducted at the timepoints specified *after the beginning of study drug administration*. At timepoints when multiple assessments coincide, the NRS pain intensity assessment will be conducted first, if applicable.

[1] Or on Day 1 prior to surgery.

[2] Prior to surgery.

[3] Vital signs (heart rate and blood pressure) will be measured after subject has rested in a supine position.

[4] NRS pain intensity scores also will be recorded immediately prior to each administration of rescue pain medication through 96 hours.

[5] Subjects should only receive opioid rescue medication (oral oxycodone 5-10 mg) upon request for breakthrough pain, as needed (maximum of every 4 hours). During the 96-hour observation period, no other analgesic agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), are allowed. After 96 hours, the analgesic regimen may be adjusted.

[6] If a cardiac event (e.g., myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmia, or cardiac arrest) or neurological event (e.g., persistent anesthesia, paresthesia, weakness, or paralysis) occurs during the study, an unscheduled PK blood sample should be obtained and, for cardiac events, an ECG should be conducted within 2 hours
of the time that the event is noted. If there is a scheduled PK blood draw and ECG within 2 hours before or after the event, an additional PK blood draw and ECG are not needed.

11. 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 either Times New Roman, Courier New or SAS Monospace type face. All final TLFs will be provided in both PDF and Word (or RTF) file formats.

Percentages should not appear if the count is zero.

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

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

On all listings the treatments, in order of appearance, are: EXAPAREL, PLACEBO and, if applicable, NOT RANDOMIZED. Always insert a page break between treatments.

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

Table and listing shells follow.

11.1. Table of Contents for Table Mock-ups

Table 14.1-1: Summary of Subject Disposition – All Screened Subjects 39

Table 14.1-2.1: Summary of Subject Demographics and Baseline Characteristics - Safety Analysis Set 41

Table 14.1-2.2.2: Subject Demographics and Baseline Characteristics – Secondary Efficacy Analysis Set 42

Table 14.1-2.3: Subject Demographics and Baseline Characteristics - Pharmacokinetics Analysis Set 42

Table 14.1-3.1: Summary of Duration of Surgery (hours) - Safety Analysis Set 43

Table 14.1-3.2.2: Surgery and Study Drug Exposure – Secondary Efficacy Analysis Set 43

Table 14.2-1.1.1: Analysis of AUC of NRS Pain Intensity Scores through 48 hours – Primary Efficacy Analysis Set - Multiple Imputation Results 44

Table 14.2-1.1.2: Sensitivity Analysis of AUC of NRS Pain Intensity Scores through 48 hours – Secondary Efficacy Analysis Set - Multiple Imputation Results 44

Table 14.2-1.1.3: Sensitivity Analysis of AUC of NRS Pain Intensity Scores through 48 hours – Primary Efficacy Analysis Set – Mixed Model Repeated Measures Results 44

Table 14.2-1.1.4: Sensitivity Analysis of AUC of NRS Pain Intensity Scores through 48 hours – Primary Efficacy Analysis Set – Tipping Point Analysis - Multiple Imputation Results 45

Table 14.2-1.1.5: Sensitivity Analysis of AUC of NRS Pain Intensity Scores through 48 hours – Primary Efficacy Analysis Set – wWOCF with LOCF Single Imputation (Historical Imputation) 46

Table 14.2-1.2: Summary of AUC of NRS Pain Intensity Scores through 48 hours – Primary Efficacy Analysis Set - Analysis of Variance (ANOVA) Model Results - Multiple Imputation Results 47

Table 14.2-1.3: Summary of AUC of NRS Pain Intensity Scores through 48 hours by Site – Primary Efficacy Analysis Set - Multiple Imputation Results 48

Table 14.2-2.1: Analysis of AUC of NRS Pain Intensity Scores through 24 hours - Primary Efficacy Analysis Set - Multiple Imputation Results 48

Table 14.2-2.2: Summary of AUC of NRS Pain Intensity Scores through 24 hours - Primary Efficacy Analysis Set - Analysis of Variance Model Results - Multiple Imputation Results 48

Table 14.2-2.3: Summary of AUC of NRS Pain Intensity Scores through 24 hours by Site - Primary Efficacy Analysis Set - Multiple Imputation Results 48

Table 14.2-3.1: Analysis of AUC of NRS Pain Intensity Scores through 72 hours - Primary Efficacy Analysis Set - Multiple Imputation Results 48

Table 14.2-3.2: Summary of AUC of NRS Pain Intensity Scores through 72 hours - Primary Efficacy Analysis Set - Analysis of Variance Model Results - Multiple Imputation Results 48

Table 14.2-3.3: Summary of AUC of NRS Pain Intensity Scores through 72 hours by Site - Primary Efficacy Analysis Set - Multiple Imputation Results 49

Table 14.2-4: Summary of SPIS of NRS Pain Intensity Scores - Primary Efficacy Analysis Set - Multiple Imputation Results 50

Pacira Pharmaceuticals(Page X of Y) Protocol: 402-C-329 51

Table 14.2-5.1: Analysis of Opioid-Free Subjects through 24 hours - Primary Efficacy Analysis Set 51

Table 14.2-5.2: Analysis of Opioid Free Subjects through 48 hours - Primary Efficacy Analysis Set 51

Table 14.2-5.3: Analysis of Opioid Free Subjects through 72 hours - Primary Efficacy Analysis Set 51

Table 14.2-6.1: Summary of Numerical Rating Scale (NRS) Pain Intensity Scores - By Assessment Timepoint - Efficacy Analysis Set - Multiple Imputation Results..... 52

Table 14.2-6.2: Summary of Numerical Rating Scale (NRS) Pain Intensity Scores at Rescue - Efficacy Analysis Set 53

Table 14.2-7.1: Summary of AUC(0.25-96) and AUC(0.25-Day 10) of NRS Pain Intensity Scores - Primary Efficacy Analysis Set – Multiple Imputation Results..... 54

Table 14.2-7.2: Summary of AUC(24-48) and AUC(48-72) of NRS Pain Intensity Scores - Primary Efficacy Analysis Set – Multiple Imputation Results 55

Table 14.2-8: Tabulation of Pain-Free Subjects at Assessment Time Points - Primary Efficacy Analysis Set..... 56

Table 14.2-9: Summary of Time to First Rescue Medication Use (hours) - Primary Efficacy Analysis Set..... 57

Table 14.2-10: Summary of Integrated Rank Assessment of NRS Pain Intensity Scores and Opioid Use - By Assessment Timepoint - Primary Efficacy Analysis Set 58

Table 14.2-11: Summary of Satisfaction with Postsurgical Pain Control Questionnaire Score by Timepoint - Primary Efficacy Analysis Set 59

Table 14.2-12.1: Summary of Postoperative Symptom Severity (PoSSe) Questionnaire - Total Score [1] Summary - Primary Efficacy Analysis Set..... 60

Table 14.2-12.2: Summary of Postoperative Symptom Severity (PoSSe) Questionnaire - Individual Question Score Tabulation - Primary Efficacy Analysis Set 61

Table 14.2-13: Summary of Number of Unscheduled Phone Calls or Office Visits Related to Pain - Primary Efficacy Analysis Set 65

Table 14.2-14.1: Summary of Total Rescue Medication Consumption (MED) - Primary Efficacy Analysis Set..... 66

Table 14.2-14.2: Summary of the Number of Times Rescue Medication was Used by Subject - Primary Efficacy Analysis Set 67

Table 14.3-1: Tabulation of Neurological Assessments by Timepoint- Safety Analysis Set 68

Table 14.3-2.1 Summary of Electrocardiogram Parameters – Central Read - Safety Analysis Set..... 69

Table 14.3-2.2: Summary of Potentially Clinically Meaningful Abnormal Electrocardiogram Results – Central Read - Safety Analysis Set 71

Table 14.3-3.1: Summary of Vital Signs – Safety Analysis Set 76

Table 14.3-3.2: Summary of Potentially Clinically Significant Abnormal Vital Signs – Safety Analysis Set..... 77

Table 14.3-4.1.1: Overview of Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set 80

Table 14.3-4.1.2: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set .. 81

Table 14.3-4.1.3: Summary of Incidence of Study Drug-Related Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set 81

Table 14.3-4.1.4: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) Leading to Study Withdrawal - Safety Analysis Set 81

Table 14.3-4.1.5: Summary of Incidence of Study Drug-Related Treatment-Emergent Adverse Events (TEAEs) Leading to Study Withdrawal - Safety Analysis Set 81

Table 14.3-4.1.6: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) by Severity - Safety Analysis Set 82

Table 14.3-4.1.7: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) by Relationship to Study Drug - Safety Analysis Set 83

Table 14.3-4.2.1: Overview of Serious Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set 84

Table 14.3-4.2.2: Summary of Incidence of Serious Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set 84

Table 14.3-4.2.3: Summary of Incidence of Study Drug-Related Serious Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set 84

Table 14.3-4.2.4: Summary of Incidence of Serious Treatment-Emergent Adverse Events (TEAEs) Leading to Study Withdrawal - Safety Analysis Set 84

Table 14.3-4.2.5: Summary of Incidence of Study Drug-Related Serious Treatment-Emergent Adverse Events (TEAEs) Leading to Study Withdrawal - Safety Analysis Set 84

Table 14.3-4.2.6: Summary of Incidence of Serious Treatment-Emergent Adverse Events (TEAEs) Resulting in Death - Safety Analysis Set 84

Table 14.3-4.2.7: Summary of Incidence of Study Drug-Related Serious Treatment-Emergent Adverse Events (TEAEs) Resulting in Death - Safety Analysis Set 84

Table 14.3-5.1: Summary of Incidence of Prior Medications - Safety Analysis Set 85

Table 14.3-5.2: Incidence of Concomitant Medications – Safety Analysis Set 85

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.1-1: Summary of Subject Disposition – All Screened Subjects
Site: Overall

	EXPAREL [N=XX] n (%)	Placebo [N=XX] n (%)	Total [N=XX] n (%)
Screened [1]			xx
Randomized	xx	xx	xx
Not Treated	xx	xx	xx
Treated	xx	xx	xx
Safety Analysis Set [2](as treated)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Primary Efficacy Analysis Set [3] (as randomized)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Secondary Efficacy Analysis Set [3] (as randomized)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PK Analysis Set [4] (as treated)	xx (xx.x)	NA	xx (xx.x)
Completed Study (as randomized)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued from Study (as randomized)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reasons for Discontinuation (as randomized)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death(as randomized)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse Event(as randomized)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of Efficacy(as randomized)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to Follow-up(as randomized)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal by Subject(as randomized)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other(as randomized)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[1] All subjects who signed the informed consent form
[2] All subjects who received study drug
[3] Subjects who received study drug and underwent surgery
[4] Subjects who received EXPAREL and provided sufficient samples for calculation of PK parameters
Number of subjects randomized is used as denominator for all percentages.
Subjects randomized to EXPAREL but treated with placebo:
Subjects randomized to placebo but treated with EXPAREL:
Source: *list SAS datasets used to create table* DDMONYYYYTHH:MM
SAS X.Y program_name

Note to programmer: *First page will present overall sites; subsequent pages will present each site – one site per page. For individual sites the label should be the site number. For the foonotes "Subjects treated with..." if no subjects were mistreated, then put 'NONE' after the colon; otherwise list all subjects who were mistreated.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.1-2.1: Summary of Subject Demographics and Baseline Characteristics - Safety Analysis Set
Site: Overall

	Statistic	EXPAREL [N=XX]	Placebo [N=XX]	Total [N=XX]
Age (yrs)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	Standard Deviation	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
Sex				
Female	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Male	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity				
Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race				
American Indian or Alaska Native	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black or 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 or Pacific Islander	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Multiple	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Height (cm)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	Standard Deviation	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.1-2.1: Summary of Subject Demographics and Baseline Characteristics - Safety Analysis Set
Site: Overall

	Statistic	EXPAREL [N=XX]	Placebo [N=XX]	Total [N=XX]
Weight (kg)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	Standard Deviation	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)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	Standard Deviation	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	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: *First page will present overall sites; subsequent pages will present each site – one site per page. For individual sites the label should be the site number. Use this template also for table:*
Table 14.1-2.2.1: Subject Demographics and Baseline Characteristics – Primary Efficacy Analysis Set
Table 14.1-2.2.2: Subject Demographics and Baseline Characteristics – Secondary Efficacy Analysis Set
Table 14.1-2.3: Subject Demographics and Baseline Characteristics - Pharmacokinetics Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.1-3.1: Summary of Duration of Surgery (hours) - Safety Analysis Set
Site: Overall

Statistic	EXPAREL [N=XX]	Placebo [N=XX]
N	xx	xx
Mean	xx.x	xx.x
Standard Deviation	x.xx	x.xx
Median	xx	xx
Minimum	xx.x	xx.x
Maximum	xx	xx

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

Note to programmer: *First page will present overall sites; subsequent pages will present each site – one site per page. For individual sites the label should be the site number.*

Use this template also for table:
Table 14.1-3.2.1: Surgery and Study Drug Exposure – Primary Efficacy Analysis Set
Table 14.1-3.2.2: Surgery and Study Drug Exposure – Secondary Efficacy Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329

Table 14.2-1.1.1: Analysis of AUC of NRS Pain Intensity Scores through 48 hours – Primary Efficacy Analysis Set - Multiple Imputation Results

Statistic	EXPAREL [N=XX]	Placebo [N=XX]	EXPAREL – Placebo
N	xx	xx	
Mean	xxx.x	xxx.x	
Standard Deviation	xxx.xx	xxx.xx	
Median	xxx.x	xxx.x	
Minimum	xx	xx	
Maximum	xxx	xxx	
Least squares mean [1]	xxx.x	xxx.x	xxx.x
Least squares standard error of mean [1]	xxx.xx	xxx.xx	xxx.xx
95% confidence interval for treatment difference [1]			(xxx.x, xxx.x)
p-value for treatment difference[1]			0.xxxx

Note: AUC = area under the curve calculated using the trapezoidal method;
NRS = numeric rating scale at rest, where 0 = no pain and 10 = worst possible pain;
Summary statsitics based on the subject mean AUC from the multiple imputations;
wWOCF + LOCF = imputation using the worst observation prior to use of rescue medication within a medication window and last-observation-carried-forward for missing values.
[1] From an ANOVA with main effects of treatment and site.

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 14.2-1.1 & 14.2-1.2 series tables should be saved as a possible appendix to the clinical study report (CSR). Use this template for the following tables:*

Table 14.2-1.1.2: Sensitivity Analysis of AUC of NRS Pain Intensity Scores through 48 hours – Secondary Efficacy Analysis Set - Multiple Imputation Results
Table 14.2-1.1.3: Sensitivity Analysis of AUC of NRS Pain Intensity Scores through 48 hours – Primary Efficacy Analysis Set – Mixed Model Repeated Measures Results

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329

Table 14.2-1.1.4: Sensitivity Analysis of AUC of NRS Pain Intensity Scores through 48 hours – Primary Efficacy Analysis Set – Tipping Point Analysis - Multiple Imputation Results

Statistic	EXPAREL [N=XX]	Placebo [N=XX]	EXPAREL – Placebo
N	xx	xx	
Mean	xxx.x	xxx.x	
Standard Deviation	xxx.xx	xxx.xx	
Median	xxx.x	xxx.x	
Minimum	xx	xx	
Maximum	xxx	xxx	
Least squares mean [1]	xxx.x	xxx.x	xxx.x
Least squares standard error of mean [1]	xxx.xx	xxx.xx	xxx.xx
95% confidence interval for treatment difference [1]			(xxx.x, xxx.x)
p-value for treatment difference[1]			0.xxxx
Tipping Point [2]			xx

Note: AUC = area under the curve calculated using the trapezoidal method;
NRS = numeric rating scale at rest, where 0 = no pain and 10 = worst possible pain;
Summary statsitics based on the subject mean AUC from the multiple imputations;
wWOCF + LOCF = imputation using the worst observation prior to use of rescue medication within a medication window and last-observation-carried-forward for missing values.
[1] From an ANOVA with main effects of treatment and site.
[2] Tipping point is the value added to EXPAREL to reverse the statistical significance observed in the primary analysis.

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 14.2-1.1 & 14.2-1.2 series tables should be saved as a possible appendix to the clinical study report (CSR). Use template 14.2-1.1.1 for the following tables:*

Table 14.2-1.1.5: Sensitivity Analysis of AUC of NRS Pain Intensity Scores through 48 hours – Primary Efficacy Analysis Set – wWOCF with LOCF Single Imputation (Historical Imputation)

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329

Table 14.2-1.2: Summary of AUC of NRS Pain Intensity Scores through 48 hours – Primary Efficacy Analysis Set - Analysis of Variance (ANOVA) Model Results - 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

Note: AUC = area under the curve calculated using the trapezoidal method;
NRS = numeric rating scale at rest, where 0 = no pain and 10 = worst possible pain;
wWOCF + LOCF = imputation using the worst observation prior to use of rescue medication within a medication window and last-observation-carried-forward for missing values.
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 14.2-1.1 & 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-329

Table 14.2-1.3: Summary of AUC of NRS Pain Intensity Scores through 48 hours by Site – Primary Efficacy Analysis Set - Multiple Imputation Results

Site	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
XXXX	N	xx	xx
	Mean	xxx.x	xxx.x
	Standard Deviation	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Minimum	xx	xx
	Maximum	xxx	xxx
Etc.	N	xx	xx
	Mean	xxx.x	xxx.x
	Standard Deviation	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Minimum	xx	xx
	Maximum	xxx	xxx

Note: AUC = area under the curve calculated using the trapezoidal method;
NRS = numeric rating scale at rest, where 0 = no pain and 10 = worst possible pain;
Summary statsitics based on the subject mean AUC from the multiple imputations;
wWOCF + LOCF = imputation using the worst observation prior to use of rescue medication within a medication window and last-observation-carried-forward for missing values.
Source: *list SAS datasets used to create table* *DDMONYYYYTHH:MM*
SAS X.Y *program_name*

Note to programmer: *Use mock-ups Table 14.2-1.1.1, 14.2-1.2 and 14.2-1.3 for the following tables respectively:*

Table 14.2-2.1: Analysis of AUC of NRS Pain Intensity Scores through 24 hours - Primary Efficacy Analysis Set - Multiple Imputation Results
Table 14.2-2.2: Summary of AUC of NRS Pain Intensity Scores through 24 hours - Primary Efficacy Analysis Set - Analysis of Variance Model Results - Multiple Imputation Results
Table 14.2-2.3: Summary of AUC of NRS Pain Intensity Scores through 24 hours by Site - Primary Efficacy Analysis Set - Multiple Imputation Results
Table 14.2-3.1: Analysis of AUC of NRS Pain Intensity Scores through 72 hours - Primary Efficacy Analysis Set - Multiple Imputation Results
Table 14.2-3.2: Summary of AUC of NRS Pain Intensity Scores through 72 hours - Primary Efficacy Analysis Set - Analysis of Variance Model Results - Multiple Imputation Results

Table 14.2-3.3: Summary of AUC of NRS Pain Intensity Scores through 72 hours by Site - Primary Efficacy Analysis Set - Multiple Imputation Results

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329

Table 14.2-4: Summary of SPIS of NRS Pain Intensity Scores - Primary Efficacy Analysis Set - Multiple Imputation Results

SPIS	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
SPIS(0.25-24)	N	xx	xx
	Mean	xxx.x	xxx.x
	Standard Deviation	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Minimum	xx	xx
	Maximum	xxx	xxx
SPIS(0.25-48)	N	xx	xx
	Mean	xxx.x	xxx.x
	Standard Deviation	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Minimum	xx	xx
	Maximum	xxx	xxx
SPIS(0.25-72)	N	xx	xx
	Mean	xxx.x	xxx.x
	Standard Deviation	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Minimum	xx	xx
	Maximum	xxx	xxx
SPIS(0.25-96)	N	xx	xx
	Mean	xxx.x	xxx.x
	Standard Deviation	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Minimum	xx	xx
	Maximum	xxx	xxx

Note: SPIS = sum of pain intensity scores;
NRS = numeric rating scale at rest, where 0 = no pain and 10 = worst possible pain;
Summary statsitics based on the subject mean SPIS from the multiple imputations;
wWOCF + LOCF = imputation using the worst observation prior to use of rescue medication within a medication window and last-observation-carried-forward for missing values.
Source: *list SAS datasets used to create table* *DDMONYYYYTHH:MM*
SAS X.Y *program_name*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329

Table 14.2-5.1: Analysis of Opioid-Free Subjects through 24 hours - Primary Efficacy Analysis Set

Site / Time Period / Opioid Use	Statistic	EXPAREL [N=XX]	Placebo [N=XX]	EXPAREL vs PLACEBO Difference [1]	95% CI [1]	p-value [2]
Overall						
0-24 hours						
No	n (%)	xx (xx.x)	xx (xx.x)	xx.x	(xx.x, xx.x)	0.xxxx
Yes	n (%)	xx (xx.x)	xx (xx.x)			
Site XXX						
0-24 hours						
No	n (%)	xx (xx.x)	xx (xx.x)	xx.x	(xx.x, xx.x)	NA
Yes	n (%)	xx (xx.x)	xx (xx.x)			
Site XXX						
0-24 hours						
No	n (%)	xx (xx.x)	xx (xx.x)	xx.x	(xx.x, xx.x)	NA
Yes	n (%)	xx (xx.x)	xx (xx.x)			

[1] 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* DDMONYYYYTHH:MM
SAS X.Y program_name

Note to programmer: *Do not split sites across pages. Use mock-up 14.2-5.1 for the following tables:*

Table 14.2-5.2: Analysis of Opioid Free Subjects through 48 hours - Primary Efficacy Analysis Set
Table 14.2-5.3: Analysis of Opioid Free Subjects through 72 hours - Primary Efficacy Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329

Table 14.2-6.1: Summary of Numerical Rating Scale (NRS) Pain Intensity Scores - By Assessment Timepoint - Efficacy Analysis Set - Multiple Imputation Results

Assessment Timepoint	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
15 minute	N	xx	xx
	Mean	xx.x	xx.x
	Standard Deviation	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx
30 minute	N	xx	xx
	Mean	xx.x	xx.x
	Standard Deviation	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx
1 hour	N	xx	xx
	Mean	xx.x	xx.x
	Standard Deviation	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx
X hour	N	xx	xx
	Mean	xx.x	xx.x
	Standard Deviation	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx

Summary statsitics based on the subject mean NRS scores from the multiple imputations.
Source: *list SAS datasets used to create table* DDMONYYYYTHH:MM
SAS X.Y program_name

Note to programmer: *Timepoints to appear on this table are 15 and 30 minute followed by 1, 2, 4, 8, 12, 24, 48, 72 and 96 hours. Do not split timepoints across pages.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.2-6.2: Summary of Numerical Rating Scale (NRS) Pain Intensity Scores at Rescue - Efficacy Analysis Set

Relative Rescue for Subject	Parameter	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
First Rescue	NRS Score	N	xx	xx
		Mean	xx.x	xx.x
		Standard Deviation	x.xx	x.xx
		Minimum	xx	xx
		Median	xx.x	xx.x
		Maximum	xx	xx
	Time to Rescue (hrs)	Median	xx.x	xx.x
		Minimum	xx	xx
		Maximum	xx	xx
Second Rescue	NRS Score	N	xx	xx
		Mean	xx.x	xx.x
		Standard Deviation	x.xx	x.xx
		Minimum	xx	xx
		Median	xx.x	xx.x
		Maximum	xx	xx
	Time to Rescue (hrs)	Median	xx.x	xx.x
		Minimum	xx	xx
		Maximum	xx	xx

Summary statsitics based on the subject mean NRS scores from the multiple imputations.
Source: *list SAS datasets used to create table* DDMONYYYYTHH:MM
SAS X.Y program_name

Note to programmer: *Do not split rescue block across pages.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329

Table 14.2-7.1: Summary of AUC(0.25-96) and AUC(0.25-Day 10) of NRS Pain Intensity Scores - Primary Efficacy Analysis Set – Multiple Imputation Results

	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
AUC(0.25-96)	N	Xx	xx
	Mean	xxx.x	xxx.x
	Standard Deviation	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Minimum	Xx	xx
	Maximum	Xxx	xxx
AUC(0.25-Day 10)	n	Xx	xx
	Mean	xxx.x	xxx.x
	Standard Deviation	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Minimum	Xx	xx
	Maximum	Xxx	xxx

Note: AUC = area under the curve calculated using the trapezoidal method;
NRS = numeric rating scale at rest, where 0=no pain and 10=worst possible pain;
Summary statsitics based on the subject mean AUC scores from the multiple imputations;
wWOCF + LOCF = imputation using the worst observation prior to use of rescue medication within a medication window and last-observation-carried-forward for missing values.

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329

Table 14.2-7.2: Summary of AUC(24-48) and AUC(48-72) of NRS Pain Intensity Scores - Primary Efficacy Analysis Set – Multiple Imputation Results

AUC	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
AUC(24-48)	n	xx	xx
	Mean	xxx.x	xxx.x
	Standard Deviation	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Minimum	xx	xx
	Maximum	xxx	xxx
AUC(48-72)	n	xx	xx
	Mean	xxx.x	xxx.x
	Standard Deviation	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Minimum	xx	xx
	Maximum	xxx	xxx

Note: AUC = area under the curve calculated using the trapezoidal method;
NRS = numeric rating scale at rest, where 0 = no pain and 10 = worst possible pain;
Summary statsitics based on the subject mean AUC scores from the multiple imputations;
wWOCF + LOCF = imputation using the worst observation prior to use of rescue medication within a medication window and last-observation-carried-forward for missing values.

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329

Table 14.2-8: Tabulation of Pain-Free Subjects at Assessment Time Points - Primary Efficacy Analysis Set

Time Point	Pain Free	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
15 min	No	n (%)	xx (xx.x)	xx (xx.x)
	Yes	n (%)	xx (xx.x)	xx (xx.x)
30 min	No	n (%)	xx (xx.x)	xx (xx.x)
	Yes	n (%)	xx (xx.x)	xx (xx.x)
1 hour	No	n (%)	xx (xx.x)	xx (xx.x)
	Yes	n (%)	xx (xx.x)	xx (xx.x)
Etc.	No	n (%)	xx (xx.x)	xx (xx.x)
	Yes	n (%)	xx (xx.x)	xx (xx.x)

Pain-free is a NRS score of 0 or 1 with no prior rescue medication use.

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

Note to programmer: *Do not split time point across pages. Time points to appear on this tables are 15 min, 30 min and 1 hour, 2 hour, 4 hour, 6 hour, 8 hour, 12 hour, 24 hour, 48 hour, 72 hour, 96 hour and Day 10.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.2-9: Summary of Time to First Rescue Medication Use (hours) - Primary Efficacy Analysis Set
Site: Overall

	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
Rescued	n (%)	xx (xx.x)	xx (xx.x)
No Rescue (censored)	n (%)	xx (xx.x)	xx (xx.x)
Quartiles [1]			
First (25% rescued)	Est. (95% CI)	xxx (xxx,xxx)	xxx (xxx,xxx)
Median (50% rescued)	Est. (95% CI)	xxx (xxx,xxx)	xxx (xxx,xxx)
Third (75% rescued)	Est. (95% CI)	xxx (xxx,xxx)	xxx (xxx,xxx)
Minimum	Observed	xxx	xxx
Maximum	Observed	xxx*	xxx*

* indicates censored observation
Est. = Point estimate; CI = confidence interval
[1] Estimates from Kaplan-Meier analysis.
Source: *list SAS datasets used to create table*
DDMONYYYYTHH:MM
SAS X.Y
program_name

Note to programmer: *First page will present overall sites; subsequent pages will present each site – one site per page.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329

Table 14.2-10: Summary of Integrated Rank Assessment of NRS Pain Intensity Scores and Opioid Use - By Assessment Timepoint - Primary Efficacy Analysis Set

Site: Overall

Assessment Timepoint	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
24 hours	n	xx	xx
	Mean	xx.x	xx.x
	Standard Deviation	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx
48 hours	n	xx	xx
	Mean	xx.x	xx.x
	Standard Deviation	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx
72 hours	n	xx	xx
	Mean	xx.x	xx.x
	Standard Deviation	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx

Positive numbers indicate less pain or opioid use; negative numbers indicate greater pain or opioid use.

Source: *list SAS datasets used to create table* DDMONYYYYTHH:MM

SAS X.Y program_name

Note to programmer: *Only present overall sites.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.2-11: Summary of Satisfaction with Postsurgical Pain Control Questionnaire Score by Timepoint - Primary Efficacy Analysis Set
Site: Overall

Timepoint	Score	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
24 hour	Summary	n	xx	xx
		Mean	xx.x	xx.x
		Standard Deviation	x.xx	x.xx
		Minimum	xx	xx
		Median	xx.x	xx.x
		Maximum	xx	xx
	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* DDMONYYYYTHH:MM
SAS X.Y program_name

Note to programmer: *Only present overall sites. Timepoints to appear on this table are 24, 48, 72 and 96 hour. Do not split timepoint across pages.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.2-12.1: Summary of Postoperative Symptom Severity (PoSSe) Questionnaire - Total Score [1] Summary - Primary Efficacy Analysis Set
Site: Overall

Timepoint	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
72 hour	N	xx	xx
	Mean	xx.x	xx.x
	Standard Deviation	x.xx	x.xx
	Minimum	xx	Xx
	Median	xx.x	xx.x
	Maximum	xx	Xx
Day 10	N	xx	Xx
	Mean	xx.x	xx.x
	Standard Deviation	x.xx	x.xx
	Minimum	xx	Xx
	Median	xx.x	xx.x
	Maximum	xx	Xx

[1] Total score is the sum all questions scores for a subject.
Subjects missing total score in 72 hr:
Subjects missing total score in Day 10:

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

Note to programmer: *Only present overall sites. If PoSSe total score calculated for all subjects put "none" after "Subjects missing total score…"; otherwise list subject numbers after appropriate timepoint.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.2-12.2: Summary of Postoperative Symptom Severity (PoSSe) Questionnaire - Individual Question Score Tabulation - Primary Efficacy Analysis Set
Site: Overall

Timepoint Question	Score	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
72 hour				
1 EATING, in last week:				
1a: Enjoyment of food	No, not at all	n (%)	XX (XX.X)	XX (XX.X)
	Yes, a little	n (%)	XX (XX.X)	XX (XX.X)
	Yes, very much	n (%)	XX (XX.X)	XX (XX.X)
1b: Days unable to open mouth normally	0 days	n (%)	XX (XX.X)	XX (XX.X)
	1-2 days	n (%)	XX (XX.X)	XX (XX.X)
	3-4 days	n (%)	XX (XX.X)	XX (XX.X)
	5-6 days	n (%)	XX (XX.X)	XX (XX.X)
	7 days	n (%)	XX (XX.X)	XX (XX.X)
2 SPEECH, in last week:				
2a: Days voice affected	0 days	n (%)	XX (XX.X)	XX (XX.X)
	1-2 days	n (%)	XX (XX.X)	XX (XX.X)
	3-4 days	n (%)	XX (XX.X)	XX (XX.X)
	5-6 days	n (%)	XX (XX.X)	XX (XX.X)
	7 days	n (%)	XX (XX.X)	XX (XX.X)
2b: On worst day how badly speech affected	Not at all	n (%)	XX (XX.X)	XX (XX.X)
	Slightly	n (%)	XX (XX.X)	XX (XX.X)
	Moderately	n (%)	XX (XX.X)	XX (XX.X)
	Severely	n (%)	XX (XX.X)	XX (XX.X)
	Unable to speak	n (%)	XX (XX.X)	XX (XX.X)

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.2-12.2: Summary of Postoperative Symptom Severity (PoSSe) Questionnaire - Individual Question Score Tabulation - Primary Efficacy Analysis Set
Site: Overall

Timepoint Question	Score	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
72 hour (continued)				
3 SENSATION, in last week:				
3a: Days lips or tongue tingled	None at all	n (%)	XX (XX.X)	XX (XX.X)
	1-2 days	n (%)	XX (XX.X)	XX (XX.X)
	3-4 days	n (%)	XX (XX.X)	XX (XX.X)
	5-6 days	n (%)	XX (XX.X)	XX (XX.X)
	7 days	n (%)	XX (XX.X)	XX (XX.X)
3b: Days lips or tongue numb	None at all	n (%)	XX (XX.X)	XX (XX.X)
	1-2 days	n (%)	XX (XX.X)	XX (XX.X)
	3-4 days	n (%)	XX (XX.X)	XX (XX.X)
	5-6 days	n (%)	XX (XX.X)	XX (XX.X)
	7 days	n (%)	XX (XX.X)	XX (XX.X)
4 APPEARANCE, in last week:				
4a: Days face or neck bruised	None at all	n (%)	XX (XX.X)	XX (XX.X)
	1-2 days	n (%)	XX (XX.X)	XX (XX.X)
	3-4 days	n (%)	XX (XX.X)	XX (XX.X)
	5-6 days	n (%)	XX (XX.X)	XX (XX.X)
	7 days	n (%)	XX (XX.X)	XX (XX.X)
4b: Days face or neck swollen	None at all	n (%)	XX (XX.X)	XX (XX.X)
	1-2 days	n (%)	XX (XX.X)	XX (XX.X)
	3-4 days	n (%)	XX (XX.X)	XX (XX.X)
	5-6 days	n (%)	XX (XX.X)	XX (XX.X)
	7 days	n (%)	XX (XX.X)	XX (XX.X)

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.2-12.2: Summary of Postoperative Symptom Severity (PoSSe) Questionnaire - Individual Question Score Tabulation - Primary Efficacy Analysis Set
Site: Overall

Timepoint Question	Score	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
72 hour (continued)				
5 PAIN, in last week:				
5a: Days experience pain	0 days	n (%)	XX (XX.X)	XX (XX.X)
	1-2 days	n (%)	XX (XX.X)	XX (XX.X)
	3-4 days	n (%)	XX (XX.X)	XX (XX.X)
	5-6 days	n (%)	XX (XX.X)	XX (XX.X)
	7 days	n (%)	XX (XX.X)	XX (XX.X)
5b: Contolled by painkillers	Had no pain	n (%)	XX (XX.X)	XX (XX.X)
	Comletely controlled	n (%)	XX (XX.X)	XX (XX.X)
	Some discomfort	n (%)	XX (XX.X)	XX (XX.X)
	Poorly controlled	n (%)	XX (XX.X)	XX (XX.X)
	No controlled	n (%)	XX (XX.X)	XX (XX.X)
6 SICKNESS				
6a: Last week, days vomit/nauseated	0 days	n (%)	XX (XX.X)	XX (XX.X)
	1-2 days	n (%)	XX (XX.X)	XX (XX.X)
	3-4 days	n (%)	XX (XX.X)	XX (XX.X)
	5-6 days	n (%)	XX (XX.X)	XX (XX.X)
	7 days	n (%)	XX (XX.X)	XX (XX.X)
6b: Worst day, how many times vomit/nauseated	None	n (%)	XX (XX.X)	XX (XX.X)
	One day	n (%)	XX (XX.X)	XX (XX.X)
	2-3 times	n (%)	XX (XX.X)	XX (XX.X)
	> 3 times	n (%)	XX (XX.X)	XX (XX.X)
	All the time	n (%)	XX (XX.X)	XX (XX.X)

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.2-12.2: Summary of Postoperative Symptom Severity (PoSSe) Questionnaire - Individual Question Score Tabulation - Primary Efficacy Analysis Set
Site: Overall

Timepoint Question	Score	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
72 hour (continued)				
7 INTERFERENCE DAILY ACTIVITIES, in last week				
7a: Prevent work/housework	Not at all	n (%)	XX (XX.X)	XX (XX.X)
	Work suffered	n (%)	XX (XX.X)	XX (XX.X)
	1 day	n (%)	XX (XX.X)	XX (XX.X)
	2-6 days	n (%)	XX (XX.X)	XX (XX.X)
	7 days	n (%)	XX (XX.X)	XX (XX.X)
7b: Leisure activities affected	Not affected	n (%)	XX (XX.X)	XX (XX.X)
	Mildly	n (%)	XX (XX.X)	XX (XX.X)
	Moderately	n (%)	XX (XX.X)	XX (XX.X)
	Severely	n (%)	XX (XX.X)	XX (XX.X)
	Prevented activities	n (%)	XX (XX.X)	XX (XX.X)
7c: Pain affect life				
	None	n (%)	XX (XX.X)	XX (XX.X)
	Slightly	n (%)	XX (XX.X)	XX (XX.X)
	Moderately	n (%)	XX (XX.X)	XX (XX.X)
	Severely	n (%)	XX (XX.X)	XX (XX.X)

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

Note to programmer: *Only present overall sites. Timepoints to appear on this table are 72 hour and Day 10.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.2-13: Summary of Number of Unscheduled Phone Calls or Office Visits Related to Pain - Primary Efficacy Analysis Set
Site: Overall

	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
Count Summary	n	xx	xx
	Mean	xx.x	xx.x
	Standard Deviation	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* DDMONYYYYTHH:MM
SAS X.Y program_name

Note to programmer: *Only present overall sites. Distribution should present all counts up to the highest number of visits in the data (U).*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.2-14.1: Summary of Total Rescue Medication Consumption (MED) - Primary Efficacy Analysis Set
Site: Overall

Time Period	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
0-24 hrs	n	xx	xx
	Mean	xx.x	xx.x
	Standard Deviation	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx
0-48 hrs	n	xx	xx
	Mean	xx.x	xx.x
	Standard Deviation	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx
0-72 hrs	n	xx	xx
	Mean	xx.x	xx.x
	Standard Deviation	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx
0-96 hrs	n	xx	xx
	Mean	xx.x	xx.x
	Standard Deviation	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.2-14.2: Summary of the Number of Times Rescue Medication was Used by Subject - Primary Efficacy Analysis Set
Site: Overall

	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
Count Summary	n	xx	xx
	Mean	xx.x	xx.x
	Standard Deviation	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* DDMONYYYYTHH:MM
SAS X.Y program_name

Note to programmer: *Present table overall sites and for each site. Distribution should present all counts up to the highest number of visits in the data (U).*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329

Table 14.3-1: Tabulation of Neurological Assessments by Timepoint- Safety Analysis Set

Timepoint	Assessment	Score	Statistic	EXPAREL [N=XX]	Placebo [N=XX]	Total [N=XXX]
Baseline (Prior to Surgery)						
	Numbness of lips, tongue or mouth	No	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
		Yes	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Metallic taste	No	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
		Yes	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Hearing problems	No	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
		Yes	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Vision problems	No	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
		Yes	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Muscle twitching	No	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
		Yes	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
At anytime after baseline						
	Numbness of lips, tongue or mouth	No	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
		Yes	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Metallic taste	No	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
		Yes	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Hearing problems	No	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
		Yes	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Vision problems	No	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
		Yes	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Muscle twitching	No	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)
		Yes	n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)

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

Note to programmer: *Only present overall sites. Timepoints to appear on this table are, in order of appearance, Baseline (prior to surgery), At anytime after baseline, 15 and 30 minutes and 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 84 and 96 hours. Do not split a timepoint across pages. For the timepoint 'anytime after baseline' if there is at least one 'yes' at any timepoint but baseline, the subject will be a 'yes'.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.3-2.1 Summary of Electrocardiogram Parameters – Central Read - Safety Analysis Set
Site: Overall

ECG Parameter	Timepoint	Value	Statistic	EXPAREL [N=XX]	Placebo [N=XX]	Total [N=XXX]
Heart Rate (bpm)						
	Baseline	Actual	n	xx	xx	xx
			Mean	xx.x	xx.x	xx.x
			Standard Deviation	x.xx	x.xx	x.xx
			Minimum	xx	xx	xx
			Median	xx.x	xx.x	xx.x
			Maximum	xx	xx	xx
	At Median Tmax (XX Hour)	Baseline Actual[1]	n	xx	xx	xx
			Mean	xx.x	xx.x	xx.x
			Standard Deviation	x.xx	x.xx	x.xx
			Minimum	xx	xx	xx
			Median	xx.x	xx.x	xx.x
			Maximum	xx	xx	xx
		Actual	n	xx	xx	xx
			Mean	xx.x	xx.x	xx.x
			Standard Deviation	x.xx	x.xx	x.xx
			Minimum	xx	xx	xx
			Median	xx.x	xx.x	xx.x
			Maximum	xx	xx	xx
		Change from Baseline	n	xx	xx	xx
			Mean	xx.x	xx.x	xx.x
			Standard Deviation	x.xx	x.xx	x.xx
			Minimum	xx	xx	xx
			Median	xx.x	xx.x	xx.x
			Maximum	xx	xx	xx

[1] Baseline (prior to surgery) for subjects with data at the timepoint.
QTcF = corrected QT interval using Fridericia's correction
QTcB = corrected QT interval using Bazett's correction
Source: *list SAS datasets used to create table* DDMONYYYYTHH:MM
SAS X.Y program_name

Note to programmer: *Only present overall sites. Electrocardiogram intervals are 'Heart Rate (bpm)', 'RR Interval (msec)', 'PR Interval (msec)', 'QRS Interval (msec)', 'QT Interval (msec)', 'QTcF Interval (msec)', 'QTcB Interval (msec).' Timepoints to appear on this table are, in order of appearance, Baseline, At Median Tmax (XX Hour), At Subjects' Tmax, 15 and 30 minutes and 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 84 and 96 hours. Don't split timepoint across pages. Note that the X hour (Tmax) timepoint will be a duplicate of X hour summary.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329

Table 14.3-2.2: Summary of Potentially Clinically Meaningful Abnormal Electrocardiogram Results – Central Read - Safety Analysis Set

ECG Parameter	Timepoint	Criteria	Statistic	EXPAREL [N=XX]	Placebo [N=XX]	Total [N=XXX]
Heart Rate (bpm)						
	Baseline	< 50	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Decrease >= 25	n (%)	NA	NA	NA
		< 50 & Decrease >= 25	n (%)	NA	NA	NA
		> 100	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Increase >= 25	n (%)	NA	NA	NA
		> 100 & Increase >= 25	n (%)	NA	NA	NA
	Any time after Baseline	< 50	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Decrease >= 25	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		< 50 & Decrease >= 25	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		> 100	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Increase >= 25	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		> 100 & Increase >= 25	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	At Median Tmax (XX hours)	< 50	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Decrease >= 25	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		< 50 & Decrease >= 25	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		> 100	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Increase >= 25	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		> 100 & Increase >= 25	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	15 minutes	< 50	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Decrease >= 25	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		< 50 & Decrease >= 25	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		> 100	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Increase >= 25	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		> 100 & Increase >= 25	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

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

Note to programmer: *Only present overall sites. Electrocardiogram intervals are 'Heart Rate (bpm)', 'PR Interval (msec)', 'QRS Interval (msec)', 'QT Interval (msec)', 'QTcF Interval (msec)', 'QTcB Interval (msec).' Timepoints to appear on this table are, in order of appearance, Baseline, Any time after Baseline, At Median Tmax (X hour), At Subjects' Tmax, 15 and 30 minutes and 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 84 and 96 hours. Don't split timepoint across pages. Note that the At Median Tmax (X hour) timepoint will be a duplicate of X hour summary.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329

Table 14.3-2.3: Tabulation Electrocardiogram Morphology Results – Central Read - Safety Analysis Set

Time Point	Morphology	Statistic	EXPAREL [N=XX]	Placebo [N=XX]	Total [N=XXX]
Any Time After Baseline					
	No Findings	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	At Least One Finding	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Abnormal U Wave	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	ST Segment Elevation	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	ST Segment Depression	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	T Wave Inversion	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Second or Third Degree Heart Block	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	LBBB	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	RBBB	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Atrial Fibrillation	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Atrial Flutter	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	MI	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Baseline					
	No Findings	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	At Least One Finding	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Abnormal U Wave	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	ST Segment Elevation	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	ST Segment Depression	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	T Wave Inversion	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Second or Third Degree Heart Block	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	LBBB	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	RBBB	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Atrial Fibrillation	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Atrial Flutter	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	MI	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

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

Note to programmer: *Only present overall sites. Electrocardiogram morphology list presented in mock-up may not be complete (or may contain items not found during study), the list should only present those morphologies found during the study. Timepoints to appear on this table are, in order of appearance, At Any Time After Baseline, Baseline, X hour (Tmax), 15 and 30 minutes and 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48,*

54, 60, 66, 72, 84 and 96 hours. Don't split timepoint across pages. Note that the X hour (Tmax) timepoint will be a duplicate of X hour summary.

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329

Table 14.3-2.4: Tabulation Electrocardiogram Interpretation – Investigator Read - Safety Analysis Set

Time Point	Interpretation	Statistic	EXPAREL [N=XX]	Placebo [N=XX]	Total [N=XXX]
Any Time After Baseline					
	Normal	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Abnormal, Not clinically siginificant	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Abnormal, Clinically siginificant	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Baseline	Normal	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Abnormal, Not clinically siginificant	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Abnormal, Clinically siginificant	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

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

Note to programmer: *Only present overall sites. Timepoints to appear on this table are, in order of appearance, At Any Time After Baseline, Baseline, X hour (Tmax), 15 and 30 minutes and 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 84 and 96 hours. Don't split timepoint across pages. Note that the X hour (Tmax) timepoint will be a duplicate of X hour summary.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.3-3.1: Summary of Vital Signs – Safety Analysis Set
Site: Overall

Vital Sign	Timepoint	Value	Statistic	EXPAREL [N=XX]	Placebo [N=XX]	Total [N=XXX]
Resting Heart Rate (bpm)						
	Baseline	Actual	n	xx	xx	xx
			Mean	xx.x	xx.x	xx.x
			Standard Deviation	x.xx	x.xx	x.xx
			Minimum	xx	xx	xx
			Median	xx.x	xx.x	xx.x
			Maximum	xx	xx	xx
	1 hour	Baseline Actual[1]	n	xx	xx	xx
			Mean	xx.x	xx.x	xx.x
			Standard Deviation	x.xx	x.xx	x.xx
			Minimum	xx	xx	xx
			Median	xx.x	xx.x	xx.x
			Maximum	xx	xx	xx
		Actual	n	xx	xx	xx
			Mean	xx.x	xx.x	xx.x
			Standard Deviation	x.xx	x.xx	x.xx
			Minimum	xx	xx	xx
			Median	xx.x	xx.x	xx.x
			Maximum	xx	xx	xx
		Change from Baseline	n	xx	xx	xx
			Mean	xx.x	xx.x	xx.x
			Standard Deviation	x.xx	x.xx	x.xx
			Minimum	xx	xx	xx
			Median	xx.x	xx.x	xx.x
			Maximum	xx	xx	xx

[1] Baseline (prior to surgery) for subjects with data at the timepoint.
Source: *list SAS datasets used to create table* DDMONYYYYTHH:MM
SAS X.Y program_name

Note to programmer: *Only present overall sites. Vital signs are 'Resting Heart Rate (bpm)', 'Systolic Blood Pressure (mmHg)' and 'Diastolic Blood Pressure (mmHg)'. Timepoints to appear on this table are Baseline, 1, 2 and 4 hour. Don't split timepoint across pages.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.3-3.2: Summary of Potentially Clinically Significant Abnormal Vital Signs – Safety Analysis Set
Site: Overall

Vital Sign	Timepoint	Criteria	Statistic	EXPAREL [N=XX]	Placebo [N=XX]	Total [N=XXX]
Resting Heart Rate (bpm)						
	Baseline	<= 50	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Decrease >= 15	n (%)	NA	NA	NA
		<= 50 & Decrease >= 15	n (%)	NA	NA	NA
		>= 120	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Increase >= 15	n (%)	NA	NA	NA
		>= 120 & Increase >= 15	n (%)	NA	NA	NA
	1 hour	<= 50	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Decrease >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		<= 50 & Decrease >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>= 120	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Increase >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>= 120 & Increase >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	2 hour	<= 50	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Decrease >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		<= 50 & Decrease >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>= 120	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Increase >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>= 120 & Increase >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	4 hour	<= 50	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Decrease >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		<= 50 & Decrease >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>= 120	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Increase >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>= 120 & Increase >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.3-3.2: Summary of Potentially Clinically Significant Abnormal Vital Signs – Safety Analysis Set
Site: Overall

Vital Sign	Timepoint	Criteria	Statistic	EXPAREL [N=XX]	Placebo [N=XX]	Total [N=XXX]
Systolic Blood Pressure (mmHg)						
	Baseline	<= 90	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Decrease >= 20	n (%)	NA	NA	NA
		<= 90 & Decrease >= 20	n (%)	NA	NA	NA
		>= 180	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Increase >= 20	n (%)	NA	NA	NA
		>= 180 & Increase >= 20	n (%)	NA	NA	NA
	1 hour	<= 90	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Decrease >= 20	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		<= 90 & Decrease >= 20	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>= 180	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Increase >= 20	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>= 180 & Increase >= 20	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	2 hour	<= 90	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Decrease >= 20	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		<= 90 & Decrease >= 20	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>= 180	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Increase >= 20	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>= 180 & Increase >= 20	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	4 hour	<= 90	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Decrease >= 20	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		<= 90 & Decrease >= 20	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>= 180	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Increase >= 20	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>= 180 & Increase >= 20	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.3-3.2: Summary of Potentially Clinically Significant Abnormal Vital Signs – Safety Analysis Set
Site: Overall

Vital Sign	Timepoint	Criteria	Statistic	EXPAREL [N=XX]	Placebo [N=XX]	Total [N=XXX]
Diatolic Blood Pressure (mmHg)						
	Baseline	<= 50	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Decrease >= 15	n (%)	NA	NA	NA
		<= 50 & Decrease >= 15	n (%)	NA	NA	NA
		>= 105	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Increase >= 15	n (%)	NA	NA	NA
		>= 105 & Increase >= 15	n (%)	NA	NA	NA
	1 hour	<= 50	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Decrease >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		<= 50 & Decrease >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>= 105	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Increase >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>= 105 & Increase >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	2 hour	<= 50	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Decrease >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		<= 50 & Decrease >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>= 105	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Increase >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>= 105 & Increase >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	4 hour	<= 50	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Decrease >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		<= 50 & Decrease >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>= 105	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Increase >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		>= 105 & Increase >= 15	n (%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Source: *list SAS datasets used to create table* DDMONYYYYTHH:MM
SAS X.Y program_name
Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329

Table 14.3-4.1.1: Overview of Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set
Site: Overall

Number of	EXPAREL [N=XX] n (%)	Placebo [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* DDMONYYYYTHH:MM
SAS X.Y program_name

Note to programmer: *Only present overall sites.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.3-4.1.2: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set
Site: Overall

System Organ Class Preferred Term	EXPAREL [N=XX] n (%)	Placebo [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)
	xx (xx.x)	xx (xx.x)	xx (xx.x)
ETC.			

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* DDMONYYYYTHH:MM
SAS X.Y program_name

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

Table 14.3-4.1.3: Summary of Incidence of Study Drug-Related Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set
Table 14.3-4.1.4: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) Leading to Study Withdrawal - Safety Analysis Set
Table 14.3-4.1.5: 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-329
Table 14.3-4.1.6: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) by Severity - Safety Analysis Set
Site: Overall

System Organ Class Preferred Term	Severity	EXPAREL [N=XX] n (%)	Placebo [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)
PT1.2	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC2	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)
	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)
PT2.1	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)
ETC.				

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* DDMONYYYYTHH:MM
SAS X.Y program_name

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.3-4.1.7: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) by Relationship to Study Drug - Safety Analysis Set
Site: Overall

System Organ Class Preferred Term	Severity	EXPAREL [N=XX] n (%)	Placebo [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)
PT1.2	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)
SOC2	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)
ETC.				

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* DDMONYYYYTHH:MM
SAS X.Y program_name

Note to programmer: *Only present overall sites.*
Note to programmer: *Only present overall sites. Use templates 14.3.1-1 through 14.3.1-7 respectively for the following tables:*

Table 14.3-4.2.1: Overview of Serious Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set
Table 14.3-4.2.2: Summary of Incidence of Serious Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set
Table 14.3-4.2.3: Summary of Incidence of Study Drug-Related Serious Treatment-Emergent Adverse Events (TEAEs) - Safety Analysis Set
Table 14.3-4.2.4: Summary of Incidence of Serious Treatment-Emergent Adverse Events (TEAEs) Leading to Study Withdrawal - Safety Analysis Set
Table 14.3-4.2.5: Summary of Incidence of Study Drug-Related Serious Treatment-Emergent Adverse Events (TEAEs) Leading to Study Withdrawal - Safety Analysis Set
Table 14.3-4.2.6: Summary of Incidence of Serious Treatment-Emergent Adverse Events (TEAEs) Resulting in Death - Safety Analysis Set
Table 14.3-4.2.7: Summary of Incidence of Study Drug-Related Serious Treatment-Emergent Adverse Events (TEAEs) Resulting in Death - Safety Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.3-5.1: Summary of Incidence of Prior Medications - Safety Analysis Set
Site: Overall

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

Medications are coded using World Health Organization Drug Dictionary (WHO-DD) March 2015.
Sorted by descending total incidence by ATC and preferred name within ATC.
Prior medications are those stopped before end of 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* DDMONYYYYTHH:MM
SAS X.Y program_name

Note to programmer: *Only present overall sites. Use this template for the following tables:*

Table 14.3-5.2: Incidence of Concomitant Medications – Safety Analysis Set.

On these tables change the footnote 'Prior medications are those stopped before end of surgery' to read 'Concomitant medications are those taken between the end of surgery and discharge from study' on Table 14.3-5.2.

11.2. Table of Contents for Listing Mock-ups

Listing 16.2-1: Subject Disposition – All Subjects 88
Listing 16.2-2: Randomization and Analysis Sets – Randomized Subjects 89
Listing 16.2-3: Demographics – All Subjects 90
Listing 16.2-4: Surgery – Randomized Subjects 91
Listing 16.2-5: Study Drug Administration – Randomized Subjects 92
Listing 16.2-6.1: Numeric Rating Scale (NRS) – Randomized Subjects 93
Listing 16.2-6.2.1: Area Under the Average NRS Score (Multiple Imputations) Curve - Randomized Subjects 94
Listing 16.2-6.2.2: Area Under the NRS Score (wWOCF+LOCF) - Randomized Subjects 94
Listing 16.2-7: Integrated Rank Assessment (IRA) - Randomized Subjects 95
Listing 16.2-8.1: Rescue Medication – Randomized Subjects 96
Listing 16.2-8.2: Rescue Medication Total Dose 97
Listing 16.2-9: Pain-free Status through Timepoint – Randomized Subjects 98
Listing 16.2-10: Subject Satisfaction with Post-Surgical Pain Control – Randomized Subjects 99
Listing 16.2-11.1: Postoperative Symptom Severity (PoSSe) Scale Questionnaire – Randomized Subjects 100
Listing 16.2-11.2: Postoperative Symptom Severity (PoSSe) Scale Questionnaire – Questions 101
Listing 16.2-12: Day 30 Phone Contact – Pain-Related Calls/Visits – Randomized Subjects 103
Listing 16.2-13: Neurological Assessment – Randomized Subjects 104
Listing 16.2-14.1: Electrocardiogram Findings – Investigator Assessment – Randomized Subjects 105
Listing 16.2-14.2.1: Electrocardiogram Morphology – Central Read Assessment – Randomized Subjects 106
Listing 16.2-14.2.2: Electrocardiogram Intervals – Central Read Assessment – Randomized Subjects 107
Listing 16.2-15: Vital Signs – All Subjects 108
Listing 16.2-16.1: All Adverse Events – All Subjects 109
Listing 16.2-16.2.1: Treatment-emergent Adverse Events – Randomized Subjects 109
Listing 16.2-16.2.2: Treatment-emergent Study Drug Related Adverse Events – Randomized Subjects 109
Listing 16.2-16.3: All Serious Adverse Events – All Subjects 109
Listing 16.2-16.4.1: Treatment-emergent Serious Adverse Events – Randomized Subjects 109
Listing 16.2-16.4.2: Treatment-emergent Study Drug Related Serious Adverse Events – Randomized Subjects 109
Listing 16.2-17.1: All Prior and Concomitant Medications – Randomized Subjects 110
Listing 16.2-17.2: Prior Medications – Randomized Subjects 110
Listing 16.2-17.3: Concomitant Medications – Randomized Subjects 110
Listing 16.2-18: Dental Examination – Randomized Subjects 111

Listing 16.2-19: Medical/Surgical History – Randomized Subjects 112
Listing 16.2-20: Informed Consent – All Subjects 113
Listing 16.2-21.1: Subject Eligibility – All Subjects 114
Listing 16.2-21.2: Subject Eligibility – Inclusion/Exclusion Criteria 115
Listing 16.2-22: Screening Tests – All Subjects 117
Listing 16.2-23: Deviations – All Subjects 118
Listing 16.2-24.1: Pharmacokinetic Concentrations – EXPAREL Subjects 119
Listing 16.2-24.2: Pharmacokinetic Parameters – EXPAREL Subjects 119
Listing 16.2-25: Unique Adverse Events Terms and Associated Coded Terms 121
Listing 16.2-26: Unique Medication Terms and Associated Coded Terms 122

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-1: Subject Disposition – All Subjects
Treatment: TTTTTTT

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

Source: *list SAS datasets used to create listing* *DDMONYYYYTHH:MM*
SAS *X.Y* *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-329
Listing 16.2-2: Randomization and Analysis Sets – Randomized Subjects
Treatment: TTTTTTT

Site	Subject	Date and Time	Randomization	Analysis Sets			
			Number	Safety	PK	Primary Efficacy	Secondary Efficacy
XXX	XXX-YYYY	DDMONYYYYTHH:MM	XXXXX	XXX	XXX	XXX	XXX

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-3: Demographics – All Subjects
Treatment: TTTTTTT

Site	Subject	Birth Date	Age (yrs)	Sex	Race	Ethnicity
XXX	XXX-YYYY	DDMONYYYY	XX	XXXXXX	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	XXXXXXXXXXXXXXXXXXXXXXX

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-4: Surgery – Randomized Subjects
Treatment: TTTTTTT

			Anesthesia Time		Surgery Time				Impaction			
Site	Subject	Date	Start	Stop	Start	Stop	Duration (hr)	All 4 Molars	1	16	17	32
XXX	XXX-YYYY											
		DDMONYYYY	HH:MM	HH:MM	HH:MM	HH:MM	XX.X	XXX	X	X	X	X
XXX	XXX-YYYY											
		DDMONYYYY	HH:MM	HH:MM	HH:MM	HH:MM	XX.X	XXX	X	X	X	X
XXX	XXX-YYYY											
		DDMONYYYY	HH:MM	HH:MM	HH:MM	HH:MM	XX.X	XXX	X	X	X	X
XXX	XXX-YYYY											
		DDMONYYYY	HH:MM	HH:MM	HH:MM	HH:MM	XX.X	XXX	X	X	X	X
XXX	XXX-YYYY											
		DDMONYYYY	HH:MM	HH:MM	HH:MM	HH:MM	XX.X	XXX	X	X	X	X
XXX	XXX-YYYY											
		DDMONYYYY	HH:MM	HH:MM	HH:MM	HH:MM	XX.X	XXX	X	X	X	X

Impaction: F=Fully bony; P=Partially bony; S=Soft tissue; E=Erupted
Source: *list SAS datasets used to create listing* *DDMONYYYYTHH:MM*
SAS *X.Y* *program_name*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-5: Study Drug Administration – Randomized Subjects
Treatment: TTTTTTT

Site	Subject	Date	Start Time	Stop Time	Molar	Total Volume (mL)
XXX	XXX-YYYY	DDMONYYYY	HH:MM	HH:MM	1	X
					16	X
					17	X
					32	X
					Total	XX
XXX	XXX-YYYY	DDMONYYYY	HH:MM	HH:MM	1	X
					16	X
					17	X
					32	X
					Total	XX

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-6.1: Numeric Rating Scale (NRS) – Randomized Subjects
Treatment: TTTTTTT

			Time From Dose					
Site	Subject	Date and Time	Scheduled (hr)	Actual (hr)	Deviation (mins)	NRS	Average NRS[1]	Comments
XXX	XXX-YYYY	DDMONYYYYTHH:MM	0.25	0.XX	X	XX	XX	
		DDMONYYYYTHH:MM	0.50	0.XX	X	XX	XX	
		DDMONYYYYTHH:MM	1	X	X	XX	XX	
		DDMONYYYYTHH:MM	2	ND			XX	
		DDMONYYYYTHH:MM	RESCUE	X		XX	NA	
		DDMONYYYYTHH:MM	4	X	X	XX	XX	
		DDMONYYYYTHH:MM	6	X	-X	XX	XX	
		DDMONYYYYTHH:MM	8	X	X	XX	XX	
		DDMONYYYYTHH:MM	12	XX	X	XX	XX	
		DDMONYYYYTHH:MM	24	XX	X	XX	XX	
		DDMONYYYYTHH:MM	48	XX	X	XX	XX	
		DDMONYYYYTHH:MM	72	XX	X	XX	XX	
		DDMONYYYYTHH:MM	96	XX	X	XX	XX	

NRS: 0=No Pain to 10=Worst Pain Imaginable ND=Not Done NA=Not Applicable
[1] Average NRS score from the multiple imputations; RESCUE NRS scores not imputed.
Source: *list SAS datasets used to create listing* *DDMONYYYYTHH:MM*
SAS *X.Y* *program_name*

Note to programmer: *Sort by NRS collection date and time. If NRS 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.*

```
Pacira Pharmaceuticals                          (Page X of Y)                            Protocol: 402-C-329
Listing 16.2-6.2.1: Area Under the Average NRS Score (Multiple Imputations) Curve - Randomized Subjects
Treatment: TTTTTTT
```

Site	Subject	AUC(0.25-48)	AUC(0.25-24)	AUC(0.25-72)	AUC(0.25-96)	AUC(24-48)	AUC(48-72)
XXX	XXX-YYYY	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X
	XXX-YYYY	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X
	XXX-YYYY	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X
	XXX-YYYY	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X
	XXX-YYYY	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X
	XXX-YYYY	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X
	XXX-YYYY	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X
	XXX-YYYY	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X
	XXX-YYYY	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X
XXX	XXX-YYYY	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X
	XXX-YYYY	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X
	XXX-YYYY	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X
	XXX-YYYY	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X
	XXX-YYYY	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X
	XXX-YYYY	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X
	XXX-YYYY	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X
	XXX-YYYY	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X
	XXX-YYYY	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X

```
NRS: 0=No Pain to 10=Worst Pain Imaginable                                            ND=Not Done
Source: list SAS datasets used to create listing                                 DDMONYYYYTHH:MM
SAS X.Y                                                                             program_name
```

Note to programmer: *Use this template for the following table:*

Listing 16.2-6.2.2: Area Under the NRS Score (wWOCF+LOCF) - Randomized Subjects

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329

Listing 16.2-7: Integrated Rank Assessment (IRA) - Randomized Subjects

Treatment: TTTTTTT

		48 hr			24 hr			72 hr		
Site	Subject	Opioid (MED) [Rank]	NRS [Rank]	IRA	Opioid (MED) [Rank]	NRS [Rank]	IRA	Opioid (MED) [Rank]	NRS [Rank]	IRA
XXX	XXX-YYYY	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX
	XXX-YYYY	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX
	XXX-YYYY	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX
	XXX-YYYY	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX
	XXX-YYYY	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX
XXX	XXX-YYYY	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX
	XXX-YYYY	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX
	XXX-YYYY	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX
	XXX-YYYY	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX
	XXX-YYYY	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX
XXX	XXX-YYYY	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX
	XXX-YYYY	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX
	XXX-YYYY	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX
	XXX-YYYY	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX
	XXX-YYYY	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX	XXX.X [XX]	XX [XX]	XXXX

NRS: 0=No Pain to 10=Worst Pain Imaginable ND=Not Done

NRS Rank based on reported values without imputation.

Source: *list SAS datasets used to create listing* *DDMONYYYYTHH:MM*

SAS *X.Y* *program_name*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-8.1: Rescue Medication – Randomized Subjects
Treatment: TTTTTTT

Site	Subject	Date and Time	Time to Rescue (hr)	Medication	Dose (mg)	Conversion Factor	Dose (MED)	Route	Number
XXX	XXX-YYYY	DDMONYYYYTHH:MM	XX.X	Oxycodone	XX	0.5	XX.XX	PO	X

Time to rescue is time from end of surgery to rescue medication dose.
Source: *list SAS datasets used to create listing* *DDMONYYYYTHH:MM*
SAS *X.Y* *program_name*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-8.2: Rescue Medication Total Dose from End of Surgery through Timepoint – Randomized Subjects
Treatment: TTTTTTT

Site	Subject	24 hr	48 hr	72 hr
XXX	XXX-YYYY	XXXX.XX	XXXX.XX	XXXX.XX
	XXX-YYYY	XXXX.XX	XXXX.XX	XXXX.XX
	XXX-YYYY	XXXX.XX	XXXX.XX	XXXX.XX
	XXX-YYYY	XXXX.XX	XXXX.XX	XXXX.XX

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-9: Pain-free Status through Timepoint – Randomized Subjects
Treatment: TTTTTTT

Site	Subject	24 hr	48 hr	72 hr	96 hr
XXX	XXX-YYYY	XXX	XXX	XXX	XXX
	XXX-YYYY	XXX	XXX	XXX	XXX
	XXX-YYYY	XXX	XXX	XXX	XXX
	XXX-YYYY	XXX	XXX	XXX	XXX

Pain-free is defined as an NRS score ≤ 0 at that timepoint and no prior rescue medication use.
Source: *list SAS datasets used to create listing* *DDMONYYYYTHH:MM*
SAS *X.Y* *program_name*

Note to programmer: *Pain-free is a YES/NO value.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-10: Subject Satisfaction with Post-Surgical Pain Control – Randomized Subjects
Treatment: TTTTTTT

Site	Subject	Assessment	Date and Time	Rating	Score
XXX	XXX-YYYY	24 hr	DDMONYYYYTHH:MM	EXTREMELY DISSATISFIED	1
	XXX-YYYY	48 hr	DDMONYYYYTHH:MM	DISSATISFIED	2
	XXX-YYYY	72 hr	DDMONYYYYTHH:MM	NEITHER SATISFIED NOR DISSATISFIED	3
	XXX-YYYY	96 hr	DDMONYYYYTHH:MM	SATISFIED	4
	XXX-YYYY	Day 10	DDMONYYYYTHH:MM	EXTREMELY SATISFIED	5
XXX	XXX-YYYY	24 hr	DDMONYYYYTHH:MM	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	X
	XXX-YYYY	48 hr	DDMONYYYYTHH:MM	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	X
	XXX-YYYY	72 hr	DDMONYYYYTHH:MM	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	X
	XXX-YYYY	96 hr	DDMONYYYYTHH:MM	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	X
	XXX-YYYY	Day 10	DDMONYYYYTHH:MM	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	X

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

Note to programmer: *Possible values for rating and score are indicated in first 5 rows of mock-up.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-11.1: Postoperative Symptom Severity (PoSSe) Scale Questionnaire – Randomized Subjects
Treatment: TTTTTTT

		Question Score (%) (see Listing 16.2-11.2 for question text & scoring)															Total
Site	Subject	1a	1b	2a	2b	3a	3b	4a	4b	5a	5b	6a	6b	7a	7b	7c	(%)
XXX	XXX-YYYY	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	XXX-YYYY	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	XX.XX
	XXX-YYYY	X.XX	NA	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	NC

NA=Not answered NC=Not calculated
Total = sum of all scores; ranging from 0% (least severe) to 100% (most severe).
Source: *list SAS datasets used to create listing* *DDMONYYYYTHH:MM*
SAS *X.Y* *program_name*

Pacira Pharmaceuticals (Page 1 of 2) Protocol: 402-C-329
Listing 16.2-11.2: Postoperative Symptom Severity (PoSSe) Scale Questionnaire – Questions

Eating:
1a. In the last week, has your operation affected your enjoyment of food?
[0]No, not at all; [5.25] Yes, a little; [10.5] Yes, very much
1b. In the last week, for how many days were you unable to open your mouth normally because of your operation?
[0]0 days; [2.63]1-2 days; [5.25]3-4 days; [7.88]5-6 days; [10.5] 7 days
Speech:
2a. In the last week, for how many days was your voice affected because of your operation?
[0]0 days; [1.25]1-2 days; [2.5]3-4 days; [3.75]5-6 days; [5] 7 days
2b. On the worst day of the last week, how badly was your speech affected by your operation?
[0]Not at all; [1.25]Slightly; [2.5]Moderately; [3.75]Severely; [5]Unable to speak at all
Sensation:
3a. Thinking of the last week, for how many days were your lips or tongue felling tingling because of your operation?
[0]None at all; [2]1-2 days; [4]3-4 days; [6]5-6 days; [8] 7 days
3b. Thinking of the last week, for how many days were you lips or tongue felling numb because of your operation?
[0]None at all; [2]1-2 days; [4]3-4 days; [6]5-6 days; [8] 7 days
Appearance:
4a. Thinking of the last wekk, for how many days were your face and/or neck bruised because of your operation?
[0]None at all; [1.5]1-2 days; [3]3-4 days; [4.5]5-6 days; [6] 7 days
4b. Thinking of the last week, for how many days were your face and/or neck swollen because of you operation?
[0]None at all; [1.5]1-2 days; [3]3-4 days; [4.5]5-6 days; [6] 7 days

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

Pacira Pharmaceuticals (Page 2 of 2) Protocol: 402-C-329
Listing 16.2-11.2: Postoperative Symptom Severity (PoSSe) Scale Questionnaire – Questions

Pain:
5a. Thinking of the last week, for how many days did you experience pain from your operation?
[0]None at all; [2.38]1-2 days; [4.75]3-4 days; [7.13]5-6 days; [9.5] 7 days
5b. Thinking of the last week, has the pain from your operation been controlled by pain killers?
[0] I have had no pain; [2.38] Yes, completely controlled;
[4.75] Controlled mostly but still some discomfort; [7.13] Poorly controlled;
[9.5] Not controlled at all

Sickness:
6a. Thinking of the last week, for how many days did you vomit or feel nauseated?
[0]None at all; [1.25]1-2 days; [2.5]3-4 days; [3.75]5-6 days; [5] 7 days
6b. On the worse day of the last week, how many times did you vomit of feel nauseated?
[0]None at all; [1.25]One day; [2.5]2-3 times; [3.75]More than 3 times;
[5]All the time (all day long)

Interference with daily activities:
7a. In the last week, did the operation prefvent you from carrying out work/housework and other daily activities?
[0]None at all; [0.83]I could continue with my work, but my work suffered; [1.65]Yes, for 1 day;
[2.48]Yes, for 2-6 days; [3.3]Yes, for 7 days
7b. In the last week, have your leisure activities been affected by your operation? (including sports, hobbies and social life)
[0]Not affected by the operation; [0.83]Mildly affected by the operation;
[1.65]Moderately affected by the operation; [2.48]Severely affected by the operation;
[3.3]The operation prevented any social life at all
7c. Thinking of the last wekk, how badly did the pain affect your life?
[0]Not at all; [1.1]Slightly; [2.2]Moderately; [3.3]Severely

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-12: Day 30 Phone Contact – Pain-Related Calls/Visits – Randomized Subjects
Treatment: TTTTTTT

				Number of pain-related		
Site	Subject	Date	Visit	Phone calls	Office Visits	Total
XXX	XXX-YYYY	DDMONYYYY	Day 7	XX	XX	
	XXX-YYYY	DDMONYYYY	Day 10	XX	XX	
	XXX-YYYY	DDMONYYYY	Day 30	XX	XX	XXX

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-13: Neurological Assessment – Randomized Subjects
Treatment: TTTTTTTT

Site	Subject	Date and Time Of Assessment	Time From Dose: Scheduled (hr)	Time From Dose: Actual (hr)	Time From Dose: Deviation (mins)	Questions: 1	2	3	4	5	6
XXX	XXX-YYYY	DDMONYYYYTHH:MM	0	XX	X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	0.25	0.XX	X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	0.50	0.XX	X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	1	X	X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	2	ND							
		DDMONYYYYTHH:MM	4	X	X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	8	X	X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	12	XX	X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	18	XX	X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	24	XX	X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	30	XX	X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	36	XX	X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	42	XX	X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	48	XX	X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	54	XX	-X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	60	XX	X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	66	XX	X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	72	XX	X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	84	XX	X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	96	XX	X	XX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	240	XX	X	XX	XXX	XXX	XXX	XXX	XXX

1) Is subject oriented?
2) Do you have numbness of the lips, the tongue or around the mouth?
3) Do you have a metallic taste in your mouth?
4) Are you having problems with your hearing not related to the use of a hearing aid?
5) Are you having problems with your vision no related to the use of eye glasses?
6) Are your muscles twitching?

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-14.1: Electrocardiogram Findings – Investigator Assessment – Randomized Subjects
Treatment: EXPAREL

		Date and Time of		Time From Dose			
Site	Subject	Dose	Sample	Scheduled (hr)	Actual (hr)	Deviation (mins)	Finding
XXX	XXX-YYYY	NA	DDMONYYYYTHH:MM	Screening	NA		
		DDMONYYYYTHH:MM	DDMONYYYYTHH:MM	0	XX	X	
			DDMONYYYYTHH:MM	0.25	0.XX	X	
			DDMONYYYYTHH:MM	0.50	0.XX	X	
			DDMONYYYYTHH:MM	1	X	X	
			DDMONYYYYTHH:MM	2	ND		
			DDMONYYYYTHH:MM	4	X	-X	
			DDMONYYYYTHH:MM	6	X	X	
			DDMONYYYYTHH:MM	8	X	X	
			DDMONYYYYTHH:MM	12	XX	-X	
			DDMONYYYYTHH:MM	18	XX	X	
			DDMONYYYYTHH:MM	24	XX	X	
			DDMONYYYYTHH:MM	30	XX	X	
			DDMONYYYYTHH:MM	36	XX	X	
			DDMONYYYYTHH:MM	42	XX	-X	
			DDMONYYYYTHH:MM	48	XX	X	
			DDMONYYYYTHH:MM	54	XX	X	
			DDMONYYYYTHH:MM	60	XX	X	
			DDMONYYYYTHH:MM	66	XX	X	
			DDMONYYYYTHH:MM	72	XX	-X	
			DDMONYYYYTHH:MM	84	XX	X	
			DDMONYYYYTHH:MM	96	XX	X	
			DDMONYYYYTHH:MM	168	XX	X	
			DDMONYYYYTHH:MM	240	XX	X	

NA=Not applicable ND=Not done
Source: *list SAS datasets used to create listing* *DDMONYYYYTHH:MM*
SAS *X.Y* *program_name*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-14.2.1: Electrocardiogram Morphology – Central Read Assessment – Randomized Subjects
Treatment: EXPAREL

			Time from Dose			
Site	Subject	Sample	Scheduled (hr)	Actual (hr)	Deviation (mins)	Morphology
XXX	XXX-YYYY	DDMONYYYYTHH:MM	Screening	NA		
		DDMONYYYYTHH:MM	0	XX	X	
		DDMONYYYYTHH:MM	0.25	0.XX	X	
		DDMONYYYYTHH:MM	0.50	0.XX	X	
		DDMONYYYYTHH:MM	1	X	X	
		DDMONYYYYTHH:MM	2	ND		
		DDMONYYYYTHH:MM	4	X	X	
		DDMONYYYYTHH:MM	6	X	-X	
		DDMONYYYYTHH:MM	8	X	X	
		DDMONYYYYTHH:MM	12	XX	X	
		DDMONYYYYTHH:MM	18	XX	X	
		DDMONYYYYTHH:MM	24	XX	X	
		DDMONYYYYTHH:MM	30	XX	X	
		DDMONYYYYTHH:MM	36	XX	X	
		DDMONYYYYTHH:MM	42	XX	X	
		DDMONYYYYTHH:MM	48	XX	X	
		DDMONYYYYTHH:MM	54	XX	-X	
		DDMONYYYYTHH:MM	60	XX	X	
		DDMONYYYYTHH:MM	66	XX	X	
		DDMONYYYYTHH:MM	72	XX	X	
		DDMONYYYYTHH:MM	84	XX	X	
		DDMONYYYYTHH:MM	96	XX	X	
		DDMONYYYYTHH:MM	168	XX	X	
		DDMONYYYYTHH:MM	240	XX	X	

NA=Not applicable ND=Not done
Source: *list SAS datasets used to create listing* *DDMONYYYYTHH:MM*
SAS *X.Y* *program_name*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-14.2.2: Electrocardiogram Intervals – Central Read Assessment – Randomized Subjects
Treatment: EXPAREL

		Date and Time Of	Time From Dose				Intervals (msec)					
Site	Subject	Sample	Scheduled (hr)	Actual (hr)	Deviation (mins)	Heart Rate (bpm)	RR	PR	QRS	QT	QTcB	QTcF
XXX	XXX-YYYY	DDMONYYYYTHH:MM	Screening	NA		XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	0	XX	X	XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	0.25	0.XX	X	XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	0.50	0.XX	X	XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	1	X	X	XX	XXX*	XXX*^	XXX*	XXX*	XXX*	XXX*
		DDMONYYYYTHH:MM	2	ND								
		DDMONYYYYTHH:MM	4	X	X	XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	8	X	X	XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	12	XX	X	XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	18	XX	X	XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	24	XX	X	XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	30	XX	X	XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	36	XX	X	XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	42	XX	X	XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	48	XX	X	XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	54	XX	-X	XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	60	XX	X	XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	66	XX	X	XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	72	XX	X	XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	84	XX	X	XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	96	XX	X	XX	XXX	XXX	XXX	XXX	XXX	XXX
		DDMONYYYYTHH:MM	240	XX	X	XX	XXX	XXX	XXX	XXX	XXX	XXX

NA=Not applicable potentially clinically meaningful value=*; change from baseline=^ ND=Not done
Source: *list SAS datasets used to create listing* *DDMONYYYYTHH:MM*
SAS *X.Y* *program_name*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-15: Vital Signs – All Subjects
Treatment: TTTTTTTT

SITE: XXX

			Time from Dose				Blood Pressure				
Subject	Visit	Date and Time	Sched (hr)	Actual (hr)	Devi-ation (mins)	Heart Rate (bpm)	Sys. (mmHg)	Dia. (mmHg)	Height (cm)	Weight (kg)	Body Mass Index (m/kg^2)
XXX-YYYY	Screening	DDMONYYYYTHH:MM	NA	NA	NA	XX	XXX	XXX	XXX	XXX	XXX
	Day 1	DDMONYYYYTHH:MM	0	X	X	XX	XXX	XXX			
		DDMONYYYYTHH:MM	1	X	X	XX	XXX	XXX*^			
		DDMONYYYYTHH:MM	2	X	X	XX	XXX*^	XXX			
		DDMONYYYYTHH:MM	4	X	-X	XX*	XXX	XXX			

potentially clinically meaningful value=*; change from baseline=^
Source: *list SAS datasets used to create listing* *DDMONYYYYTHH:MM*
SAS *X.Y* *program_name*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-16.1: All Adverse Events – All Subjects
Treatment: TTTTTTT

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

TEAE: Treatment-emergent AE (Y=TEAE/N=Not TEAE)
Source: *list SAS datasets used to create listing* *DDMONYYYYTHH:MM*
SAS *X.Y* *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. This this template for the following listings:*
Listing 16.2-16.2.1: Treatment-emergent Adverse Events – Randomized Subjects
Listing 16.2-16.2.2: Treatment-emergent Study Drug Related Adverse Events – Randomized Subjects
Listing 16.2-16.3: All Serious Adverse Events – All Subjects
Listing 16.2-16.4.1: Treatment-emergent Serious Adverse Events – Randomized Subjects
Listing 16.2-16.4.2: Treatment-emergent Study Drug Related Serious Adverse Events – Randomized Subjects

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-17.1: All Prior and Concomitant Medications – Randomized Subjects
Treatment: TTTTTTT

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* *DDMONYYYYTHH:MM*
SAS *X.Y* *program_name*

Note to programmer: *If medication is ongoing, put ONGOING in stop row. Do not split an 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 16.2-17.2: Prior Medications – Randomized Subjects
Listing 16.2-17.3: Concomitant Medications – Randomized Subjects

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-18: Dental Examination – Randomized Subjects
Treatment: TTTTTTT

Site	Subject	Performed?	Date of Exam	Impaction Confirmation	Date of X-ray
XXX	XXX-YYYY	YES	DDMONYYYYTHH:MM	XXXXXXXXXXX	DDMONYYYYTHH:MM
	XXX-YYYY	NO			

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

Note to programmer: *Values for performed are YES or NO; impaction confirmation are VISUAL or RADIOLOGICAL.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-19: Medical/Surgical History – Randomized Subjects
Treatment: TTTTTTT

Site	Subject	Date Start	Stop	Number	Classification	Term
XXX	XXX-YYYY	DDMONYYYY	DDMONYYYY	X	System Organ Class: Preferred Term: Verbatim:	

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

Note to programmer: *If ongoing put ONGOING in stop date column.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-20: Informed Consent – All Subjects
Treatment: TTTTTTT

			Date				Met Criteria	
Site	Subject	Subject Initials	Screening Visit	Signed Consent	ICF Version	Protocol Version	Inclusion	Exclusion
XXX	XXX-YYYY	ABC	DDMONYYYY	DDMONYYYY	DDMONYYYY	AMENDMENT 2	YES	YES

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-21.1: Subject Eligibility – All Subjects
Treatment: TTTTTTTTTTTTT

Site	Subject	Date of Informed Consent	Date of Eligibility Assessment	Criteria Failed
XXX	XXX-YYYY	DDMONYYYY	DDMONYYYY	
XXX	XXX-YYYY	DDMONYYYY	DDMONYYYY	
XXX	XXX-YYYY	DDMONYYYY	DDMONYYYY	
XXX	XXX-YYYY	DDMONYYYY	DDMONYYYY	Inclusion: 1, 4 Exclusion: 8, 10, 12

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

Note to programmer: *If subject was not randomized treatment should be 'NOT RANDOMIZED'. Criteria Failed may take any or all of the following values: Inclusion 1, 2, 3, 4 or 5 and Exclusion 1 through 12. Insert a page break after each treatment group.*

Pacira Pharmaceuticals (Page 1 of 2) Protocol: 402-C-329
Listing 16.2-21.2: Subject Eligibility – Inclusion/Exclusion Criteria

Inclusion/Exclusion Criteria	
Inclusion 1	Male or female, ≥18 years of age at screening.
Inclusion 2	Scheduled to undergo bilateral third molar extractions (i.e., extraction of all four third molars) under local anesthesia. At least one lower mandibular third molar must involve full or partial bony impaction confirmed by visual or radiological evidence.
Inclusion 3	American Society of Anesthesiology (ASA) physical status 1, 2, or 3.
Inclusion 4	Female subjects must be either surgically sterile, using a medically acceptable method of birth control, or at least 2 years postmenopausal, and must have a documented negative pregnancy test result during screening and on Day 1 prior to surgery.
Inclusion 5	Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments.

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

Pacira Pharmaceuticals (Page 2 of 2) Protocol: 402-C-329
Listing 16.2-21.2: Subject Eligibility – Inclusion/Exclusion Criteria

Inclusion/Exclusion Criteria	
Exclusion 1	History of hypersensitivity or idiosyncratic reaction to amide-type local anesthetics or opioids.
Exclusion 2	Contraindication to lidocaine, epinephrine, bupivacaine, or oxycodone.
Exclusion 3	History of significant drug allergy (e.g., anaphylaxis or hepatotoxicity).
Exclusion 4	Positive test result from the urine drug screen at screening or prior to the surgical procedure.
Exclusion 5	Currently pregnant, nursing, or planning to become pregnant during the study or within 1 month after study drug administration.
Exclusion 6	History or active psychiatric illness (including major depression, bipolar disorder, or anxiety), Type 1 or Type 2 diabetes, severe renal or hepatic impairment, significant cardiovascular disease (including cardiac rhythm disturbance), migraine headaches, frequent headaches, other pain conditions, or other medical condition that, in the opinion of the Investigator, may increase the risk of surgery or interfere with the evaluation of the study drug.
Exclusion 7	History of infection requiring intravenous (IV) antibiotics within 45 days or oral (PO) antibiotics within 30 days prior to study drug administration for reasons other than dental prophylaxis. Subjects must be afebrile, without signs or symptoms indicative of active infection.
Exclusion 8	Use of any of the following medications within the times specified before surgery: long-acting opioid medication, NSAIDs, aspirin (except for low-dose aspirin used for cardioprotection), or acetaminophen within 3 days, or any opioid medication within 24 hours.
Exclusion 9	Initiation of treatment with any of the following medications within 1 month of study drug administration or if the medication(s) are being given to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinepherine reuptake inhibitors (SNRIs), gabapentin, pregabalin (Lyrica®), or duloxetine (Cymbalta®). If a subject is taking one of these medications for a reason other than pain control, he or she must be on a stable dose for at least 1 month prior to study drug administration.
Exclusion 10	Current use of systemic glucocorticosteroids within 1 month of enrollment in this study.
Exclusion 11	Use of any concurrent therapy that could interfere with the evaluation of efficacy or safety, such as any drugs which in the Investigator's opinion may exert significant analgesic properties or act synergistically with the investigational product.
Exclusion 12	Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study.

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-22: Screening Tests – All Subjects
Treatment: TTTTTTTTT

Site	Subject	Visit	Date	Pregnancy	Drug Screen
XXX	XXX-YYYY	Screening	DDMONYYYY	XXXXXXXXXXXXXX	XXXXXXXXXXXXXX
		Day 1	DDMONYYYY	XXXXXXXXXXXXXX	XXXXXXXXXXXXXX
	XXX-YYYY	Screening	DDMONYYYY	XXXXXXXXXXXXXX	XXXXXXXXXXXXXX
		Day 1	DDMONYYYY	XXXXXXXXXXXXXX	XXXXXXXXXXXXXX
	XXX-YYYY	Screening	DDMONYYYY	XXXXXXXXXXXXXX	XXXXXXXXXXXXXX
		Day 1	DDMONYYYY	XXXXXXXXXXXXXX	XXXXXXXXXXXXXX

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

Note to programmer: *Possible results for screening tests are: POSITIVE, NEGATIVE, NOT DONE or NOT APPLICABLE.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-23: Deviations – All Subjects
Treatment: TTTTTTT

Site	Subject	Date	Category	Description
XXX	XXX-YYYY	DDMONYYYY	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-24.1: Pharmacokinetic Concentrations – EXPAREL Subjects
Treatment: EXPAREL

		Date and Time of		Time From Dose			
Site	Subject	Dose	PK Sample	Scheduled (hr)	Actual (hr)	Deviation (mins)	Concentration (ng/mL)
XXX	XXX-YYYY	DDMONYYYYTHH:MM	DDMONYYYYTHH:MM	0	XX	X	BLOQ
			DDMONYYYYTHH:MM	0.25	0.XX	X	XXX.X
			DDMONYYYYTHH:MM	0.50	0.XX	X	XXX.X
			DDMONYYYYTHH:MM	1	X	X	XXX.X
			DDMONYYYYTHH:MM	2	ND		
			DDMONYYYYTHH:MM	4	X	-X	XXX.X
			DDMONYYYYTHH:MM	6	X	X	XXX.X
			DDMONYYYYTHH:MM	8	X	X	XXX.X
			DDMONYYYYTHH:MM	12	XX	-X	XXX.X
			DDMONYYYYTHH:MM	18	XX	X	XXX.X
			DDMONYYYYTHH:MM	24	XX	X	XXX.X
			DDMONYYYYTHH:MM	30	XX	X	XXX.X
			DDMONYYYYTHH:MM	36	XX	X	XXX.X
			DDMONYYYYTHH:MM	42	XX	-X	XXX.X
			DDMONYYYYTHH:MM	48	XX	X	XXX.X
			DDMONYYYYTHH:MM	54	XX	X	XXX.X
			DDMONYYYYTHH:MM	60	XX	X	XXX.X
			DDMONYYYYTHH:MM	66	XX	X	XXX.X
			DDMONYYYYTHH:MM	72	XX	-X	XXX.X
			DDMONYYYYTHH:MM	84	XX	X	XXX.X
			DDMONYYYYTHH:MM	96	XX	X	XXX.X
			DDMONYYYYTHH:MM	168	XX	X	XXX.X
			DDMONYYYYTHH:MM	240	XX	X	XXX.X

BLOQ=below limit of quantitation ND=Not Done
Source: *list SAS datasets used to create listing* *DDMONYYYYTHH:MM*
SAS *X.Y* *program_name*

Note to programmer: *Insert a page break after each subject. If a sample was not collected – put ND in actual column under time from dose. Sort listing within subject by sample date and time.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-24.2: Pharmacokinetic Parameters – EXPAREL Subjects
Treatment: EXPAREL

Site	Subject	AUC(0-inf) (ng*hr/mL)	AUC(0-last) (ng*hr/mL)	Cmax ng/mL	Tmax (hr)	Half-life (hr)	Lamba_z (hr)
XXX	XXX-YYYY	XXXX.XX	XXXX.XX	XXX.X	XX.X	X.XXX	X.XXX
	XXX-YYYY	NC	XXXX.XX	XXX.X	XX.X	NC	NC
	XXX-YYYY	XXXX.XX	XXXX.XX	XXX.X	XX.X	X.XXX	X.XXX
	XXX-YYYY	XXXX.XX	XXXX.XX	XXX.X	XX.X	X.XXX	X.XXX
	XXX-YYYY	XXXX.XX	XXXX.XX	XXX.X	XX.X	X.XXX	X.XXX
YYY	XXX-YYYY	XXXX.XX	XXXX.XX	XXX.X	XX.X	X.XXX	X.XXX
	XXX-YYYY	XXXX.XX	XXXX.XX	XXX.X	XX.X	X.XXX	X.XXX
	XXX-YYYY	XXXX.XX	XXXX.XX	XXX.X	XX.X	X.XXX	X.XXX
	XXX-YYYY	XXXX.XX	XXXX.XX	XXX.X	XX.X	X.XXX	X.XXX
	XXX-YYYY	XXXX.XX	XXXX.XX	XXX.X	XX.X	X.XXX	X.XXX

NC=Not Calculated
Source: *list SAS datasets used to create listing* *DDMONYYYYTHH:MM*
SAS *X.Y* *program_name*

Note to programmer: *If a parameter was not calculated – put NC in column.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-25: Unique Adverse Events Terms and Associated Coded Terms

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

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

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Listing 16.2-26: Unique Medication Terms and Associated Coded Terms

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

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

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

11.3. List of Figures

Figure 14.2-1.1: Plot of Mean (±SD) NRS Scores over Time with Imputation – Efficacy Analysis Set
Figure 14.2-1.2: Plot of Mean (±SD) NRS Scores over Time without Imputation – Efficacy Analysis Set
Figure 14.2-1.3: Plot of Individual Subject NRS Scores Over Time – Efficacy Analysis Set
Figure 14.2-2: Bar Chart of Percentage of Pain-Free Subjects – Efficacy Analysis Set
Figure 14.2-3: Bar Chart of Percentage of Opioid-Free Subjects – Efficacy Analysis Set
Figure 14.2-4: Plot of Time to First Rescue Medication Use – Efficacy Analysis Set
Figure 14.2-5: Bar Chart of Subject Satisfaction with Postsurgical Pain Control – Efficacy Analysis Set

12. MULTIPLE IMPUTATION EXAMPLE PROGRAM CODE

```
** Note: INPUT_DATA is the dataset that contains the NRS 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=1000 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 USUBJID;
        VAR ENDPOINT_VARIABLE;
        OUTPUT OUT=SUMMARYSTATSA MEAN=ENDPOINTMEAN;
RUN;

** 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 - PLACEBO' 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                        **;
```

SIGNATURE PAGE

Wei Sun, MD Senior Medical Director, Clinical Research	12 Nov 2015 Date
James Jones, MD Chief Medical Officer	12 Nov 2015 Date
George M. Wagner Vice President, Regulatory Affairs and Pharmacovigilance	16 Nov 2015 Date
James Nezamis, MS Senior Director, Biostatistics	12 Nov 2015 Date

STATISTICAL ANALYSIS PLAN ADDENDUM

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Local Administration of EXPAREL for Prolonged Postsurgical Analgesia in Subject Undergoing Third Molar Extraction

Protocol No.: 402-C-329

IND No.: 69,198

Study Phase: 3

Study Drug: EXPAREL (bupivacaine liposome injectable suspension)

Date/Version: Addendum: 29 February 2016
Original: 12 November 2015

Prepared by:

James Nezamis, MS
Senior Director, Biostatistics
Pacira Pharmaceuticals

Sponsor:

Pacira Pharmaceuticals, Inc.
5 Sylvan Way
Parsippany, NJ 07054
Tel: 973-254-3560

1. PURPOSE

The purpose of this SAP addendum is to describe additional analyses not planned as part of the original SAP as well as changes to analyses planned in the SAP.

2. CHANGES TO PLANNED ANALYSES

The SAP indicated a 6 hour imputation window for oxycodone but a 4 hour dosing cycle. The imputation window was changed to 4 hours. This changed was deemed appropriate based on literature and dosing period.

Site 100 had more than one surgeon performing extractions. Therefore it was decided to look at some of the data at the surgeon level as well as site level. The following tables will be expanded to include surgeon within site summaries for site 100:

- Table 14.1-2.1 – Safety Analysis Set
- Table 14.1-2.2.1 – Primary Efficacy Analysis Set
- Table 14.1-2.2.2 – Secondary Efficacy Analysis Set
- Table 14.1-2.3 – Pharmacokinetic Analysis Set
- Table 14.1-2.4 – Per-protocol Analysis Set
- Table 14.1-3.1 – Safety Analysis Set
- Table 14.1-3.2.1 – Primary Efficacy Analysis Set
- Table 14.1-3.2.2 – Secondary Efficacy Analysis Set
- Table 14.1-3.3 – Per-protocol Analysis Set
- Table 14.2-1.3 – Primary Efficacy Analysis Set
- Table 14.2-2.3 – Primary Efficacy Analysis Set
- Table 14.2-3.3 – Primary Efficacy Analysis Set
- Table 14.2-5.1 – Primary Efficacy Analysis Set
- Table 14.2-5.2 – Primary Efficacy Analysis Set
- Table 14.2-5.3 – Primary Efficacy Analysis Set

Due to numerous protocol deviations, a per-protocol population was defined. Subjects will be excluded from the study 402-C-329 per-protocol population if any of the following criteria are true:

1) One or more of the 12 scheduled NRS assessments are either missing or 'Not Done';
2) At least one rescue medication dose without an NRS assessment within 15 minutes prior to or at the time of rescue medication dose;
3) Three or more doses of oxycodone within any 12 hour period within 96 hours after surgery;
4) Dental work (oral surgery, tooth repair, fillings) within 14 days of surgery;
5) Post-traumatic stress disorder;
6) NSAIDS or other non-protocol allowed analgesic/anti-inflammatory medications within 96 hours after surgery;
7) For subjects randomized to EXPAREL, an 8 hour PK concentration < 100 ng/mL;
8) Rescue medication received with a NRS pain score immediately prior to rescue medication dose less than 4;
9) Subjects 100-0123, 100-0124, 100-0137, 100-0138, 100-0154, 100-0157, 200-0032, 300-0029 and 300-0036 were eliminated from the per-protocol population during manual review of the protocol deviation log;
10) Subject excluded from the primary efficacy population.

Table 14.1-1 will be modified to include the per-protocol analysis set. Table A indicates the template tables (from SAP) to be produced and the table number and title for the per-protocol analysis set.

Table A: Templates and Titles for Per-protocol Efficacy Analysis Set Tables

SAP Template Number	Per-protocol Analysis Set Table Number and Title
14.2-1.1.1	14.2-1.1.6: Analysis of AUC of NRS Pain Intensity Scores through 48 hours – Per-protocol Efficacy Analysis Set
14.2-1.2	14.2-1.2.1: Summary of AUC of NRS Pain Intensity Scores through 48 hours – Per-protocol Efficacy Analysis Set - Analysis of Variance (ANOVA) Model Results
	14.2-2.2.1: Summary of AUC of NRS Pain Intensity Scores through 24 hours – Per-protocol Efficacy Analysis Set - Analysis of Variance (ANOVA) Model Results
	14.2-3.2.1: Summary of AUC of NRS Pain Intensity Scores through 72 hours – Per-protocol Efficacy Analysis Set - Analysis of Variance (ANOVA) Model Results
14.2-1.3	14.2-1.3.1: Summary of AUC of NRS Pain Intensity Scores through 48 hours by Site – Per-protocol Efficacy Analysis Set
	14.2-2.3.1: Summary of AUC of NRS Pain Intensity Scores through 24 hours by Site – Per-protocol Efficacy Analysis Set
	14.2-3.3.1: Summary of AUC of NRS Pain Intensity Scores through 72 hours by Site – Per-protocol Efficacy Analysis Set
14.2-5.1	14.2-5.1.1: Analysis of Opioid-Free Subjects through 24 hours – Per-protocol Efficacy Analysis Set
	14.2-5.2.1: Analysis of Opioid-Free Subjects through 48 hours – Per-protocol Efficacy Analysis Set
	14.2-5.3.1: Analysis of Opioid-Free Subjects through 72 hours – Per-protocol Efficacy Analysis Set
14.2-6.1	14.2-6.1.1: Summary of Numerical Rating Scale (NRS) Pain Intensity Scores - By Assessment Timepoint – Per-protocol Efficacy Analysis Set
14.2-6.2	14.2-6.2.1: Summary of Numerical Rating Scale (NRS) Pain Intensity Scores at Rescue – Per-protocol Efficacy Analysis Set
14.2-7.1	14.2-7.1.1: Summary of AUC(0.25-96) and AUC(0.25-Day 10) of NRS Pain Intensity Scores – Per-protocol Efficacy Analysis Set
14.2-7.2	14.2-7.2.1: Summary of AUC(24-48) and AUC(48-72) of NRS Pain Intensity Scores Scores – Per-protocol Efficacy Analysis Set

SAP Template Number	Per-protocol Analysis Set Table Number and Title
14.2-8	14.2-8.1: Tabulation of Pain-Free Subjects at Assessment Time Points Scores – Per-protocol Efficacy Analysis Set
14.2-9	14.2-9.1: Summary of Time to First Rescue Medication Use (hours) Scores – Per-protocol Efficacy Analysis Set
14.2-10	14.2-10.1: Summary of Integrated Rank Assessment of NRS Pain Intensity Scores and Opioid Use Scores – Per-protocol Efficacy Analysis Set
14.2-11	14.2-11.1: Summary of Satisfaction with Postsurgical Pain Control Questionnaire Score by Timepoint – Per-protocol Efficacy Analysis Set
14.2-12.1	14.2-12.1.1: Summary of Postoperative Symptom Severity (PoSSe) Questionnaire - Total Score [1] Summary – Per-protocol Efficacy Analysis Set
14.2-12.2	14.2-12.2.1: Summary of Postoperative Symptom Severity (PoSSe) Questionnaire - Individual Question Score Tabulation – Per-protocol Efficacy Analysis Set
14.2-13	14.2-13.1: Summary of Number of Unscheduled Phone Calls or Office Visits Related to Pain – Per-protocol Efficacy Analysis Set
14.2-14.1	14.2-14.1.1: Summary of Total Rescue Medication Consumption (MED) – Per-protocol Efficacy Analysis Set
14.2-14.2	14.2-14.2.1: Summary of the Number of Times Rescue Medication was Used by Subject – Per-protocol Efficacy Analysis Set

3. ADDITIONAL SUMMARIES

The effect of surgeon will be determined by replacing the site effect in the efficacy analysis of variance with surgeon and by summarizing data by surgeon within site as appropriate (see Section 2 for additional detail). Table B indicated the tables and figures to be produced to explore the surgeon effect and, if applicable, the corresponding table or figure template with a brief description of changes to the planned output.

Table B: Templates and Titles for Surgeon Tables

Surgeon Effect Notes	Table
These tables will be amended with additional information. The current data planned remains on the table.	14.1-2.1
	14.1-2.2.1
	14.1-2.2.2
	14.1-2.3
	14.1-2.4

For site 100 create new pages in the table for each surgeon at site 100. The site 100 page will remain as is unchanged.	14.1-3.1
	14.1-3.2.1
	14.1-3.2.2
	14.1-3.3
Replace site effect in ANOVA with surgeon	14.2-1.1.1.S: Analysis of AUC of NRS Pain Intensity Scores through 48 hours – Primary Efficacy Analysis Set – Surgeon Effect
	14.2-1.1.6.S: Analysis of AUC of NRS Pain Intensity Scores through 48 hours – Per-protocol Efficacy Analysis Set – Surgeon Effect
	14.2-1.2.1.S: Summary of AUC of NRS Pain Intensity Scores through 48 hours – Primary Efficacy Analysis Set - Analysis of Variance (ANOVA) Model Results – Surgeon Effect
	14.2-1.2.1.S.1: Summary of AUC of NRS Pain Intensity Scores through 48 hours – Per-protocol Efficacy Analysis Set - Analysis of Variance (ANOVA) Model Results – Surgeon Effect
	14.2-2.2.S: Summary of AUC of NRS Pain Intensity Scores through 24 hours – Primary Efficacy Analysis Set - Analysis of Variance (ANOVA) Model Results – Surgeon Effect
	14.2-2.2.1.S: Summary of AUC of NRS Pain Intensity Scores through 24 hours – Per-protocol Efficacy Analysis Set - Analysis of Variance (ANOVA) Model Results – Surgeon Effect
	14.2-3.2.S: Summary of AUC of NRS Pain Intensity Scores through 72 hours – Primary Efficacy Analysis Set - Analysis of Variance (ANOVA) Model Results – Surgeon Effect
	14.2-3.2.1.2: Summary of AUC of NRS Pain Intensity Scores through 72 hours – Per-protocol Efficacy Analysis Set - Analysis of Variance (ANOVA) Model Results – Surgeon Effect
Replace site as stratification with surgeon	14.2-5.1.S: Analysis of Opioid-Free Subjects through 24 hours – Primary Efficacy Analysis Set – Surgeon Effect
	14.2-5.1.1.S: Analysis of Opioid-Free Subjects through 24 hours – Per-protocol Efficacy Analysis Set – Surgeon Effect
	14.2-5.2.S: Analysis of Opioid-Free Subjects through 48 hours – Primary Efficacy Analysis Set
	14.2-5.2.1.S: Analysis of Opioid-Free Subjects through 48 hours – Per-protocol Efficacy Analysis Set

	14.2-5.3.S: Analysis of Opioid-Free Subjects through 72 hours – Primary Efficacy Analysis Set
	14.2-5.3.1.S: Analysis of Opioid-Free Subjects through 72 hours – Per-protocol Efficacy Analysis Set

Total lidocaine dose will be summarized (template 14.1-4.1) by treatment, site and surgeon within site. Lidocaine doses are found in dataset CM where CMCAT=SURGICAL MEDICATION / ANESTHESIA and CMDECOD=Xylocaine-epinephrine. Lidocaine was dosed 36 mg/carpule (or capsule) and will be converted from carpules/capsules to mg by multiplying the number of carpules used by 36.

Time from last lidocaine injection to first study treatment injection will be summarized (template 14.1-5.1) by treatment, site and surgeon within site.

Impacted third molars will be scored for each subject within jaw (maxillary and mandibular) and in total. Each full bony impaction is scored as 10 while partial impacted molars are scored as 1; erupted and soft tissue will be scored as 0. For example if a subject had 1 full bony impaction, 1 partial impaction, 1 erupted and 1 soft tissue, the subject's scores would be 10, 1, 0 and 0 respectively for a total impaction score of 11. Thus with each jaw the potential outcomes are 0, 1, 2, 10, 11 and 20 indicating, respectively, no impactions, a single partial bony impaction, two partial bony impactions, a single full bony impaction, one partial and one full bony impaction and two full bony impactions; and for the subject the potential outcomes are 0, 1, 2, 3, 4, 10, 11, 12, 13, 20, 21, 22, 30, 31 and 40. The impaction scores will be tabulated (template 14.1-5.1.1) by treatment, location (all, maxillary, mandibular), site and surgeon within site. Impaction scores will be presented from highest to lowest score.

Tooth impaction will be tabulated (template 14.1-6.2.1) by treatment, location, site and surgeon within site. Locations will be each tooth and maxillary (Tooth 1 and Tooth 16) and mandibular (Tooth 17 and Tooth 32). For maxillary and mandibular summaries if a subjects will be counted only once in each impaction category in the highest level of impaction reported where impaction levels from highest to lowest are 1-full bony, 2-partial bony, 3-soft tissue and 4-erupted.

Pharamcokinetic concentrations will be summarized (template 14.2-15.1.1) at each scheduled timepoint by treatment, site and surgeon within site. Plots of the mean PK concentration by time indicating each surgeon will be produced from this summary.

Pharamcokinetic parameters will be summarized (template 14.2-15.2.1) at each scheduled timepoint by treatment, site and surgeon within site.

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329

Table 14.1-4.1: Summary of Total Lidocaine Dose (mg) - by Site and Surgeon within Site - Safety Analysis Set

Site	Statistic	EXPAREL [N=XX]	Placebo [N=XX]
Overall	N	xx	xx
	Mean	xx.x	xx.x
	Standard Deviation	x.xx	x.xx
	Median	xx	xx
	Minimum	xx.x	xx.x
	Maximum	xx	xx
100	N	xx	xx
	Mean	xx.x	xx.x
	Standard Deviation	x.xx	x.xx
	Median	xx	xx
	Minimum	xx.x	xx.x
	Maximum	xx	xx
100 – Surgeon 1	N	xx	xx
	Mean	xx.x	xx.x
	Standard Deviation	x.xx	x.xx
	Median	xx	xx
	Minimum	xx.x	xx.x
	Maximum	xx	Xx
100 – Surgeon 2	N	xx	xx
	Mean	xx.x	xx.x
	Standard Deviation	x.xx	x.xx
	Median	xx	xx
	Minimum	xx.x	xx.x
	Maximum	xx	xx

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

Note to programmer: *Sites to appear on this table are Overall, 100, 100-surgeon 1, 100-surgeon 2, 200, 300). Do not split a site across pages. Use this template also for tables:*

Table 14.1-4.2: Summary of Total Lidocaine Dose (mg) - by Site and Surgeon within Site - Primary Efficacy Analysis Set
Table 14.1-4.3: Summary of Total Lidocaine Dose (mg) - by Site and Surgeon within Site - Secondary Efficacy Analysis Set
Table 14.1-4.4: Summary of Total Lidocaine Dose (mg) - by Site and Surgeon within Site - Per-protocol Efficacy Analysis Set

Table 14.1-5.1: Summary of Time from Last Lidocaine Dose to First Study Treatment Dose - by Site and Surgeon within Site - Safety Analysis Set
Table 14.1-5.2: Summary of Time from Last Lidocaine Dose to First Study Treatment Dose - by Site and Surgeon within Site - Primary Efficacy Analysis Set
Table 14.1-5.3: Summary of Time from Last Lidocaine Dose to First Study Treatment Dose - by Site and Surgeon within Site - Secondary Efficacy Analysis Set
Table 14.1-5.4: Summary of Time from Last Lidocaine Dose to First Study Treatment Dose - by Site and Surgeon within Site - Per-protocol Efficacy Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.1-6.1.1: Tabulation of Impaction Scores - by Site and Surgeon within Site - Safety Analysis Set

Site	Location	Score [1]	EXPAREL [N=XX] n (%)	Placebo [N=XX] n (%)
Overall	All	40	XX (XX.X)	XX (XX.X)
		31	XX (XX.X)	XX (XX.X)
		30	XX (XX.X)	XX (XX.X)
		22	XX (XX.X)	XX (XX.X)
		21	XX (XX.X)	XX (XX.X)
		20	XX (XX.X)	XX (XX.X)
		13	XX (XX.X)	XX (XX.X)
		12	XX (XX.X)	XX (XX.X)
		11	XX (XX.X)	XX (XX.X)
		10	XX (XX.X)	XX (XX.X)
		4	XX (XX.X)	XX (XX.X)
		3	XX (XX.X)	XX (XX.X)
		2	XX (XX.X)	XX (XX.X)
		1	XX (XX.X)	XX (XX.X)
		0	XX (XX.X)	XX (XX.X)
	Maxillary	20	XX (XX.X)	XX (XX.X)
		11	XX (XX.X)	XX (XX.X)
		10	XX (XX.X)	XX (XX.X)
		2	XX (XX.X)	XX (XX.X)
		1	XX (XX.X)	XX (XX.X)
		0	XX (XX.X)	XX (XX.X)
	Mandibular	20	XX (XX.X)	XX (XX.X)
		11	XX (XX.X)	XX (XX.X)
		10	XX (XX.X)	XX (XX.X)
		2	XX (XX.X)	XX (XX.X)
		1	XX (XX.X)	XX (XX.X)
		0	XX (XX.X)	XX (XX.X)

[1] Sum of the impaction score for each tooth where full bony impaction = 10; partially bony = 1; other = 0
Score presented from highest to lowest level of impactions.
Source: *list SAS datasets used to create table* DDMONYYYYTHH:MM
SAS X.Y program_name

Note to programmer: *Put each site and surgeon within site (Overall, 100, 100-surgeon 1, 100-surgeon 2, 200, 300) on a separate page. Use this template also for tables:*

Table 14.1-6.1.2: Tabulation of Impaction Scores - by Site and Surgeon within Site - Primary Efficacy Analysis Set
Table 14.1-6.1.3: Tabulation of Impaction Scores - by Site and Surgeon within Site - Secondary Efficacy Analysis Set
Table 14.1-6.1.4: Tabulation of Impaction Scores - by Site and Surgeon within Site - Per-protocol Efficacy Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329

Table 14.1-6.2.1: Tabulation of Third Molar Impactions - by Site and Surgeon within Site - Safety Analysis Set

Site	Location	Impaction	EXPAREL [N=XX] n (%)	Placebo [N=XX] n (%)
Overall	Maxillary [1]	Full bony	XX (XX.X)	XX (XX.X)
		Partial bony	XX (XX.X)	XX (XX.X)
		Soft Tissue	XX (XX.X)	XX (XX.X)
		Erupted	XX (XX.X)	XX (XX.X)
	Mandibular [1]	Full bony	XX (XX.X)	XX (XX.X)
		Partial bony	XX (XX.X)	XX (XX.X)
		Soft Tissue	XX (XX.X)	XX (XX.X)
		Erupted	XX (XX.X)	XX (XX.X)
	Right Maxillary	Full bony	XX (XX.X)	XX (XX.X)
		Partial bony	XX (XX.X)	XX (XX.X)
		Soft Tissue	XX (XX.X)	XX (XX.X)
		Erupted	XX (XX.X)	XX (XX.X)
	Left Maxillary	Full bony	XX (XX.X)	XX (XX.X)
		Partial bony	XX (XX.X)	XX (XX.X)
		Soft Tissue	XX (XX.X)	XX (XX.X)
		Erupted	XX (XX.X)	XX (XX.X)
	Left Mandible	Full bony	XX (XX.X)	XX (XX.X)
		Partial bony	XX (XX.X)	XX (XX.X)
		Soft Tissue	XX (XX.X)	XX (XX.X)
		Erupted	XX (XX.X)	XX (XX.X)
	Right Mandible	Full bony	XX (XX.X)	XX (XX.X)
		Partial bony	XX (XX.X)	XX (XX.X)
		Soft Tissue	XX (XX.X)	XX (XX.X)
		Erupted	XX (XX.X)	XX (XX.X)

[1] Subject counted only once at the highest level of impaction, presented from highest to lowest.
Source: *list SAS datasets used to create table* DDMONYYYYTHH:MM
SAS X.Y program_name

Note to programmer: *Put each site (Overall, 100, 100-Surgeon 1, 100-Surgeon 2, 200, 300) on a separate page. Use this template also for tables:*

Table 14.1-6.2.2: Tabulation of Third Molar Impactions - by Site and Surgeon within Site - Primary Efficacy Analysis Set
Table 14.1-6.2.3: Tabulation of Third Molar Impactions - by Site and Surgeon within Site - Secondary Efficacy Analysis Set
Table 14.1-6.2.4: Tabulation of Third Molar Impactions - by Site and Surgeon within Site - Per-protocol Efficacy Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.2-15.1.1: Summary of Pharmacokinetic Concentrations (ng/mL) - by Scheduled Collection Time, Site and Surgeon within Site - Pharmacokinetic Analysis Set
Site: Overall

Time Point	Statistic	EXPAREL [N=XX]
Prior to Surgery	n	xx
	Mean	xxx.x
	Standard Deviation	xxx.xx
	Median	xxx.x
	Minimum	xx
	Maximum	xxx
	n (%) BLQ	xx (xx.x)
15 min	n	xx
	Mean	xxx.x
	Standard Deviation	xxx.xx
	Median	xxx.x
	Minimum	xx
	Maximum	xxx
	n (%) BLQ	xx (xx.x)

BLQ = below limit of quantitation
Source: list SAS datasets used to create table DDMONYYYYTHH:MM
SAS X.Y program_name

Note to programmer: *Do not split time point across pages. Time points to appear on this tables are Prior to Surgery, 15 min, 30 min and 1 hour, 2 hour, 4 hour, 8 hour, 12 hour, 18 hour, 24 hour, 30 hour, 36 hour, 42 hour, 48 hour, 54 hour, 60 hour, 66 hour, 72 hour, 84 hour, 96 hour, Day 7 and Day 10. Sites are Overall, 100, 100-Surgeon 1, 100-Surgeon 2, 200 and 300. Use this template for the following table:*

Table 14.2-15.1.2: Summary of Pharmacokinetic Concentrations (ng/mL) - by Scheduled Collection Time, Site and Surgeon within Site – Subjects in Pharmacokinetic and Per-protocol Efficacy Analysis Sets

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-329
Table 14.2-15.2.1: Summary of Pharmacokinetic Parameters - by Site and Surgeon within Site - Pharmacokinetic Analysis Set
Site: Overall

Parameter	Statistic	EXPAREL [N=XX]
Cmax	n	xx
	Mean	xxx.x
	Standard Deviation	xxx.xx
	Median	xxx.x
	Minimum	xx
	Maximum	xxx
Tmax	n	xx
	Mean	xxx.x
	Standard Deviation	xxx.xx
	Median	xxx.x
	Minimum	xx
	Maximum	xxx

BLQ = below limit of quantitation
Source: list SAS datasets used to create table DDMONYYYYTHH:MM
SAS X.Y program_name

Note to programmer: *Do not split a parameter across pages. Parameters to appear on this table, in order of appearance, are Cmax, Early(0-2hr) Cmax, Early Tmax, Late (> 2hr) Cmax, Late Tmax, AUC(0-t), AUC(0-inf), Lambda_z, Half-life. Sites are Overall, 100, 100-Surgeon 1, 100-Surgeon 2, 200 and 300. Use this template for the following table:*

Table 14.2-15.2.2: Summary of Pharmacokinetic Concentrations (ng/mL) - by Scheduled Collection Time, Site and Surgeon within Site – Subjects in Pharmacokinetic and Per-protocol Efficacy Analysis Sets