STATISTICAL ANALYSIS PLAN

Protocol Title	A Multicenter, Randomized, Active-controlled Study to Evaluate the Efficacy and Safety of EXPAREL When Administered via Infiltration into the Transversus Abdominis Plane (TAP) Versus Standard of Care in Subjects Undergoing Elective Cesarean Section.
Protocol Number	402-C-414
Protocol Version	Final
Protocol Date	Original: 16 August 2018 Amendment 1: 15Nov2018. Amendment 2: 07 February 2019
Study Drug	EXPAREL (bupivacaine liposome injectable suspension)
Study Phase	4
IND Number	069,198
Sponsor	Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 Tel: 973-254-3560
SAP Version	1.0
Date	16 March 2020

1 SIGNATURE PAGE

Alfred Mbah Alfred Mbah, PhD Principal Statitician Pharma Data Asociates, LLC	18-Mar-2020 Date
Chao Wang Chao Wang, PhD Principal Statitician Pharma Data Asociates, LLC	17-Mar-2020 Date
Vincent Yu Vincent Yu, PhD Vice President, Biometrics Pacira Pharmaceuticals, Inc	17-Mar-2020 Date
Alla Nagaev Alla Nagaev, MD Associate Medical Director, Clinical Operations Pacira Pharmaceuticals, Inc	17-Mar-2020 Date
Julia Yang Julia Yang, MD VP, Clinical Research Pacira Pharmaceuticals, Inc	18-Mar-2020 Date
Michael Rozycki Michael Rozycki, PhD Senior Vice President, Regulatory Affairs Pacira Pharmaceuticals, Inc	17-Mar-2020 Date

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse event
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
ATC	Anatomical therapeutic class
BMI	Body mass index
bpm	Beats per minute
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CSE	Combined spinal epidural
CSR	Clinical study report
d	Day
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
hr, h	Hour
ICF	Informed consent form
ICH	International Conference on Harmonization
ICU	Intensive care unit
IV	Intravenous
LOCF	Last observation carried forward
LS	Least square
MedDRA	Medical dictionary for regulatory affairs
MMRM	Mixed model repeated measures
MPADSS	Modified Postanesthesia Discharge Scoring System
min	Minutes
OMED	Oral morphine equivalent dose in mg
n	Number of subjects
OR	Operating room
PACU	Postanesthesia care unit
PCA	Patient-controlled analgesia
PO	Oral
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
TAP	Transversus abdominis plane
TEAE	Treatment-emergent adverse event
TLF	Table, listings and figures
TUG	Timed up-and-go
VAS	Visual analog scale
WHO	World Health Organization
WHODD	World Health Organization – Drug Dictionary

4 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analysis and reporting of the clinical study 402-C-414 titled "A Multicenter, Randomized, Active-controlled Study to Evaluate the Efficacy and Safety of EXPAREL When Administered via Infiltration into the Transversus Abdominis Plane (TAP) Versus Standard of Care in Subjects Undergoing Elective Cesarean Section."

The structure and content of this SAP provide sufficient detail to meet the requirements identified by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials (1998). All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association (1999) and the Royal Statistical Society (1993), for statistical practice.

The purposes of this SAP are to:

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

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

The following documents related to clinical study Protocol 402-C-414 were reviewed in preparation of this SAP:

- Original Protocol issued on 16 August 2019.
- Amendment 1 issued on 15Nov2018
- Amendment 2 issued on 07Feb2019
- CRF version 1.0 issued on 04Feb2019
- CRF version 2.0 issued on 05Apr2019
- ICH Guidance on Statistical Principles for Clinical Trials (E9).

The reader of this SAP is encouraged to also read the clinical protocol and other identified documents for details on the planned conduct of this study. Operational aspects related to

collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

5 STUDY OBJECTIVES

5.1 Primary Objective

The primary objective of this study is to compare total opioid consumption through 72 hours following EXPAREL infiltration into the transversus abdominis plane (TAP) with standard of care (SOC) in subjects undergoing an elective cesarean section (C-section).

5.2 Secondary Objectives

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

6 STUDY OVERVIEW

This is a Phase-4, multicenter, randomized, active-controlled study in approximately 182 adult subjects undergoing elective C-section. All subjects will remain in the hospital for up to 72 hours postsurgery.

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

- Group 1: 150 mcg Duramorph (SOC).
- Group 2: 50 mcg Duramorph + EXPAREL TAP infiltration.
- Group 3: EXPAREL TAP infiltration.

In all treatment groups, a combined spinal epidural (CSE) anesthesia technique may also be used provided the epidural component is not used.

Subjects will be allowed rescue medication upon request to control their pain. Rescue medication will be oral (PO) immediate release oxycodone. If subject cannot tolerate PO medication or fails the PO oxycodone rescue, intravenous (IV) morphine or hydromorphone may be used as rescue medication.

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

Other postsurgical assessments include:

- Opioid use
    - Total opioid burden
- Date and time of first unassisted ambulation
- Pain intensity scores using a 10-cm VAS at rest
- Discharge readiness
- Opioid related symptom distress scale
- Date and time of first bowel movement
- Incidence of itching
- Subject's satisfaction with postsurgical pain control
- Calls to physician about pain
- Total time in post-anesthesia care unit (PACU)
- Persistent opioid use at Day 30
- Emergency department (ED) visits
- Recovery from Cesarean Section Scale

7 DEFINITIONS

Study Day

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

Treatment-emergent Adverse Events

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

Time 0 (zero)

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

Time Periods

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

Table 1: Time Window for VAS Assessment

Defined time VAS Time Point (hrs)	Acceptable Window (hrs)
12, 24	± 1
48	± 2
72	± 4

If there are two or more VAS data points that fit into the same time window, the data point close to the center of the window will be used. If two data points are of equal distance to the center, the one with higher VAS score will be used for analysis. For programming purpose, the VAS time point for analysis (ANL01FL=Y) will be numbered by their schedule, eg, ATPTN = 12, 24, …, 72. Other VAS time points will be numbered by the VAS time relative to the surgical end time in hours (with 1 decimal point), eg, 47.5.

If after applying the time window, the VAS data point for the scheduled window becomes missing, it will be imputed as per Section 10.1.1.3.

Baseline

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

Ready for Discharge

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

Discharge Time

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

Time to Event

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

Opioid-free

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

Opioid-sparing

Opioid-sparing is defined as meeting both of the following conditions:

- Total opioid consumption through 72 hours (all doses) ≤15mg (oral morphine equivalent dose [OMED])
- Total itching scores at 12, 24, 48 and 72 hours ≤1;

- No opioid-related AEs - Nausea/Abdominal distension/Dizziness

8 ANALYSIS SETS

8.1 Safety set

The safety set will be defined as follows

- Group 1 subjects who underwent C-section surgery and received SOC as scheduled
- Group 2 and Group 3 subjects, who underwent C-section surgery and received study drug through TAP infiltration as scheduled.

All analyses based on the safety set will be by actual treatment received.

8.2 Efficacy set

All the subjects in Safety Set who completed through 72 hours postsurgery. All analyses based on the efficacy set will be by planned treatment at randomization.

8.3 Sensitivity set

All the subjects in Efficacy set who did not receive the correct TAP infiltration based on ultrasound image/video will be excluded from sensitivity analysis. The ultrasound image/video for each patient was reviewed by independent ultrasound review committee. Incorrect TAP infiltration would only be confirmed if two rejections are received.

9 STUDY ENDPOINTS

9.1 Efficacy Endpoints

9.1.1 Primary Efficacy

The primary endpoint is the total opioid consumption (in mg of oral morphine equivalent dose [OMED, see 9.3.1]) to cover postsurgical pain in morphine equivalents through 72 hours. Duramorph, though administered prior to surgery, is used to cover postsurgical pain thus is included in opioid consumption to cover postsurgical pain.

9.1.2 Key Secondary Efficacy

The key secondary endpoint is the average postsurgical itching scores through 72 hours.

9.1.3 Secondary Efficacy

The following secondary endpoints will be analyzed:

- Postsurgical itching scores through 12, 24 and 48

- Total Opioid Consumption through 24 and 48 hours, Day 7 (168 hours) and Day 14 (336 hours)
- Average VAS pain intensity scores (general pain and pain at incision site) through 24, 48 and 72 hours after surgery or hospital discharge, whichever occurs first
- Percentage of postsurgical opioid-free and opioid-sparing subjects through 72 hours
- ORSDS at 24, 48, and 72 hours after surgery or at hospital discharge, whichever occurs first
- Proportion of subject discharge-ready at 24, 48, and 72 hours or at hospital discharge, whichever occurs first
- Overall assessment of subject satisfaction with pain control at 72 hours or at hospital discharge, whichever occurs first
- Recovery Cesarean Section Scale

9.1.4 Exploratory Efficacy

- Total postsurgical opioid consumption (in mg of OMED) in morphine equivalents through 72 hours, excluding duramorph administered prior to surgery.
- Length of hospital stay
- Number of unscheduled phone calls or office visits related to pain from discharge through Day 14
- ED visits
- Persistent opioid use at Day 30
- Time spent in the post-anesthesia care unit (PACU)
- Time to first unassisted ambulation.
- Time to first bowel movement

9.2 Safety Endpoints

- Safety will be assessed using the following: Incidence of treatment-emergent AEs (TEAEs) and SAEs through Day 14
- Vital signs at scheduled time points

9.3 Efficacy Assessment

9.3.1 Opioid Dose Conversion

Opioids dose will be converted to oral morphine equivalent dose (OMED mg) using the conversion factor from Table 2 for all summaries. Total opioid dose is the oral morphine

equivalent sum of all opioids taken during the time interval of interest. Subjects with no opioid use during the period in question will be assigned a dose of 0 mg for summaries.

Table 2. Conversion Factors to IV and Oral Morphine Equivalent Dose from Other Opioids

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

PO = oral, IV = intravenous, IM = Intramuscular, SC = subcutaneous, VAS = visual analog scale.

9.3.2 Average Postsurgical VAS pain Intensity Scores Through 72 Hours or Hospital Discharge, Whichever Occurs First.

To calculate average of postsurgical VAS pain intensity score through 72 hours or hospital discharge, whichever occurs first, we collected pain scores for each subject at each prespecified time. Subjects who did not report any pain score at any time point after surgery will be excluded from this analysis. All the pain scores will be first adjusted for rescue medication if necessary (see 10.1.1.3). Then the remaining missing pain scores will be imputed the median pain score from the patients in the same treatment group and same scheduled time point (see Section 10.1.1.3). The area under the pain-time curve (AUC) is derived using the trapezoidal

rule (see formula below) on the adjusted and imputed pain scores. AUC will start with the first obtained postsurgical pain assessment. All pain assessments through 72 hours after surgery, both scheduled and unscheduled ones, will be included in deriving AUC. Exact assessment times will be used in deriving AUC.

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

where pi is the VAS pain score at time i and t_i is the time, in hours, from end of surgery. Note t_1 is 12 hours postsurgery. It is the first time VAS score is collected.

The next step is to obtain the average pain score through 72 hours or hospital discharge from AUC. This will be accomplished by dividing AUC by the time interval between first pain assessment and last assessment for the AUC calculation. For example, if the first pain assessment time and the last pain assessment time used to calculate AUC for a subject were 5.6 hours and 72.2 hours respectively, then the average pain score through 72 hours or hospital discharge would be AUC divided by 66.6 (72.2-5.6 = 66.6).

Average postsurgical pain intensity score will be calculated for general pain and pain at incision site.

9.3.3 Opioid Related Symptom Distress Scale (ORSDS)

The Opioid-Related Symptom Distress Scale (ORSDS) is a 4-point scale that evaluates 3 symptom distress dimensions (frequency, severity, bothersomeness) for 10 symptoms. The symptom-specific ORSDS is the average of the 3 symptom distress dimensions. The composite ORSDS is the average of 10 symptom-specific scores (see Section 14). The ORSDS has been validated for outpatient laparoscopic cholecystectomy (under general anesthesia) by assessment of internal consistency, content validity, construct validity, principal components analysis, known group validity, responsiveness, and opioid dose dependency.

9.3.4 Subject Satisfaction with Pain

The subject's satisfaction with postsurgical pain control will be conducted at 72 hours after surgery (or at hospital discharge, whichever occurs first), and will be assessed using a 5-point Likert scale as follows: 1. Extremely dissatisfied; 2. Dissatisfied; 3. Neither satisfied nor dissatisfied; 4. Satisfied; 5. Extremely satisfied. Sum of the scores will be used for analysis.

9.3.5 Pain Surgical Fear Questionnaire (SFQ)

The SFQ is an eight-item instrument for the assessment of self-reported surgical fear, which can be divided into short-term (SFQ-s) and long-term (SFQ-l) surgery-related fears. All items are scored on an eleven-point numeric rating scale (NRS) ranging from 0 (not at all afraid) to 10 (very afraid). This results in a score of 0-40 for each subscale. Items are: 1. afraid of operation, 2. anesthesia, 3. postoperative pain, 4. Side effects, 5. health deterioration, 6. failed operation, 7. incomplete recovery, 8. long duration of rehabilitation. Sum of the two subscale SFQ scores by treatment group will be used for analysis.

9.3.6 Pain Calls to Physician (Single Question)

As part of the phone call to physician on Day 14, the subject will be asked pain related to surgery, and will be assessed using a 4-point Likert scale as follows: 1. 0 (I have not called my doctor); 2. 1-2 times; 3. 3-5 times; 4. More than 5 times.

9.3.7 Persistent Opioid Use

As part of the phone call to physician on Day 30, subjects will be asked if they were currently taking opioid for pain and they can either respond as yes or no. Persistent opioid use is defined as those patients who respond yes to the Day 30 opioid use question.

9.3.8 Recovery from Caesarean Section Scale (RCSS)

At 24, 48, and 72 hours postsurgery or hospital discharge, whichever comes first, subjects are asked to rate their answer (1 = strongly disagree and 7 = strongly agree) to each of the 9 RCSS questions.

10 STATISTICAL METHODS OF ANALYSIS

10.1 General Principles

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

Tables will present 150 mcg Duramorph + SOC, 50 mcg Duramorph + EXPAREL and EXPAREL as separate columns.

10.1.1 Handling Missing Values

10.1.1.1 Total Postsurgery Opioid Consumption

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

Study subjects will be given an ePRO device or an app on their smart phone to report pain score and medications they used at home. We expect that all medications will be entered, except when patients discontinued due to AE or death after surgery.

10.1.1.2 Postsurgical Itching Scores through 72 hours

No imputation will be done on the missing itching score. The missing mechanism were assumed missing at random (MAR). Under this assumption the MMRM analysis (see 10.7.1.2.1) is considered unbiased.

10.1.1.3 VAS Pain Intensity Scores

VAS pain intensity scores will first be adjusted by the amount of opioid taken before pain assessment using following method.

- For pain intensity scores on or before the scheduled 24 hours (on or before the exact 24 hours if the scheduled 24 hour pain score is missing), first calculate the total opioid amount (oral morphine equivalent dose, see section 9.3.1.3) that have been taken before this pain assessment (total_opi). Then the imputed pain score will be the sum of the original pain score and one tenth of the natural logarithm of total_opi.
- For pain intensity scores after the scheduled 24 hours (after the exact 24 hours if the scheduled 24 hour pain score is missing), first calculate the total opioid amount that have been taken from 24 hours before this pain assessment (total_opi). Then the imputed pain score will be the sum of the original pain score and one tenth of the natural logarithm of total_opi.

After adjustment, missing scheduled VAS pain intensity scores will be replaced by the median of non-missing scores from the same scheduled time point and same treatment group.

10.1.1.4 Exposure, Surgery, and Rescue Medication Date or Time

It is expected that all necessary information on study drug exposure, surgery, and postsurgical rescue medication dates and times will be complete. Any such information that is missing and cannot be obtained through query resolution may be imputed, on a case-by-case basis, in a conservative manner that minimizes bias. For example, if pain medication taken on Day 1 has no time of administration recorded, the imputed time will be the end of surgery plus 1 minute.

10.1.1.5 Adverse Event or Concomitant Medications Dates or Times

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

For partial start date/time:

- If the year is unknown, then the date will be assigned the date and time of first dose of study treatment.
- If the year is known to be different from the year of the first dose, then missing month and day will be imputed as the first month and first day of the month.
- If the year is known to be the year of the first dose,
    a) If the month is unknown or is the same as the month of the first dose, then the missing month and day will be imputed by the month and day of the first dose.
    b) If the month is known to be different from the month of the first dose, then the missing day is imputed as 01 (first day of the month).
- If the time is unknown, then:
    a) If the date (day, month, and year) matches the date of the administration of study drug, then the time of the study treatment will be used to impute the missing time.
    b) Otherwise, ’00:00’ will be assigned.

For medications with missing or partially missing dates, Section 10.5 provides rules for the determination of prior or concomitant status.

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

10.1.1.7 Time to Event

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

10.1.2 By-Center Analyses

By-site summaries will be presented for disposition, demographics, primary efficacy endpoint and secondary efficacy endpoints. In the by-site analysis, analysis stratified by site or adjusted for site as covariate, the small sites will be pooled into one pseudo site. Pseudo site will be numbered as SITEID 999, including SITEID 104,105,108,109,112,116,120,121,122 and 123

10.1.3 Non-Inferiority Margin (NIM)

For VAS pain scores, several studies used 0.8 or 1 as non-inferiority margin. We chose a more conservative NIM of 0.5 which is the same to our previous c-section study named "A Multicenter, Randomized, Double-blinded, Active-controlled Study to Evaluate the Safety and Efficacy of EXPAREL When Administered via Infiltration into the Transversus Abdominis Plane (TAP) Versus Bupivacaine Alone in Subjects Undergoing Elective Cesarean Section".

For postsurgical opioid consumption through 72 hours, from our previous c-section study listed above, postsurgical opioid consumption for bupivacaine group (which is very similar to 150 mcg Duramorph + SOC in this study) is around 30 mg OMED. Some previous studies using opioid consumption as primary endpoint use 30 mg in a 24h interval as non-inferiority margin and previous literature indicate difference of 10.6 mg in IV morphine equivalent dose (31.8 oral morphine equivalent) daily is the clinical different threshold. These difference will be more than 1 on natural logarithm scale for 72 hour interval. To be conservative, we choose 0.8 (on natural logarithm scale) to be our non-inferiority margin (NIM).

10.2 Subject Disposition

Subject disposition summaries will include the number of subjects

- Screened,
    - Screen failure
    - Enrolled (ie, randomized)
- Randomized
    - Randomized not treated,
    - Randomized treated,
- In the safety analysis set,
- In the efficacy set,
- In the sensitivity set,
- Completed the study as planned,
- Discontinued from the study, and

- Reasons for discontinuation from the study.

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

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

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

10.3 Description of Demographics and Baseline Characteristics

10.3.1 Demographics

The summary of demographic data will present:

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

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

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

10.3.2 Baseline Characteristics

The summary of baseline characteristic data will present:

- American Society of Anesthesiologists (ASA) Classification – n (%)
- Baseline ECG interpretation
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m^2)
- Surgical Fear Questionnaire (SFQ)

Weight in pounds will be converted to kilograms using the conversion factor of 2.2046 pounds to 1 kilogram. Height in inches will be converted to centimeters using the conversion factor of 2.54 centimeters to 1 inch.

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

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

10.4 Surgery Characteristics

Surgery characteristics including type of anesthesia (general, spinal, or other), use of intraoperative medication (yes or no), use of CSE anesthesia (yes or no), administration of the epidural component of the SCE (yes or no), and duration of surgery will be summarized using descriptive statistics. Summaries will be provided for each (safety and efficacy) analysis set.

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

10.5 Medications for Surgical Procedures, and Prior and Concomitant Medications

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

Preoperative, intraoperative, CSE, multimodal pain, postoperative pain, prescription daily pain, and rescue medications are medications given as part of the surgical procedure with start and stop dates on the day of surgery and start and stop times overlapping with the surgery start and stop times.

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

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

Concomitant medications are defined as medications taken after the start of study drug administration (i.e., started prior to the start of study drug administration and continued after or started after the start of study drug administration).

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

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

- Otherwise, it is concomitant medication.

- If the medication stop date is completely missing, it is concomitant medication.

All medications will be summarized separately by category using n (%) of subjects for each treatment group and across treatment groups by ATC3 term and PT for the safety analysis set. Subjects may have more than one medication per ATC3 and PT. At each level of subject summarization, a subject will be counted once if one or more medications are reported by the same subject at that level.

All medications will be included in the data listing.

10.6 Measurements of Treatment Compliance

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

10.7 Efficacy Analysis

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

10.7.1 Methods of Analysis

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

10.7.1.1 Primary Efficacy Analysis

Total opioid consumption (OMED mg) will be summarized by treatment group for the total dose consumed between 0 and 72 hours after the end of surgery. Presurgery duramorph, used to treat postsurgery pain, is counted in the total opioid dose consumption. For the frequency count of number of subjects receiving opioid medications, subjects will be counted only once regardless of how many times subjects have received the medications. The summary table will include number of subjects receiving postsurgical opioids, geometric mean and coefficient of variation (CV%), median, minimum and maximum.

Tests for the treatment effect will be based on the following one-sided null hypothesis and alternative hypothesis:

H_{01}: Mean 0-72 hour opioid consumption in EXPAREL group is not different from that in 150 mcg Duramorph (SOC) group.

- H_{a1}: Mean 0-72 hour opioid consumption is less in EXPAREL group than in 150 mcg Duramorph (SOC) group.

- H_{02}: Mean 0-72 hour opioid consumption in EXPAREL + 50 mcg Duramorph group is not different from that in 150 mcg Duramorph (SOC) group

- H_{a2}: Mean 0-72 hour opioid consumption is less in EXPAREL + 50 mcg Duramorph group than in 150 mcg Duramorph (SOC) group.

A one-sided test will be performed at 2.5% level of significance comparing each of the two dose arms of EXPAREL (EXPAREL and EXPAREL + 50 mcg Duramorph) versus 150 mcg Duramorph (SOC).

To test for significant differences between each of the two dose arms of EXPAREL (EXPAREL + 50 mcg Duramorph and EXPAREL) and the 150 mcg Duramorph (SOC), an analysis of covariance (ANCOVA) model with treatment and site as the main effects, age and height as covariates will be applied to the natural log-transformed total dose. If a subject never received an opioid medication, the total dose will be assigned 3.75 mg OMED prior to the log-transformation. The LS means of the two doses of EXPAREL (EXPAREL + 50 mcg Duramorph and EXPAREL) and 150 mcg Duramorph (SOC), LS mean difference (EXPAREL + 50 mcg Duramorph minus 150 mcg Duramorph (SOC)and EXPARE minus 150 mcg Duramorph (SOC)), two-sided 95% CI for the LS mean difference, and the one-sided p-value will be reported after back transformation (ie, taking exponential) to the original OMED scale.

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

$$\% \text{ Reduction}=100\% \times \{LSM^*_{150 \text{ mcg Duramorph(SOC)}} - LSM^*_{\text{EXPAREL+50mcg Duramorph}}\}/LSM^*_{150 \text{ mcg Duramorph(SOC)}}$$

where LSM* is back-transformed least square mean estimate from the ANCOVA.

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

10.7.1.1.1 Multiplicity Adjustments

For the efficacy analyses, pairwise comparison of the active dose groups (EXPAREL+50 mcg Duramorph and EXPAREL) will be compared to 150 mcg Duramorph (SOC) following spinal anesthesia using the 1-sided 0.025 alpha level for the efficacy analysis set.

To control the family-wise error rate at one-sided 2.5% significance level, a fixed sequence procedure (Westfall et al 1999) will be performed to test the ordered null hypotheses below at 2.5% significance level.

1) H_{01}: Mean 0-72 hour opioid consumption in EXPAREL group is not different from that in 150 mcg Duramorph (SOC) group.

2) H_{02}: Mean 0-72 hour opioid consumption in EXPAREL group is not different from that in 150 mcg Duramorph (SOC) group.

First, H_{01} will be tested at 2.5% significance level for the primary endpoint. If H_{01} is rejected, it will be claimed that the EXPAREL is superior to 150 mcg Duramorph (SOC), then H_{02} will be tested at 2.5% significance level. If H_{02} is rejected, then it will be concluded that both EXPAREL and EXPAREL + 50 mcg Duramorph groups are superior to 150 mcg Duramorph (SOC) group. If H_{01} is not rejected, then H_{02} will not be tested and the conclusion will be that neither treatment groups are efficacious.

10.7.1.1.2 Subgroup Analysis of Primary Efficacy Endpoint

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

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

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

10.7.1.2 Key Secondary Efficacy Analyses

10.7.1.1.1 Average Postsurgical Itching Scores Through 72 Hours

Postsurgical itching scores (at PACU, 12, 24, 48, and 72 hrs) will be analyzed using an MMRM model with treatment group, site, visit and treatment-by-visit interaction as main effect, age and height as covariates. LS means of each treatment group, LS mean differences between each pair of treatment groups and p-value of each LS mean differences will be presented. The average itching score through 72 hours is estimated by the LS grand mean.

A sample SAS code is provided as follows.

```
PROC MIXED DATA=XXXX ;
    CLASS trtp usubjid visit siteid;
    MODEL Response = siteid age height trtp visit trtp*visit / DDFM=kr2 ;
    REPEATED visit / SUBJECT=usubjid(trtp) TYPE=UN ;
    LSMEAN trtp*visit/ PDIFF ALPHA=0.05 ;
    LSMEAN trtp / PDIFF ;
```

```
        ESTIMATE "G1-G3 thru 12h" trtp 1 0 -1
                                Trtp*visit 1   1  0  0  0
                                           0   0  0  0  0
                                           -1 -1  0  0  0 / divisor=2 ;
        ESTIMATE "G1-G3 thru 24h" trtp 1 0 -1
                                Trtp*visit 1    1    1  0  0
                                            0   0    0  0  0
                                           -1  -1   -1  0  0 / divisor=3 ;
    RUN ;
```

Note: usubjid is subject ID, trtp is treatment variable, visit is the nominal study visit, and Response is the itching score at the scheduled time point. Depending on the convergence status in the computation, unstructured (UN), Toeplitz (TOEP), 1st order autoregressive [AR(1)] and compound symmetry variance-covariance (CS) matrix will be tried in the order. The final analysis will be based on the first matrix leading to the convergence in the computation.

10.7.1.3 Secondary Efficacy Analyses

10.7.1.3.1 Average Postsurgical Itching Scores Through 12, 24, 48 and 72 Hours

These endpoints will be analyzed using the same MMRM approach described in Section 10.7.1.2. Between-group simple contrast at each visit will be derived the ESTIMATE statement.

10.7.1.1.2 Total Opioid Consumption Through 24 and 48 Hours, Day 7 (168 hours) and Day 14 (336 hours)

Each individual timepoint will be analyzed using the ANCOVA model similar to Section 10.7.1.1. Between-group simple contrast will be derived from the LSMEAN statement.

10.7.1.3.3 Average VAS Pain Intensity Scores Through 72 Hours After Surgery or Hospital Discharge Whichever Occurs First

Average VAS pain intensities (general pain and pain at incision site) from 0 to 72 hours or hospital discharge whichever comes first will be derived for each subject as described in Section 9.3.2. They will be analyzed using ANCOVA with treatment and site as main effects, age and height as covariates. Based on the model, the LS Mean and SE will be reported for each treatment group. Non-inferiority and superiority sequential hypothesis testing will be performed afterwards, comparing each of the two dose arms of EXPAREL (EXPAREL + 50 mcg Duramorph and EXPAREL) versus 150 mcg Duramorph (SOC) simultaneously: (1) EXPAREL + 50 mcg duramorph vs. 150 mcg duramorph (SOC), and (2) EXPAREL vs. 150 mcg duramorph (SOC). LS Mean difference and 95% CI will be reported for each comparison.

The testing procedure is the same for each comparison. Here we use (1) EXPAREL + 50 mcg duramorph vs. 150 mcg duramorph (SOC) as an example:

Hypothesis 1 (non-inferiority):

- $H1_{o1}$: EXPAREL group is inferior to 150 mcg Duramorph (SOC) group with respect to average VAS score.
- $H1_{a1}$: EXPAREL group is not inferior to 150 mcg Duramorph (SOC) group with respect to average VAS score.

Hypothesis 2 (superiority):

- $H2_{o1}$: EXPAREL group is not superior to 150 mcg Duramorph (SOC) group with respect to average VAS score.
- $H2_{a1}$: EXPAREL group is superior to 150 mcg Duramorph (SOC) group with respect to average VAS score.

To test the two null hypotheses, a stepdown approach will be used by inspecting the 95% confidence interval for group difference as follows:

- Non-inferiority Test for Hypothesis 1.
  - If the upper bound of the 2-sided 95% confidence interval for the LSM for the difference of average VAS score under $H1_{o1}$ versus $H1_{a1}$ is > NIM, then stop the hypothesis tests and declare that the non-inferiority result is not achieved. NIM (non-inferiority margin) = 0.5.
  - If the upper bound of the 2-sided 95% CI is ≤ NIM then declare that the non-inferiority of EXPAREL+50 mcg Duramorph to 150 mcg Duramorph (SOC) is achieved. Move on to test for $H2_{o1}$.
- Superiority Test for Hypothesis 2
  - If the upper bound of the 2-sided 95% CI is ≥0 for the comparison (EXPAREL+50 mcg Duramorph versus 150 mcg Duramorph (SOC)), then stop the test and declare that the superiority is not achieved for $H2_{01}$.
  - If the upper bound is <0 then declare that the superiority of EXPAREL+50 mcg Duramorph to 150 mcg Duramorph (SOC)is achieved.

In the table presentation for the between group comparison, if the superiority test passes, only the 1-sided superiority test p-value will be displayed. If the superiority test fails, only the 1-sided non-inferiority test p-value will be displayed. Margin used for noninferiority test will be 0.5.

Summary and analysis of (general and at incision site) average VAS pain intensity scores through 24, and 48 hours will also be reported.

10.7.1.3.4 Percentage of Postsurgical Opioid-Free and Opioid-Sparing Subjects Through 72 Hours

The percentage of opioid-free subjects through 72 hours and hospital discharge will be analyzed using the logistic regression model with treatment, site, age, and height as explanatory variables. Percentage of opioid-free subjects from the model, odds ratios (EXPAREL+50 mcg Duramorph) / 150 mcg Duramorph (SOC) and EXPAREL / 150 mcg Duramorph (SOC), and 95% CI for the odds ratios and p-values will be presented.

Percentage of opioid sparing subjects will be analyzed using the same approach described for percentage of opioid free subjects.

Pseudo-code for logistic regression method:

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

10.7.1.3.5 Opioid Related Symptom Distress Scale (ORSDS) at 24, 48, and 72 Hours After Surgery or at Hospital Discharge, Whichever Occurs First

The ORSDS composite score as well as the 10 symptom-specific ORSDS scores will be summarized by treatment at each assessment time points of 24, 48, and 72 hours after surgery or at hospital discharge, whichever occurs first. Additionally, the ORSDS composite and each of the symptom-specific distress scores will be analyzed using a Mixed-Effect Model for Repeated Measures (MMRM). The model includes treatment, visit, and interaction between treatment and visit as fixed factors. The model parameters will be estimated using restricted maximum likelihood method with unstructured variance-covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom. The between-group comparison will be performed using the simple contrast at the respective visits. The LSM of 150 mcg Duramorph (SOC), EXPAREL + 50 mcg Duramorph and EXPAREL, the difference in the LSM (EXPAREL + 50 mcg Duramorph minus 150 mcg Duramorph (SOC) and EXPAREL minus 150 mcg Duramorph (SOC), and 95% CI for the LSM difference will be calculated. Analysis will be performed at 24, 48 and 72 hours.

A sample SAS code is provided as follows.

```
PROC MIXED DATA=XXXX ;
```

```
CLASS trtp usubjid visit;
MODEL Response = siteid trtp visit trtp*visit / DDFM=kr2 ;
REPEATED visit / SUBJECT=usubjid(trtp) TYPE=UN ;
Lsmeans trtp*visit/Pdiff alpha=0.05;
RUN ;
```

Note: usubjid is subject ID, trtp is treatment variable, visit is the nominal study visit, and Response is respective endpoints. Depending on the convergence status in the computation, unstructured (UN), Toeplitz (TOEP), 1st order autoregressive [AR(1)] and compound symmetry variance-covariance (CS) matrix will be tried in the order. The final analysis will be based on the first matrix leading to the convergence in the computation.

10.7.1.3.6 Proportion of Subjects Discharge-Ready at 24, 48, and 72 Hours or at Hospital Discharge, Whichever Occurs First

Proportion of subject discharge-ready at each timepoint of 24, 48, and 72 hours or at hospital discharge, whichever occurs first will be analyzed using logistic regression similar to section 10.7.1.3.4

10.7.1.3.7 Overall Assessment of Subject Satisfaction with Pain Control at 72 Hours or at Hospital Discharge, Whichever Occurs First

Overall assessment of subject satisfaction with pain control at 72 hours or at hospital discharge, whichever occurs first (obtained using a 5-point Likert scale) will be summarized with mean and SD and tabulated with n (%) by treatment group. The between group comparison will be carried out using the using the Cochran-Mantel-Haenszel (CMH) test for row mean score difference (RMS) with modified ridit score.

Pseudo-code for CMH method:

```
PROC FREQ;
    TABLE siteid*trt*Y / cmh SCORES=modridit scorout;
RUN;
```

where, Y is subject satisfaction scores

10.7.1.3.8 Recovery from Caesarean Section Scale (RCSS)

Subject rating on each of the 9 scales will be summarized descriptively by treatment group at 24, 48, and 72 hours, or at hospital discharge, whichever occurs first.

10.7.1.4 Exploratory Efficacy Endpoints

10.7.1.1.1 Total Postsurgical Opioid Consumption (mg) in Morphine Equivalents Through 72 Hours

Total postsurgical opioid consumption (mg) in morphine equivalents through 72 hours or hospital discharge will be analyzed using ANCOVA similar to section 10.7.1.3.3. Non-inferiority comparison will be conducted by comparing the upper bound of the 95% CI for the between treatment difference (in the log-transformed scale) against the noninferiority margin (NIM=0.8). If a subject never received any postsurgical opioid medication, the total dose will be assigned 3.75 mg OMED (half of one oral oxycodone dose) prior to the log-transformation.

10.7.1.4.2 Length of Hospital Stay

Length of hospital stay, defined as the surgical facility discharge date/time minus the facility admission date/time, will be summarized descriptively by treatment group.

10.7.1.4.3 Number of Unscheduled Phone Calls or Office Visits Related to Pain from Discharge Through Day 14

The number of unscheduled pain-related phone calls per subject after discharge through postsurgical Day 14 will be summarized with mean and SD and tabulated with n (%) of subjects with 0, 1, 2, 3, etc. phone call by treatment.

10.7.1.4.4 Number of Emergency Department (ED) Visits

The number of ED visits per subject after discharge will be summarized with mean and SD and tabulated with n (%) of subjects with 0, 1, 2, 3, etc. ED visits by treatment.

10.7.1.4.5 Persistent Opioid Use at Day 30

The number (and %) of subjects with persistent opioid use at day 30 after discharge will be summarized by treatment group.

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

The time spent (hours) in PACU is defined as date/time of admission to PACU minus date/time of discharge from PACU. This endpoint will be analyzed by treatment group using ANCOVA similar to Section 10.7.1.1**Error! Reference source not found.** Baseline value will be included in the model as covariate and assuming gamma (or normal) distribution and log link function

10.7.1.3.7 Time to First Unassisted Ambulation

Time to first unassisted ambulation will be computed in hours as the date and time of the first unassisted ambulation minus the date and time of the end of surgery. If a subject is not administered an ambulation, the time to first unassisted ambulation will be censored at 72 hours after surgery or at the time of last follow-up, whichever is early.

Time to first unassisted ambulation will be analyzed in two steps: Kaplan-Meier Curves for each treatment group with log-rank test for the between group difference. Cox proportional hazards regression with treatment and site as factors, age and height as covariates, followed by chi-squared test. The n (%) of subjects with unassisted ambulation as well as the n (%) of subjects without unassisted ambulation will be presented for each treatment group.

10.7.1.4.8Time to First Bowel Movement

Time to first bowel movement will be computed in hours as the date and time of the first bowel movement minus the date and time of the end of surgery. If a subject does not have bowel movement, the time to first bowel movement will be censored at 72 hours after surgery or at the time of last follow-up, whichever is early. Time to first bowel movement will be analyzed by the method similar to time to first unassisted ambulation.

10.8 Safety Analyses

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

10.8.1 Adverse Events

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

An AE will be considered TEAE if it starts on/after the start time of the first study medication subject received. Specifically, if subjects receive study medications according to the protocol, Group 1 and 2 subjects will use Duramorph and Group 3 subjects will use EXPAREL start time for reference.

If an AE has a partial onset date and time the imputed start dates and time will be used to determine treatment-emergence (Section 10.1.1.5). All AE summaries will present TEAEs only. AEs that are not treatment-emergent will be included in listings but not summarized.

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

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

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

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

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

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

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

Table 3. Adverse Events of Special Interest

Group	MedDRA System Organ Class	MedDRA Preferred Terms
FALL	Injury, poisoning and procedural complications	Fall
LAST	Cardiac Disorders	Arrhythmia
	Cardiac Disorders	Atrial Fibrillation
	Cardiac Disorders	Atrial Tachycardia
	Cardiac Disorders	Atrioventricular Block
	Cardiac Disorders	Atrioventricular Block First Degree
	Cardiac Disorders	Bradycardia
	Cardiac Disorders	Bundle Branch Block Left
	Cardiac Disorders	Bundle Branch Block Right
	Cardiac Disorders	Cardiac Arrest
	Cardiac Disorders	Cardiac Failure Acute
	Cardiac Disorders	Cardiac Failure Congestive
	Cardiac Disorders	Conduction Disorder

Group	MedDRA System Organ Class	MedDRA Preferred Terms
	Cardiac Disorders	Myocardial Infarction
	Cardiac Disorders	Sinus Arrest
	Cardiac Disorders	Sinus Arrhythmia
	Cardiac Disorders	Sinus Bradycardia
	Cardiac Disorders	Sinus Tachycardia
	Cardiac Disorders	Supraventricular Tachyarrhythmia
	Cardiac Disorders	Supraventricular Tachycardia
	Cardiac Disorders	Tachyarrhythmia
	Cardiac Disorders	Tachycardia
	Cardiac Disorders	Ventricular Extrasystoles
	Cardiac Disorders	Ventricular Tachycardia
	Nervous System	Dizziness
	Nervous System	Dysgeusia
	Nervous System	Somnolence
	Nervous System	Tremors

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

10.8.2 Vital Signs

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

10.8.3 Interim Analysis

After approximately 20 subjects per treatment group were randomized and treated (i.e., a total of 60 subjects were treated in this study), a preplanned interim analysis was conducted in accordance with Amendments 1 & 2 of the study protocol and the 26Sep2019 Interim Analysis Plan. The decision from the interim analysis was made to enroll a total of at least 140 treated subjects.

11 SAMPLE SIZE CALCULATIONS

Assuming a log-normal distribution for total opioid consumption with a 70% coefficient of variation (CV), 5% alpha, an equal randomization ratio, and 80% power, a total of 77 subjects per treatment group will be sufficient to detect a 25% reduction in total opioid consumption. Assuming 5% of the subjects are not evaluable and one of the two EXPAREL groups will be dropped after interim analysis when a total of 60 subjects are treated, a total sample size of

approximately 182 treated subjects is needed. This sample size will be re-evaluated after the interim analysis.

12 REFERENCES

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

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

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

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

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

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

13 TIME AND EVENTS SCHEDULE OF STUDY PROCEDURES

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

Table 1. Assessment Schedule (Screening through 72 hours after Surgery)

Study Procedure	Within 30 days of scheduled surgery	Screening (up to 30 days prior to day of surgery)	Day 1			Hours after Surgery		
			OR	PACU	12 hr (± 1hr)	24 hr (± 1hr)	48 hr (± 2hr)	72 hr (± 4hr)
Explain study purpose and procedures; obtain signed ICF	X[1]	X[1]						
Assess/confirm eligibility		X	X					
Record/confirm medical and surgical history		X	X					
Record prior and concomitant medications		X	X					
Record demographics and baseline characteristics		X						
Measure vital signs (blood pressure, heart rate, respiratory rate, and temperature)		X[2]	X	X[11]		X	X	X[3]
Measure pulse oximetry per SOC[10]			←	———	———	→		
Physical examination (according to the investigational site's SOC)		X	X					
Drug screen/alcohol test		X						
Clinical laboratory tests (hematology and chemistry; Appendix 5)[4]		X						
12-lead electrocardiogram		X						
Explain ePRO device and expectations of the subject regarding the device		X						
Randomize subject and prepare study drug			X					
Administer intrathecal preservative-free morphine injection in conjunction with single-shot spinal anesthesia per the treatment group (Section 13.4)			X					
Record surgery start and stop times			X					
Perform TAP needle placement and saline hydrodissection under ultrasound guidance using up to 10 mL normal saline **(per the treatment group)**				X				
Capture ultrasound image or video of the TAP needle placement after saline hydrodissection				X				
Perform 2-point classic TAP infiltration no more than 90 min after skin-incision closure of the C-section **(per the treatment group)**				X				
Take ultrasound image of the 2-point classic TAP needle placement after study drug infiltration				X				
Record start and stop times of study drug infiltration				X				
Record intraoperative opioid medications administered and doses			X					

Study Procedure	Within 30 days of scheduled surgery	Screening (up to 30 days prior to day of surgery)	Day 1			Hours after Surgery		
			OR	PACU	12 hr (± 1hr)	24 hr (± 1hr)	48 hr (± 2hr)	72 hr (± 4hr)
Record date, time in and out of the PACU				X				
Record SFQ (Appendix 6)		X						
Record **scheduled** 10 cm VAS pain intensity scores (General and Site of Incision) at rest through ePRO[5,6,7] (Appendix 1)					X	X	X	X
Record 10 cm VAS pain intensity (through ePRO) **immediately prior to any postsurgical opioid medication** administered while in the hospital (Appendix 1)				X	X	X	X	X
Record date, time, and dose of all postsurgical pain medication[8]				X	X	X	X	X
Record date, time, and dose of all standardized multimodal pain medications administered				X	X	X	X	X
Record date and time of first unassisted ambulation				X	X	X	X	X
Record date and time of first bowel movement				X	X	X	X	X
Assess itching (Numeric Rating Scale of 0 to 10)		X		X[11]	X	X	X	X
Record overall rating of subject's satisfaction with postsurgical pain control through ePRO (Appendix 3)								X[3]
Record RCSS through ePRO (Appendix 4)						X	X	X[3]
Record ORSDS through ePRO (Appendix 7)						X	X	X
Assess discharge readiness[9] (Appendix 2)						X	X	X
Record concomitant medications for treatment of AEs		X	X	X	X	X	X	X
Record AEs/SAEs (starting at signing of ICF)		X	X	X	X	X	X	X

1. Potential participants may provide informed consent up to 30 days before their scheduled surgery. If a subject can only be screened on the day of surgery, the consent process must be started at least 24 hours prior to the day of surgery in order to ensure ample time for the subject to review the ICF and have all her questions answered by the investigator/study staff prior to providing informed consent. Screening procedures that are SOC at the institution may be completed prior to written informed consent. Any screening procedures that are not SOC, must be completed after written informed consent is provided and prior to surgery.
   If a subject can only be screened on the day of surgery, the informed consent process must still be started at least 24 hours prior to the conduct of any screening procedures that are not considered SOC at the institution and such procedures may not be performed until written informed consent is provided.
2. Vital signs at screening will include height, weight, blood pressure, heart rate, respiratory rate, and temperature.
3. At 72 hours postsurgery or prior to hospital discharge, whichever occurs first.
4. Clinical laboratory tests will be conducted in accordance with the investigator's SOC, including direct bilirubin; either gamma-glutamyl transpeptidase and lactate dehydrogenase or alanine transaminase and aspartate transaminase; and either serum creatinine or blood urea nitrogen.
5. To assess pain intensity (VAS) general and at incision site at rest, the subject should rest quietly in a supine or seated position that does not exacerbate her postsurgical pain for 3-5 minutes before entering the pain score. This assessment should not be completed immediately following assessment of ambulation.
6. If a subject is discharged prior to any of the scheduled VAS assessments (general and at incision site) to be collected at 12 to 72 hours after surgery, a member of the study site staff will contact the subject at the appropriate scheduled times (i.e., the time of each assessment scheduled to be collected that occurs after hospital discharge) to remind her to complete the VAS and ORSDS assessments and to record the scheduled assessments in the device. This will ensure that, for any subject discharged prior to 72 hours, all VAS and ORSDS assessments required for calculation of the study endpoints are captured. These phone calls will only be made if a subject is discharged prior to 72 hours.

7. For pain intensity scores at 12, 24, 48, or 72 hours, if the subject is sleeping, do not wake her to assess pain. If she awakens within the assessment window (i.e., 1 hour for the 12- and 24-hour assessments, 2 hours for the 48-hour assessments, and 4 hours for the 72-hour assessments), a pain score may be collected then.
8. Subjects should only receive opioid pain medication (e.g., morphine, hydromorphone [Dilaudid], oxycodone) upon request for breakthrough pain.
9. Discharge readiness will be assessed at 24, 48, and 72 hours, or hospital discharge, or until the subject attains score of 9, whichever occurs first.
10. Pulse oximetry measured once prior to surgery and per your site's SOC from surgery end up to 24 hours.
11. Assess vital signs (blood pressure, heart rate, respiratory rate, and temperature) and itching in PACU prior to PACU discharge.

Note: No more than 30 days should pass between signing of the ICF and performance of the surgery. Screening on the day of surgery will be permitted but is discouraged.

Note: The end of surgery is defined as the time of skin-incision closure of the C-section wound (following delivery and prior to TAP infiltration).

AE=adverse event; C-section=cesarean section; ePRO=electronic patient-reported outcome; hr=hour(s); ICF=informed consent form; OR=operating room; ORSDS=Opioid Related Symptom Distress scale; PACU=post-anesthesia care unit; RCSS=Recovery from Cesarean Section scale; SAE=serious adverse event; SFQ=Surgical Fear Questionnaire; SOC=standard of care; TAP= transversus abdominis plane; VAS=visual analog scale

14 OPIOID RELATED SYMPTOM DISTRESS SCALE (ORSDS)

Symptoms	Did not have	(If yes), how often did you have it?				(If yes), how severe was it usually?				(If yes), how much did it distress or bother you?				
		1 Rarely	2 Occasionally	3 Frequently	4 Almost Constantly	1 Slight	2 Moderate	3 Severe	4 Very Severe	0 Not at all	1 A little Bit	2 Somewhat	3 Quite a Bit	4 Very Much
Fatigue	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Drowsiness	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Inability to concentrate	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Nausea	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Dizziness	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Constipation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Itching	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Difficulty with urination	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Confusion	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Retching/vomiting	☐	__ # of episodes				☐	☐	☐	☐	☐	☐	☐	☐	☐

15 LAYOUT OF TABLES, LISTINGS AND FIGURES

The following are planned summary tables. Tables will be numbered according to the nomenclature used to support the CSR. The final table numbering may be different from the SAP. No amendment will be made for changes in table numbering. All headers, titles, footnotes, and footers specified in the table mock-ups will be displayed in the produced output unless otherwise specified. Notes to programmers will not be included in the tables.

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

Percentages should not appear if the count is zero.

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

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

Titles on the TLFs in the mock-ups are presented left-justified as a single line of text. However, the presentation for final TFLs should be center-justified with the TLF number on one line and the remaining titles on multiple lines of text where the line breaks are delimited by hyphens (-) in the TLF mock-ups titles. For example, for Table 14.2-1.1a the title in the mock-up appears as:

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

but should appear as follows on the final TLF:

```
Table 14.2-1.1a

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

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

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

All tables will present treatment Active (for EXPAREL+50 mcg Duramorph or EXPAREL) and 150 mcg Duramorph (SOC) as separate columns.

On all figures, EXPAREL+50 mcg Duramorph will be represented in red with solid lines and dots, EXPAREL will be represented in blue with solid lines and filled squares and 150 mcg Duramorph (SOC) will be represented in black with solid lines and filled diamonds.

On all listings the treatments, in the order of appearance, are: EXPAREL+50 mcg Duramorph, EXPAREL, 150 mcg Duramorph (SOC)and, if applicable, NOT RANDOMIZED. Always insert a page break between treatments.

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

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

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

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

16 LIST OF TABLES

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Table 14.1-1: Summary of Subject Disposition – All Screened Subjects

Site: Overall

	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)	Total (N=XX) n (%)
Screened [1]				xx
Screen Failure				xx (xx.x)
Enrolled				xx (xx.x)
Randomized	xx	xx	xx	xx
Not Treated	xx	xx	xx	xx
Treated	xx	xx	xx	xx
TAP Infiltration Error per Ultrasound Image	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Safety Analysis Set [2]#	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Efficacy Analysis Set [3]@	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol				
Enrolled under Protocol Amendment2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Enrolled under Protocol Amendment1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Enrolled under Original Protocol				
Completed Study@	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued from Study@	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reasons for Discontinuation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of Efficacy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to Follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal by Subject	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

= as treated @ = as randomized
[1] Signed the informed consent form [2] Received study drug [3] Received study drug and surgery
Percentages for screen failure and enrolled based on number screened; others on number randomized.

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.1-2.1: Summary of Subject Demographics – Efficacy Analysis Set

Site: Overall

	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)	Total (N=XX)
Age (yrs)	n	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Sex					
Female	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Male	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity					
Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race					
American Indian/Alaska Native	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black/African American	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
White	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian/Pacific Islander	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

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

Use this mock-up also for table:

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

Table 14.1-2.3: Summary of Subject Demographics – Safety Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

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

		150 mcg Duramorph (SOC) (N=XX)	EXPAREL+50mcg Duramorph (N=XX)	EXPAREL (N=XX)	Total (N=XXX)
ASA Class	2 – n (%)	xx	xx	xx	xx
	3 – n (%)	xx.x	xx.x	xx.x	xx.x
	4 – n (%)	x.xx	x.xx	x.xx	x.xx
		xx.x	xx.x	xx.x	xx.x
		xx, xx	xx, xx	xx, xx	xx, xx
ECG Interpretation	Normal – n (%)	xx	xx	xx	xx
	Abnormal, NCS – n (%)	xx.x	xx.x	xx.x	xx.x
	Abnormal, CS – n (%)	x.xx	x.xx	x.xx	x.xx
		xx.x	xx.x	xx.x	xx.x
		xx, xx	xx, xx	xx, xx	xx, xx
Height (cm)	n	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Weight (kg)	n	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
BMI (kg/m2)	n	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx

		150 mcg Duramorph (SOC) (N=XX)	EXPAREL+50mcg Duramorph (N=XX)	EXPAREL (N=XX)	Total (N=XXX)
Direct Bili (unit)	n	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
GGT (unit)	n	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
LDH (unit)	n	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
ALT (unit)	n	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
AST (unit)	n	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
BUN (unit)	n	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx

	150 mcg Duramorph (SOC) (N=XX)	EXPAREL+50mcg Duramorph (N=XX)	EXPAREL (N=XX)	Total (N=XXX)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx

CS = clinically significant. NCS = not clinically significant.

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

Table 14.1-3.3: Summary of Subject Baseline Characteristics – Safety Analysis Set

Table 14.1-4.1: Summary of Subject Surgical Fear Questionnaire – Efficacy Analysis Set

		150 mcg Duramorph (SOC) (N=XX)	EXPAREL+50mcg Duramorph (N=XX)	EXPAREL (N=XX)	Total (N=XXX)
1. I am afraid of operation	n	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
2. I am afraid of the anesthesia	n	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
3. I am afraid of the pain after the operation	n	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
4. I am afraid of the unpleasant side effects (like nausea) after the operation		xx	xx		xx
	n			xx	
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
5. I am afraid my health will deteriorate because of the operation		xx	xx		xx
	n			xx	

	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
6. I am afraid the operation will fail		xx	xx		xx
	n			xx	
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
8. I am afraid of the long duration of the rehabilitation after the operation		xx	xx		xx
	n			xx	
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx

0 = not at all afraid, 10 = very afraid.

Table 14.1-4.2: Summary of Subject Surgical Fear Questionnaire – Sensitivity Analysis Set

Table 14.1-4.3: Summary of Subject Surgical Fear Questionnaire – Safety Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.1-5.1: Summary of Surgery Characteristics – Efficacy Analysis Set

Characteristic	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)	Total (N=XX)
Duration of Surgery (hours)	n	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	xx	xx	xx	xx
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Type of Anesthesia					
General	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Spinal	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other	N (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Intraoperative Med Used					
No	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Yes	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
CSE Anesthesia Performed					
No	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Yes	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Epidural Component of CSE					
No	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Yes	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Note, epidural component question is a follow up when CSE answer is Yes.

Use this mock-up also for tables:

Table 14.1-5.2: Summary of Surgery Characteristics – Sensitivity Analysis Set

Table 14.1-5.3: Summary of Surgery Characteristics – Safety Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.1-6.1: Incidence of Intraoperative Medications - Efficacy Analysis Set

Anatomical Therapeutic Class (ATC) Preferred Name	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)	Total (N=XX) n (%)
Subjects taking at least one medication	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PN1.1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PN1.2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PN2.1	xx (xx.x)	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)	xx (xx.x)	xx (xx.x)
ETC.				

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

Table 14.1-6.2: Incidence of Intraoperative Medications - Safety Analysis Set
T

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

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

Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
LS Mean [1]	xxx.x	xxx.x	xxx.x
Standard Error of LS Mean [1]	xxx.xx	xxx.xx	xxx.xx
% Reduction [2]	xxx.x	xxx.x	
LSM Treatment Difference [1][3]		xx.x	xx.x
95% Confidence Interval [1][3]		(xx.x, xx.x)	(xx.x, xx.x)
P-value, 1-sided [1][3]		0.xxx	0.xxx

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

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

Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
n	xx	xx	xx
GeoMean	xx.x	xx.x	xx.x
CV%	x.xx	x.xx	x.xx
Median	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx

GeoMean = Geometric mean. CV% = Coefficient of variation (%).

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-1.2a: Subgroup Analysis of Total Opioid Consumption (OMED mg) Through 72 hours by Age – Efficacy Analysis Set

Age	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
<35 years	LS Mean [1]	xxx.x	xxx.x	xxx.x
	Standard Error of LS Mean [1]	xxx.xx	xxx.xx	xxx.xx
	% Reduction [2]	xxx.x	xxx.x	
	LSM Treatment Difference [1][3]	xx.x	xx.x	
	95% Confidence Interval [1][3]	(xx.x, xx.x)	(xx.x, xx.x)	
	P-value, 1-sided [1][3]	0.xxx	0.xxx	
>= 35 years	LS Mean [1]	xxx.x	xxx.x	xxx.x
	Standard Error of LS Mean [1]	xxx.xx	xxx.xx	xxx.xx
	% Reduction [2]		xxx.x	xxx.x
	LSM Treatment Difference [1][3]		xx.x	xx.x
	95% Confidence Interval [1][3]		(xx.x, xx.x)	(xx.x, xx.x)
	P-value, 1-sided [1][3]		0.xxx	0.xxx

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-1.2b: Subgroup Summary of Total Opioid Consumption (OMED mg) Through 72 hours by Age – Efficacy Analysis Set

Age	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
<35 years	N	xx	xx	xx
	GeoMean	xxx.x	xxx.x	xxx.x
	CV%	xxx.xx	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x	xxx.x
	Min, Max	xx, xx	xx, xx	xx, xx
>= 35 years	N	xx	xx	xx
	GeoMean	xxx.x	xxx.x	xxx.x
	CV%	xxx.xx	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x	xxx.x
	Min, Max	xx, xx	xx, xx	xx, xx

GeoMean = Geometric mean. CV% = Coefficient of variation (%).

Use Table 14.2-1.3a and 1.3b shell for (see SAP Section 9.7.2.1.2 for subgroup categories)

Table 14.2-1.3a: Subgroup Analysis of Total Opioid Consumption (OMED mg) Through 72 hours by Race – Efficacy Analysis Set

Table 14.2-1.3b: Subgroup Summary of Total Opioid Consumption (OMED mg) Through 72 hours by Race – Efficacy Analysis Set

Table 14.2-1.4a: Subgroup Analysis of Total Opioid Consumption (OMED mg) Through 72 hours by BMI Status – Efficacy Analysis Set

Table 14.2-1.4b: Subgroup Summary of Total Opioid Consumption (OMED mg) Through 72 hours by BMI Status – Efficacy Analysis Set

Table 14.2-1.5a: Subgroup Analysis of Total Opioid Consumption (OMED mg) Through 72 hours by Number of Prior C-Sections – Efficacy Analysis Set

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

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

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

Table 14.2-1.7a: Subgroup Analysis of Total Opioid Consumption (OMED mg) Through 72 hours by Anxiety Medical History – Efficacy Analysis Set

Table 14.2-1.7b: Subgroup Summary of Total Opioid Consumption (OMED mg) Through 72 Hours by Anxiety Medical History – Efficacy Analysis Set

Table 14.2-1.8a: Analysis of Total Opioid Consumption (OMED mg) Through 72 hours – Sensitivity Analysis Set

Table 14.2-1.8b: Summary of Total Opioid Consumption (OMED mg) Through 72 Hours - Sensitivity Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-2a: Analysis of Average Itching Scores Through 72 hours – Efficacy Analysis Set

Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
LS Mean [1]	xxx.x	xxx.x	xxx.x
Standard Error of LS Mean [1]	xxx.xx	xxx.xx	xxx.xx
LSM Treatment Difference [1][2]		xx.x	xx.x
95% Confidence Interval [1][2]		(xx.x, xx.x)	(xx.x, xx.x)
P-value, 1-sided [1][2]		0.xxx	0.xxx

[1] From the Mixed Models.
[2] Test of Ha: LSM (Active) < LSM (150 mcg Duramorph (SOC)).

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-2b: Summary of Average Itching Scores Through 72 hours – Efficacy Analysis Set

Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Median	xx	xx	xx
Min, Max	xx, xx	xx, xx	xx, xx

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-3.1a: Analysis of Average Postsurgical Itching Scores Through 12, 24 and 48 Hours - Efficacy Analysis Set

Timepoint	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
12 hours	LS Mean [1]	xxx.x	xxx.x	xxx.x
	Standard Error of LS Mean	xxx.xx	xxx.xx	xxx.xx
	LSM Treatment Difference [1]		xx.x	xx.x
	95% Confidence Interval		(xx.x, xx.x)	(xx.x, xx.x)
	P-value, 1-sided [2]		0.xxxx	0.xxxx
24 hours				
48 hours				

[1] From the MMRM with age, height, treatment, site, timepoint and treatment-by-timepoint as factors and subjects as repeated measure unit over timepoints.
[2] Test of Ha: LSM (Active) < LSM (150 mcg Duramorph [SOC]).

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-3.1b: Summary of Average Postsurgical Itching Scores Through 12, 24 and 48 hours - Efficacy Analysis Set

Timepoint	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
12 hours	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx	xx	xx
	Min, Max	xx, xx	xx, xx	xx, xx
24 hours				
48 hours				

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

Table 14.2-3.2a: Analysis of Total Opioid Consumption (OMED mg) Through 24 and 48 hours, Day 7 (168 hours) and Day 14 (336 hours) - Efficacy Analysis Set

	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
24 hrs	LS Mean [1]	xxx.x	xxx.x	xxx.x
	Standard Error of LS Mean [1]	xxx.xx	xxx.xx	xxx.xx
	% Reduction [2]		xxx.xx	xxx.xx
	LSM Treatment Difference [1][3]		xx.x	xx.x
	95% Confidence Interval [1][3]		(xx.x, xx.x)	(xx.x, xx.x)
	P-value, 1-sided [1][3]		0.xxx	0.xxx
48 hrs	LS Mean [1]	xxx.x	xxx.x	xxx.x
	Standard Error of LS Mean [1]	xxx.xx	xxx.xx	xxx.xx
	% Reduction [2]		xxx.xx	xxx.xx
	LSM Treatment Difference [1][3]		xx.x	xx.x
	95% Confidence Interval [1][3]		(xx.x, xx.x)	(xx.x, xx.x)
	P-value, 1-sided [1][3]		0.xxx	0.xxx

. . .

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

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

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

Table 14.2-3.2b: Summary of Total Opioid Consumption (OMED mg) Through 24 and 48 hours, Day 7 (168 hours) and Day 14 (336 hours) - Efficacy Analysis Set

Time Interval	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
24 hrs	n	xx	xx	xx
	GeoMean	xxx.x	xxx.x	xxx.x
	CV%	xxx.xx	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x	xxx.x
	Min, Max	xx, xx	xx, xx	xx, xx
48 hrs	n	xx	xx	xx
	GeoMean	xxx.x	xxx.x	xxx.x
	CV%	xxx.xx	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x	xxx.x
	Min, Max	xx, xx	xx, xx	xx, xx

. . .

GeoMean = Geometric mean. CV% = Coefficient of variation (%).

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-3.3a1: Analysis of Average VAS Pain Intensity Scores Through 72 Hours After Surgery or Hospital Discharge Whichever Occurs First (General Pain) - Efficacy Analysis Set

Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
LS Mean [1]	xxx.x	xxx.x	xxx.x
Standard Error of LS Mean	xxx.xx	xxx.xx	xxx.xx
LSM Treatment Difference [1]		xx.x	xx.x
95% Confidence Interval [2]		(xx.x, xx.x)	(xx.x, xx.x)
Noninferiority Test P-value, 1-sided		0.xxx	0.xxx
Superiority Test P-value, 1-sided			

LS = Least Squares;
VAS = 10 cm visual analog scale for pain, where 0 = no pain and 10 = worst possible pain.
[1] From an ANCOVA with main effects of treatment and site and covariates of age and height.
[2] The non-inferiority of Active to 150 mcg Duramorph (SOC)is demonstrated if the upper limit is <=0.5. The superiority is demonstrated if the upper limit is <0.

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-3.3b1: Summary of Average VAS Pain Intensity Scores Through 72 Hours After Surgery or Hospital Discharge Whichever Occurs First (General Pain) – Efficacy Analysis Set

Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Median	xx	xx	xx
Min, Max	xx, xx	xx, xx	xx, xx

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-3.4a1: Analysis of Average VAS Pain Intensity Scores Through 24 And 48 (General Pain) - Efficacy Analysis Set - Multiple Imputation Results

Timepoint	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
24 hours	LS Mean [1]	xxx.x	xxx.x	xxx.x
	Standard Error of LS Mean	xxx.xx	xxx.xx	xxx.xx
	LSM Treatment Difference [1]	xx.x	xx.x	
	95% Confidence Interval [2]	(xx.x, xx.x)	(xx.x, xx.x)	
	Noninferiority Test P-value, 1-sided	0.xxx	0.xxx	
	Superiority Test P-value, 1-sided	0.xxx	0.xxx	
48 hours	LS Mean [1]	xxx.x	xxx.x	xxx.x
	Standard Error of LS Mean	xxx.xx	xxx.xx	xxx.xx
	LSM Treatment Difference [1]		xx.x	xx.x
	95% Confidence Interval [2]		(xx.x, xx.x)	(xx.x, xx.x)
	Noninferiority Test P-value, 1-sided		0.xxx	0.xxx
	Superiority Test P-value, 1-sided		0.xxx	0.xxx

LS = Least Squares;
VAS = 10 cm visual analog scale for pain, where 0 = no pain and 10 = worst possible pain.
[1] From an ANCOVA with main effects of treatment and site and covariates of age and height.
[2] The non-inferiority of Active to 150 mcg Duramorph (SOC) is demonstrated if the upper limit is <=0.5. The superiority is demonstrated if the upper limit is <0.

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-3.4b1: Summary of Average VAS Pain Intensity Scores Through 24 and 48 (General Pain) - Efficacy Analysis Set

Timepoint	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
24 hours	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx	xx	xx
	Min, Max	xx, xx	xx, xx	xx, xx
48 hours				

Table 14.2-3.3a2: Analysis of Average VAS Pain Intensity Scores Through 72 Hours After Surgery or Hospital Discharge Whichever Occurs First (Pain at Incision Site) - Efficacy Analysis Set

Table 14.2-3.3b2: Summary of Average VAS Pain Intensity Scores Through 72 Hours After Surgery or Hospital Discharge Whichever Occurs First (Pain at Incision Site) – Efficacy Analysis Set

Table 14.2-3.4a2: Analysis of Average VAS Pain Intensity Scores Through 24 And 48 (Pain at Incision Site) - Efficacy Analysis Set - Multiple Imputation Results

Table 14.2-3.4b2: Summary of Average VAS Pain Intensity Scores Through 24 and 48 (Pain at Incision Site) - Efficacy Analysis Set

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-411
Table 14.2-3.5: Analysis of Postsurgical Opioid-Free and Opioid-Sparing Subjects Through 72 hours - Efficacy Analysis Set

	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
Opioid-free				
No Opioid-Free Percentage [1]	(%)	xx.x	xx.x	xx.x
Opioid-Free Percentage	(%)	xx.x	xx.x	xx.x
	Odds Ratio [2]	xx.x	xx.x	
	95% CI for Odds Ratio	(xx.x, xx.x)	(xx.x, xx.x)	
	P-value, 1-sided [3]	0.xxxx	0.xxxx	
Opioid-sparing				
No Opioid-sparing Percentage [1]	(%)	xx.x	xx.x	xx.x
Opioid-sparing Percentage	(%)	xx.x	xx.x	xx.x
	Odds Ratio [2]		xx.x	xx.x
	95% CI for Odds Ratio		(xx.x, xx.x)	(xx.x, xx.x)
	P-value, 1-sided [3]		0.xxxx	0.xxxx
	P-value, 1-sided [3]		0.xxxx	0.xxxx

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-3.6a: Analysis of Opioid Related Symptom Distress Scale (ORSDS) at 12, 24, 48 and 72 hours - Efficacy Analysis Set

Composite Score

Timepoint	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
12 hours	LS Mean [1]	xxx.x	xxx.x	xxx.x
	Standard Error of LS Mean	xxx.xx	xxx.xx	xxx.xx
	LSM Treatment Difference [1]		xx.x	xx.x
	95% Confidence Interval		(xx.x, xx.x)	(xx.x, xx.x)
	P-value, 1-sided [2]		0.xxxx	0.xxxx
24 hours				
48 hours				
72 hours				

[1] From a Mixed Models with main effects of treatment visit and treatment by visit as covariates.
[2] Test of Ha: LSM (Active) < LSM (SOC). For Question 7 score, Test of Ha: LSM (Active) > LSM (SOC).

Note to programmer: *Timepoints to appear on this table, in order, are 24, 48 and 72 hours.*

First page is Composite Score, followed by Fatigue Score, Drowsiness Score, Inability to Concentration Score, Nausea Score, Constipation Score, Itching …, Difficult with Urination Score, Confusion Score, and Retching/Vomiting Score.

Each symptom score is the average of frequency, severity, and botherness dimension scores.

Do not split a question's statistics across pages.

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-3.6b: Summary of Opioid Related Symptom Distress Scale (ORSDS) at 12, 24, 48 and 72 hours - Efficacy Analysis Set

Composite Score

Timepoint	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
24 hours	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx
	Median	xx	xx	xx
	Min, Max	xx, xx	xx, xx	xx, xx
48 hours				
72 hours				

Repeat for symptom scores

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-3.7a: Analysis of Subjects Meeting Modified Post Anesthesia Discharge Scoring System (MPADSS) Criteria for Discharge Readiness at 12, 24, 48 and 72 hours - Efficacy Analysis Set

Time Point	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
24	Odds Ratio [3]	xx.xx	xx.xx	
	95% CI for Odds Ratio	xx.xxx	xx.xxx	
	P-value, 1-sided [4]	0.xxxx	0.xxxx	
Etc.	Odds Ratio		xx.xx	xx.xx
	95% CI for Odds Ratio		xx.xxx	xx.xxx
	P-value, 1-sided		0.xxxx	0.xxxx

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

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-3.7b: Summary of Subjects Meeting Modified Post Anesthesia Discharge Scoring System (MPADSS) Criteria for Discharge Readiness at Each Assessed Timepoint – Efficacy Analysis Set

Time Point	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
24	Criterion Met [1] (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Criterion not Met (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.	Criterion Met (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Criterion not Met (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

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

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-3.8: Summary of Overall Assessment of Subject's Satisfaction with Pain Control at 72 hours or Hospital Discharge, Whichever Occurs First After Surgery – Efficacy Analysis Set

Score	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
Summary	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
	P-value, 2-sided[1]	0.xxxx	0.xxxx	
Score				
1: Extremely dissatisfied	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2: Dissatisfied	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3: Neither satisfied nor dissatisfied	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
4: Satisfied	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
5: Extremely Satisfied	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

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

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

Table 14.2-3.9: Summary of Recovery from Caesarean Section Scale at 24, 48, and 72 Hours or Hospital Discharge, Whichever Comes First – Efficacy Analysis Set

Question	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
1. I recovered quickly from my cesarean	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
2. I was able to get out of bed soon after my cesarean	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
3. My mobility was seriously affected by the cesarean	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
4. The cesarean interfered with my ability to care for my baby	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
5. The cesarean prevented me from	n	xx	xx	xx

Question	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
feeding my baby				
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
6. I was able to change my baby soon after the cesarean		xx	xx	
	n			xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
7. I was able to care for my own hygiene needs soon after surgery		xx	xx	
	n			xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
8. The pain from the surgery prevented me from doing what I wanted		xx	xx	
	n			xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
I was tired for a long time after surgery		xx	xx	
	n			xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx

Question	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx

0 = strongly disagree and 7 = strongly agree.

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-4.1a: Analysis of Total Postsurgical Opioid Consumption (mg) in Morphine Equivalents Through 72 hours – Efficacy Analysis Set

Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
LS Mean [1]	xxx.x	xxx.x	xxx.x
Standard Error of LS Mean	xxx.xx	xxx.xx	xxx.xx
LSM Treatment Difference [1]		xx.x	xx.x
95% Confidence Interval [2]		(xx.x, xx.x)	(xx.x, xx.x)
Noninferiority Test P-value, 1-sided		0.xxx	0.xxx
Superiority Test P-value, 1-sided			

LS = Least Square;
[1] From an ANCOVA with main effects of treatment and site and covariates of age and height.
[2] The non-inferiority of Active to 150 mcg Duramorph (SOC)is demonstrated if the upper limit on logarithm scale is <=0.8. The superiority is demonstrated if the upper limit is <0.

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-4.1b: Summary of Total Postsurgical Opioid Consumption (mg) in Morphine Equivalents Through 72 hours – Efficacy Analysis Set

Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
n	xx	xx	xx
GeoMean	xx.x	xx.x	xx.x
CV%	xx.xx	xx.xx	xx.xx
Median	xx	xx	xx
Min, Max	xx, xx	xx, xx	xx, xx

GeoMean = Geometric mean. CV% = Coefficient of variation (%).

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

Table 14.2-4.2: Summary of Length of Hospital Stay – Efficacy Analysis Set

Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+ 50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
N	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x
SD	xxx.xx	xxx.xx	xxx.xx
Median	xxx.x	xxx.x	xxx.x
Min, Max	xx, xx	xx, xx	xx, xx

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

Table 14.2-4.3: Summary of Number of Unscheduled Phone Calls or Office Visits Related to Pain from Discharge Through Day 14 – Efficacy Analysis Set

Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
N	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x
SD	xxx.xx	xxx.xx	xxx.xx
Median	xxx.x	xxx.x	xxx.x
Min, Max	xx, xx	xx, xx	xx, xx

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

Table 14.2-4.4: Summary of Number of Emergency Department (ED) Visits – Efficacy Analysis Set

Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
N	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x
SD	xxx.xx	xxx.xx	xxx.xx
Median	xxx.x	xxx.x	xxx.x
Min, Max	xx, xx	xx, xx	xx, xx

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-4.5: Analysis of Subjects with Persistent Opioid Use at Day 30 - Efficacy Analysis Set

	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
NO	xx.x	xx.x	xx.x
Yes	xx.x	xx.x	xx.x

Note, persistent opioid use is defined for subjects who answered Yes to the question of opioid use at Day 30.

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

Table 14.2-4.6a: Analysis of Time Spent in Post-Anesthesia-Care Unit (PACU) – Efficacy Analysis Set

Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
LS Mean [1]	xxx.x	xxx.x	xxx.x
Standard Error of LS Mean [1]	xxx.xx	xxx.xx	xxx.xx
LSM Treatment Difference [1][2]		xx.x	xx.x
95% Confidence Interval [1][2]		(xx.x, xx.x)	(xx.x, xx.x)
P-value, 1-sided [1][2]		0.xxxx	0.xxxx

[1] From the gamma (or normal) distribution and log link function and main effects of treatment and site and covariates of age and height on time spent in PACU.
[2] Test of Ha: LSM (Active) < LSM (150 mcg Duramorph (SOC)).

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

Table 14.2-4.6b: Summary of Time Spent in Post-Anesthesia-Care Unit (PACU) – Efficacy Analysis Set

Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
N	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x
SD	xxx.xx	xxx.xx	xxx.xx
Median	xxx.x	xxx.x	xxx.x
Min, Max	xx, xx	xx, xx	xx, xx

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-4.7: Analysis of Time to First Unassisted Ambulation - Efficacy Analysis Set

	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
0-72 hours				
Number of Subjects with				
Ambulation (observed)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No Ambulation (censored)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Time to Ambulation				
Quartiles [1]				
First (25% Ambulated)	Estimate	xx.xx	xx.xx	xx.xx
	(95% CI)	(xx.xx, xx.xx)	(xx.xx, xx.xx)	(xx.xx, xx.xx)
Median (50% Ambulated)	Estimate	xx.xx	xx.xx	xx.xx
	(95% CI)	(xx.xx,xx.xx)	(xx.xx,xx.xx)	(xx.xx,xx.xx)
Third (75% Ambulated)	Estimate	xx.xx	xx.xx	xx.xx
	(95% CI)	(xx.xx,xx.xx)	(xx.xx,xx.xx)	(xx.xx,xx.xx)
Minimum	Observed	xx.xx	xx.xx	xx.xx
Maximum	Observed	xx.xx*	xx.xx*	xx.xx
Log-rank p-value, 2-sided				
Cox regression Hazard Ratio[2]	Estimate	xx.xx	xx.xx	xx.xx
	(95% CI)	(xx.xx, xx.xx)	(xx.xx, xx.xx)	(xx.xx, xx.xx)
P-value, 2-sided			0.xxxx	0.xxxx

* indicates censored observation. CI = confidence interval

[1] Estimates from the Kaplan-Meier survival curve.

[2] P-value for the Active to SOC comparison using the Cox regression model with treatment and site as factors and age and height as covariates.

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Table 14.2-4.8: Summary of Time to First Bowel Movement - Efficacy Analysis Set

	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)
0-72 hours				
Number of Subjects with				
Bowel Movement (observed)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No Bowel Movement (censored)	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Time to Bowel Movement				
Quartiles [1]				
First (25% Bowel Movement)	Estimate	xx.xx	xx.xx	xx.xx
	(95% CI)	(xx.xx, xx.xx)	(xx.xx, xx.xx)	(xx.xx, xx.xx)
Median (50% Bowel Movement)	Estimate	xx.xx	xx.xx	xx.xx
	(95% CI)	(xx.xx,xx.xx)	(xx.xx,xx.xx)	(xx.xx,xx.xx)
Third (75% Bowel Movement)	Estimate	xx.xx	xx.xx	xx.xx
	(95% CI)	(xx.xx,xx.xx)	(xx.xx,xx.xx)	(xx.xx,xx.xx)
Minimum	Observed	xx.xx	xx.xx	xx.xx
Maximum	Observed	xx.xx*	xx.xx*	xx.xx
Log-rank p-value, 2-sided				
Cox regression Hazard Ratio[2]	Estimate	xx.xx	xx.xx	xx.xx
	(95% CI)	(xx.xx, xx.xx)	(xx.xx, xx.xx)	(xx.xx, xx.xx)
P-value, 2-sided			0.xxxx	0.xxxx

* indicates censored observation. CI = confidence interval

[1] Estimates from the Kaplan-Meier survival curve.

[2] P-value for the Active to SOC comparison using the Cox regression model with treatment and site as factors and age and height as covariates.

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

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

Number of	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)	Total (N=XX) n (%)
Subjects with Any TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Maximum Severity of Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Maximum Severity of Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Maximum Severity of Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
At Least One Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
At Least One Serious	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects Discontinued due to TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Died on Study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

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

Preferred Term	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)	Total (N=XX) n (%)
Subjects with ≥1 TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
...	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

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

System Organ Class Preferred Term	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)	Total (N=XX) n (%)
Subjects with ≥1 TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT1.1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT1.2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT2.1	xx (xx.x)	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)	xx (xx.x)	xx (xx.x)
ETC.				

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

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

System Organ Class Preferred Term	Worst Severity	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)	Total (N=XX) n (%)
Subjects with ≥1 TEAE	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC1	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT1.1	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT1.2	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

...

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

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

System Organ Class Preferred Term	Strongest Relation	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)	Total (N=XX) n (%)
Subjects with ≥1 TEAE	Not Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC1	Not Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT1.1	Not Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

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

Group Preferred Term	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)	Total (N=XX) n (%)
Subjects with ≥1 TEAESI	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
FALL	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cardiac TEAESI	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Angina	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Myocardial infarction	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
...				
Neurologic TEAESI	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Tinnitus	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Perioral numbness	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
...				

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

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

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

Heart Rate (bpm)

Timepoint	Value	Statistic	150 mcg Duramorph (SOC) (N=XX) n (%)	EXPAREL+50mcg Duramorph (N=XX) n (%)	EXPAREL (N=XX) n (%)	Total (N=XXX)
Baseline	Actual	n	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x
		SD	x.xx	x.xx	x.xx	x.xx
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
OR	Baseline [1]	n	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x
		SD	x.xx	x.xx	x.xx	x.xx
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
	Actual	n	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x
		SD	x.xx	x.xx	x.xx	x.xx
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
	Change	n	xx	xx	xx	xx
		Mean	xx.x	xx.x	xx.x	xx.x
		SD	x.xx	x.xx	x.xx	x.xx
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx

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

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

Note to programmer: *Use mock-up 14.1-6.1 for tables:*

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

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

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

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

17 LIST OF LISTINGS

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-1: Subject Disposition – All Randomized Subjects

TREATMENT: *treatment-name*

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

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-2: Randomization and Analysis Sets – All Randomized Subjects

	Randomization				
Subject	Date and Time	Number	Treatment Group	Safety	Efficacy
XXX-YYYY	DDMONYYYYTHH:MM	XXXXX	EXPAREL+50 mcg Duramorph	X	X
			EXPAREL		
			SOC		

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-3: Inclusion/Exclusion criteria – Failures – All Randomized Subjects

TREATMENT: *treatment-name*

Subject	Visit	Protocol Enrolled Under	Version	Criteria Not Met
XXX-YYYY	DDMONYYYY	Amendment 1		xxxxxxxxxx
		Amendment 2		

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-4: Demographics – All Randomized Subjects
TREATMENT: *treatment-name*

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

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-5: Height and Weight – All Randomized Subjects

TREATMENT: *treatment-name*

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-6: Surgery – All Randomized Subjects

TREATMENT: *treatment-name*

Subject	Date (Day)	Start Time	Stop Time	Duration (hrs)	Location	Incision Length (cm)	SOC Admin Time	Anesthesia Type	Intraoperative Medications Administered	CSEPerformed/	Component of CSE Administered
XXX-YYYY	DDMONYYYY (XX)	HH:MM	HH:MM	X.X	XXXXX	XX.X	HH:MM				
									Yes	Yes	No
									No	Yes	Yes
										No	

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-7: Visual Analog Scale (VAS) – All Randomized Subjects

TREATMENT: *treatment-name*

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

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

Note to programmer: *Sort by VAS collection date and time. If VAS was taken due to rescue medication dosing, put RESCUE in scheduled column and hours from dose in actual column – leave deviation column blank. Do not split a subject's data across pages if it can be avoided. Pain-free will have Y if VAS ≤ 1.5 otherwise blank.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-8.1: Postsurgical Total Opioid Dose (OMED mg) and O -free Status – All Randomized Subjects

Subject	0 to ≤72 hrs or at hospital discharge	Opioid-Free
XXX-YYYY	XXXX.X	NO
XXX-YYYY	-	YES

Total dose is dose from end of surgery through timepoint.

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-8.2: Postsurgical Opioid Dosing – All Randomized Subjects

TREATMENT: *treatment-name*

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

Time to Postsurgical Opioid Dosing is time from end of surgery to Postsurgical Opioid medication dose.

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-9: Prescription Daily Pain Medication – All Randomized Subjects
TREATMENT: *treatment-name*

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

Time to dosing is time from end of surgery to pain medication dose.

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-10: Rescue Mediation – All Randomized Subjects

TREATMENT: *treatment-name*

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

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

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Listing 16.2-11: Opioid Related Symptom Distress Scale (ORSDS) – All Randomized Subjects

Treatment: *treatment-name*

Subject	Date and Time (Day)	Time point	Question	Symptoms	Answer	Score
XXX-YYYY	DDMONYYYYTHH:MM (XX)	24 hrs			Rarely	
			Fatigue	Frequency		1
				Severity	Slight	1
				Bothersomeness	Not at all	1
					Average	1
			Drowsiness	Frequency	Occasionally	2
				Severity	Severe	3
				Bothersomeness	Very Much	5
					Average	3.3
			Inability to Concentrate Nausea	Frequency		
				Severity		
				Bothersomeness		
			….	….		
					Composite Score	

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Listing 16.2-12.1: Recovery from Caesarean Section Scale (RCSS) – Question Text

Question No.	Question Text
1	I recovered quickly from my caesarean
2	I was able to get out of bed soon after my caesarean
3	My mobility was seriously affected by the caesarean
4	The caesarean interfered with my ability to care for my baby
5	The caesarean prevented me from feeding my baby
6	I was able to change my baby soon after the caesarean
7	I was able to care for my own hygiene needs soon after surgery
8	The pain from the surgery prevented me from doing what I wanted
9	I was red for a long home after surgery

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Listing 16.2-12.2: Recovery from Caesarean Section Scale (RCSS) – All Randomized Subjects

TREATMENT: *treatment-name*

	Assessment				Question									
Subject	Date and Time (Day)	Scheduled	Actual (hrs)	Deviation (hrs)	1	2	3	4	5	6	7	8	9	Total Score
XXX-YYYY	DDMONYYYYTHH:MM (XX)	72 hrs	XX.X	XX.X	X	X	X	X	X	X	X	X	X	XX
	DDMONYYYYTHH:MM (XX)	Early Discharge	XX.X	XX.X	X	X	X	X	X	X	X	X	X	XX

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Listing 16.2-13: Modified Post-Anesthesia Discharge Scoring System (MPADSS) – All Randomized Subjects

TREATMENT: *treatment-name*

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

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

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Listing 16.2-14.1: Surgical Fear Questionnaire (SFQ) – Question Text

Question No.	Question Text
1	I am afraid of the operation
2	I am afraid of the anesthesia
3	I am afraid of the pain after the operation
4	I am afraid of the unpleasant side effects (like nausea) after the operation
5	I am afraid my health will deteriorate because of the operation
6	I am afraid the operation will fail
7	I am afraid that I won’t recover completely from the operation
8	I am afraid of the long duration of the rehabilitation after the operaon

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Listing 16.2-14.2: Surgical Fear Questionnaire (SFQ) – All Randomized Subjects

TREATMENT: *treatment-name*

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

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-15: Pulse Oximetry (Log Form) – All Randomized Subjects

TREATMENT: *treatment-name*

Subject	Date and Time	Time Point	Oxygen Saturation (%)
			XX.X
XXX-YYYY	DDMONYYYYTHH:MM	0 hr	
		1 hr	XX.X
		2 hrs	XX.X
		3 hrs	XX.X

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Listing 16.2-16: Subject Satisfaction with Post-Surgical Pain Control at 72 hours – All Randomized Subjects

Treatment: *treatment-name*

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

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-17: Day 14 Phone Call – All Randomized Subjects

TREATMENT: *treatment-name*

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

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Listing 16.2-18: Vital Signs Assessment – All Randomized Subjects

TREATMENT: *treatment-name*

	Assessment				Heart Rate (bpm)		Blood Pressure (mmHg) Systolic		Diastolic	
Subject	Date and Time	Schedule (hrs)	Actual (hrs)	Dev. (hrs)	Actual	Change	Actual	Change	Actual	Change
XXX-YYYY	DDMONYYYYTHH:MM	Screening	-	-	XX	-	XXX	-	XX	-
	DDMONYYYYTHH:MM	OR	-	-	XX	XX	XXX	-X	XX	X
	DDMONYYYYTHH:MM	PACU	XXX.XX	XXX	XX	-XX	XXX	X	XX	-X
	DDMONYYYYTHH:MM	12 hr	XXX.XX	XXX	XX	-XX	XXX	X	XX	-X
	DDMONYYYYTHH:MM	24 hr	XXX.XX	XXX	XX	-XX	XXX	X	XX	-X
	DDMONYYYYTHH:MM	48 hr	XXX.XX	XXX	XX	-XX	XXX	X	XX	-X
	DDMONYYYYTHH:MM	72 hr	XXX.XX	XXX	XX	-XX	XXX	X	XX	-X

*=out of window @=potentially clinically significant value

Change is change from baseline (Preop).

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-19: Electrocardiogram Findings at Screening – Investigator Assessment – All Randomized Subjects

Treatment: *treatment-name*

Subject	Date and Time	Date	Time	Finding
XXX-YYYY	DDMONYYYYTHH:MM			Normal
XXX-YYYY	DDMONYYYYTHH:MM			Abnormal, clinically significant
XXX-YYYY	DDMONYYYYTHH:MM			Abnormal, not clinically significant
XXX-YYYY	DDMONYYYYTHH:MM			Normal
XXX-YYYY	DDMONYYYYTHH:MM			Normal

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414

Listing 16.2-20: Pain Intensity Scale - Timepoint Questions – All Randomized Subjects

Treatment: *treatment-name*

	Timepoint at Which Subjects was Asleep			
Subject	12 hrs	24 hrs	48 hrs	72 hrs
XXX-YYYY	Yes	Yes	Yes	Yes
	No	No	No	No
		Yes	Unknown	Unknown

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-21: Assessment of Itching – All Randomized Subjects

Treatment: *treatment-name*

Subject	Visit	Any Itching at Screening Visit?	Date/Time	Severity of Itching*	Reason Not Done
XXX-YYYY	Screening		DDMONYYYYTHH:MM	0	xxxxxxxxxxxxxxxxxxxx
	Day 1	No	DDMONYYYYTHH:MM	1	xxxxxxxxxxxxxxxxxxxx
	Day 1-3	Yes	DDMONYYYYTHH:MM	2	xxxxxxxxxxxxxxxxxxxx
		No	DDMONYYYYTHH:MM	3	xxxxxxxxxxxxxxxxxxxx
		Yes	DDMONYYYYTHH:MM	10	xxxxxxxxxxxxxxxxxxxx

*= 0= No Itching and 10= Worst Itch

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-22.1: All Adverse Events – All Randomized Subjects

Treatment: *treatment-name*

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

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

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

Listing 16.2-22.2: Treatment-emergent Adverse Events – All Randomized Subjects
Listing 16.2-22.3: All Serious Adverse Events – All Randomized Subjects
Listing 16.2-22.4: Treatment-emergent Adverse Events of Special Interest – All Randomized Subjects

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-23.1: Prior Medications – All Randomized Subjects

Treatment: *treatment-name*

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

ATC=Anatomical therapeutic class

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

Listing 16.2-23.2: Concomitant Medications – All Randomized Subjects

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-24: Medical History/Surgery – All Subjects

Treatment: *treatment-name*

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-25: Intraoperative Medications – Randomized Subjects

TREATMENT: *treatment-name*

Subject	Start Date/Time	End Date/Time	Administered	Name	Dose	Unit	Route
XXX-YYYY	DDMMYYYY/HH:MM	DDMMYYYY/HH:MM	YES	*OPIOID-NAME*	XXX.XX	(UNITS)	XXXX
XXX-YYYY			NO				

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-26: Study Drug Administration – Randomized Subjects

Subject	Treatment	Date	Start Time	Stop Time	Total Volume (mL)
XXX-YYYY	Right Study Drug Left Study Drug	DDMONYYYY	HH:MM	HH:MM	XXX

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-27: Standard of Care – Randomized Subjects

Subject	TAP Performed/Medication	Date	Start Time	Dose (Unit)
XXX-YYYY	Yes/XXXXXX	DDMONYYYY	HH:MM	Xxxxxx(xxx)
	No			

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-28: Physical Examination – Randomized Subjects

TREATMENT: *treatment-name*

Subject	Date/Time	Body System	Findings	Details if Abnormal	Reason Not Done
XXX-YYYY	DDMONYYYY	HH:MM	XXX	XXX	XXX

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-29: Urine Drug Screen, Alcohol Blood Test and Pregnancy Test – All Subjects

TREATMENT: *treatment-name*

Subject	Visit	Urine Drug	Blood Alcohol	Pregnancy
XXX-YYYY	Screening	XXXXXXXX	XXXXXXXX	XXXXXXXX
XXX-YYYY	Screening	XXXXXXXX	XXXXXXXX	XXXXXXXX
XXX-YYYY	Screening	XXXXXXXX	XXXXXXXX	XXXXXXXX
XXX-YYYY	Screening	XXXXXXXX	XXXXXXXX	XXXXXXXX

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-30: Admission and Discharge – Randomized Subjects

TREATMENT: *treatment-name*

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

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

Listing 16.2-31: Important Protocol Deviations - Randomized Subjects

TREATMENT: *treatment-name*

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

Note to programmer: Subjects may have multiple deviations. Sort deviations by subject and date. Select DVDECOD, eg, "Restricted Medications Taken", "Non-Compliance/Ultrasound", "Primary Efficacy Assessments", "Other Important Deviations", "Improper Informed Consent Procedure" as specified by the sponsor.

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-414
Listing 16.2-32: Ultrasound Collection – Randomized Subjects

TREATMENT: *treatment-name*

Subject	Ultrasound Guidance used to perform TAP needle placement/Reason if No	Ultrasound Image/Video captured of the TAP needle after saline hydrodissection		Ultrasound Image/Video captured of the TAP needle placement after study drug infiltration	
		Right Side/ Reason if No	Left Side/ Reason if No	Right Side/ Reason if No	Left Side/ Reason if No
XXX-YYYY	Yes	Yes	Yes	Yes	Yes
XXX-YYYY	No/xxxxxxx	No/xxxxxx	No/xxxxxx	No/xxxxxx	No/xxxxxx

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-327
Listing 16.2-33: Unique Adverse Events Terms and Associated Coded Terms

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

Coded using MedDRA v21.1.

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

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-327
Listing 16.2-34: Unique Medication Terms and Associated Coded Terms

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

Coded using WHO Drug Dictionary September 2018.

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

18 LIST OF FIGURES

Figure 1: Mean (+/- 95% CI) of VAS General Pain Intensity Over Time - Efficacy Analysis Set

Figure 2: Mean (+/- 95% CI) of VAS Incision Site Pain Intensity Over Time - Efficacy Analysis Set

Programming note: include all scheduled VAS pain scores