Pacira Pharmaceuticals, Inc.
EXPAREL

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STATISTICAL ANALYSIS PLAN

A Multicenter Study to Evaluate the Pharmacokinetics and Safety of EXPAREL for Postsurgical Analgesia in Pediatric Subjects Aged 6 to Less Than 17 Years

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LIST OF ABBREVIATIONS

Abbreviation	Description
ADL	Activities of daily living
AE	Adverse event
AESI	AE of special interest
ASA	American Society of Anesthesiology
ATC	Anatomical therapeutic class
AUC	Area under the curve
BLOQ	Below the limit of quantification
BMI	Body mass index
bpm	Beats per minute
CAS	Color Analog Scale
CI	Confidence interval
CMP	Complete metabolic panel
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
GM	Geometric Mean
hr, h	hour
ICF	Informed consent form
ICH	International Conference on Harmonization
IM	Intramuscular
IV	Intravenous
MedDRA	Medical dictionary for regulatory affairs
min	minutes
MED mg	Morphine equivalent dose in mg
n	Number of subjects
NCI	National Cancer Institute
NRS-R	Numerical Rating Scale at Rest
PK	Pharmacokinetics
PO	Oral
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TLF	Table, listings and figures
WHO	World Health Organization
WHO-DD	World Health Organization – Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analyses and reporting of the clinical study 402-C-319 titled "A Multicenter Study to Evaluate the Pharmacokinetics and Safety of EXPAREL® for Postsurgical Analgesia in Pediatric Subjects Aged 6 to Less Than 17 Years".

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

The purposes of this SAP are to:

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

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

The following documents were reviewed in preparation of this SAP:

- Original Protocol 402-C-319 issued on 01Oct2018.
- CRF version 4.0 issued on 17Mar2019.
- 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.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to evaluate the pharmacokinetics (PK) of EXPAREL in pediatric subjects aged 6 to less than 17 years undergoing various types of surgeries.

2.2 Secondary Objective

The secondary objective is to evaluate the safety of EXPAREL in pediatric subjects aged 6 to less than 17 years undergoing various types of surgeries.

3. STUDY OVERVIEW

This is a two-part study to evaluate the PK and safety of EXPAREL in pediatric subjects aged 6 to less than 17 years. Part 1 will evaluate the PK and safety in subjects aged 6 to less than 17 years, while Part 2 will assess the safety in subjects aged 6 to less than 17 years. This is also a two-group study. Group 1 will include subjects aged from 12 to <17 years old undergoing spine surgery. Group 2 will include subjects aged from 6 to <12 years old undergoing spine or cardiac surgery. (**Table 1**)

In Part 1, subject enrollment will be conducted in parallel to include the older age group (12 to <17 years old; Group 1) and the younger age group (6 to <12 years old; Group 2).

Subject enrollment for Part 2 (of each group) will commence upon completion of Part 1 (of that group). In Part 2, subject enrollment will be conducted in parallel to include the older age group (12 to <17 years old; Group 1) and the younger age group (6 to <12 years old; Group 2).

Dosing of EXPAREL will be based on body weight, with a starting dose of 4 mg/kg (maximum 266 mg). Dosing of Bupivacaine HCl will be based on body weight, with a starting dose of 2 mg/kg (maximum 175 mg).

Table 1 Study 319 Design

	Part 1 (PK and Safety)	Part 2 (Safety)
Group 1: subjects aged 12 to <17 years (Surgery: Spine Surgery)	EXPAREL 4 mg/kg [N=15]; or bupivacaine HCl 2 mg/kg [N =15]	EXPAREL 4 mg/kg [N =15]; or bupivacaine HCl 2 mg/kg [N =15]
Group 2: subjects aged 6 to <12 years (Surgery: Spine or Cardiac Surgery)	EXPAREL 4 mg/kg [N=15]	EXPAREL 4 mg/kg [N =15]

Part 1 (Pharmacokinetics [PK]) - Subjects aged 6 to less than 17 years

Part 1 is a multicenter, randomized, open-label study in 45 subjects aged 6 to less than 17 years of age undergoing spine or cardiac surgeries. Part 1 is divided in 2 groups: Group 1 will include subjects aged 12 to less than 17 years of age, while Group 2 will include subjects aged 6 to less than 12 years of age.

Part 1, Group 1, is an active-controlled, open-labeled, PK evaluation study in subjects aged 12 to less than 17 years undergoing spine surgery. The active comparator will be bupivacaine HCl. The planned sample size for Part 1, Group 1 is 30 subjects (15 subjects per treatment group). Subjects will be randomized 1:1 to receive either a single dose of EXPAREL 4 mg/kg (maximum 266 mg) or bupivacaine HCl 2 mg/kg (not exceeding a maximum bupivacaine HCl dose of 175 mg total) intraoperatively at the end of surgery via local infiltration.

Part 1, Group 2, is a single arm (EXPAREL 4 mg/kg), open-label, PK evaluation study in subjects aged 6 to less than 12 years undergoing spine or cardiac surgery. The planned sample size for Part 1 Group 2 is 15 subjects. Subjects will receive a single dose of EXPAREL 4 mg/kg (maximum 266 mg) intraoperatively at the end of surgery via local infiltration.

Part 2 (Safety) - Subjects aged 6 to less than 17 years

Part 2 is a multicenter, randomized, open-label study in 45 subjects aged 6 to less than 17 years of age undergoing spine or cardiac surgeries. Part 2 is divided in 2 groups: Group 1 will include subjects aged 12 to less than 17 years of age, while Group 2 will include subjects aged 6 to less than 12 years of age.

Part 2, Group 1, is an active-controlled, open-labeled, safety evaluation study in subjects aged 12 to less than 17 years undergoing spine surgery. The active comparator will be bupivacaine HCl. The planned sample size is 30 subjects (15 subjects per treatment group) for Part 2 Group 1. Subjects will be randomized 1:1 to receive either a single dose of EXPAREL 4 mg/kg (maximum 266 mg) or bupivacaine HCl 2 mg/kg (not exceeding a maximum bupivacaine HCl dose of 175 mg total) intraoperatively at the end of surgery via local infiltration.

Part 2, Group 2, is a single arm (EXPAREL 4 mg/kg), open-label study in subjects aged 6 to less than 12 years undergoing spine or cardiac surgery. The planned sample size for Part 2 Group 2 is 15 subjects. Subjects will receive a single dose of EXPAREL 4 mg/kg (maximum 266 mg) intraoperatively at the end of surgery via local infiltration.

Screening Procedures

Subjects will be screened within 30 days prior to study drug administration. During the screening visit, subjects will be assessed for past or present neurologic, cardiac, and general medical conditions that, in

the opinion of the investigator, would preclude them from study participation. After the Informed Consent Form (ICF) is signed by the subject's legal guardian and written assent is provided by the subject (if capable), medical history, surgical history, physical examination, 12-lead electrocardiogram (ECG), vital sign measurements, neurological assessment, clinical laboratory tests (hematology, chemistry, and urinalysis), pain intensity score assessment, urine pregnancy test (for females of childbearing potential), urine drug screen and alcohol breath test will be conducted.

Study Procedures

On Day 1, eligible subjects will receive the study drug intraoperatively at the end of surgery via local infiltration to produce analgesia. Use of intraoperative opioids, acetaminophen, ketorolac, or other NSAIDs, will be permitted in accordance with the study site's standard of care.

Avoid additional use of local anesthetics within 96 hours following the administration EXPAREL.

There is no required length of stay in the hospital; subjects may be discharged based on the medical judgement of the treating physician. For subjects discharged from the hospital before all protocol-specified assessments until 96 hours are completed, a nurse will perform follow-up visits at the subject's home to perform the required postsurgical assessments and collect PK samples until 96 hours.

A follow-up phone call will be scheduled for all subjects on Day 7. For the assessment of AEs, a final follow-up visit will be made on Day 30 to all subjects who would have received the study drug.

Postsurgical Pain Management

Use of postsurgical pain medication in cases of insufficient analgesia will be permitted according to the institution's standard of care. The investigator must record all postsurgical pain management medications provided to the subjects until the hospital discharge.

Avoid additional use of local anesthetics within 96 hours following the administration EXPAREL.

Postsurgical Assessments

Postsurgical assessments to be conducted until 96 hours include pain intensity using 11-point Numerical Rating Scale at Rest (NRS-R) for subjects aged 12 to less than 17 years and the Color Analog Scale (CAS) for subjects age 6 to less than 12 years; neurological assessment, clinical laboratory tests, and vital signs.

AEs will be recorded from the time of ICF is signed/assent is given until Day 30.

The study protocol specified that if a cardiac or neurological AE of special interest (AESI) or serious AE (SAE) occurs during the study, if the investigator or medical monitor considers that the event may be related to study treatment or suggests the possible occurrence of local anesthetic systemic toxicity (LAST; with or without the need for treatment [e.g., intralipids]), or if a plausible etiology for the event cannot be found, an unscheduled PK blood sample must be collected and a 12-lead ECG, vital signs, and clinical laboratory tests (hematology and complete metabolic profile [CMP]) according to the study site's standard of care may be conducted. Cardiac and neurological AEs that do not meet one of these three criteria for AESI should be reported and captured in the database as an AE.

Cardiac AESIs include chest pain, abnormal/irregular heart rate, and shortness of breath requiring intervention. Neurologic AESIs include seizure, altered mental status/altered sensorium, rigidity, dysarthria, tremors, tinnitus, visual disturbance, and severe or worsening dizziness (see below). Additionally, the following events may be of special interest if they persist or occur beyond 72 hours post dose: dizziness, hyperesthesia, muscular twitching, and tingling/paresthesia.

Dizziness will be assessed as mild, moderate, or severe based on the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0. Mild dizziness is defined as mild

unsteadiness or sensation of movement; moderate dizziness is defined as moderate unsteadiness or sensation of movement limiting instrumental activities of daily living (ADL); and severe dizziness is defined as severe unsteadiness or sensation of movement that limits self-care ADLs. Dizziness will be captured as an AESI if it is severe or worsens or persist beyond 72 hours post dose.

4. DEFINITIONS

Study Day

If the date of the event is on or after the date of the end of study drug administration, Study Day is calculated as the date of the event minus the date of the end of study drug administration plus one (1). If the date of the event is before the date of the end of study drug administration, Study Day is the date of the event minus the date of the end of study drug administration.

Treatment-emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are those with onset on or after the start time of study drug administration, and before or at the end of the study (expected to be Study Day 30±3 days).

Time 0 (zero)

Time 0 is defined as the time of the end of study drug administration, with the exception of AE's and concomitant medications. Time 0 for AE's and concomitant medications are defined as the time of the start of study drug administration.

Time Deviation

For PK sampling time window, *Time Deviation* is the difference (actual – start/end of target window of assessment) between the actual and target window of assessment in the PK sampling. If sampling occurred before the beginning of target window of assessment, time deviation will be calculated by subtracting the actual time from the beginning of the target window of assessment. If the sampling occurred after the end of target window of assessment, time deviation will be calculated by subtracting the actual sampling time from the end of the target window of assessment. Any samples occurring with the target window will have a time deviation of 0.

Baseline

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

Last Follow-up Time

For subjects who withdraw prematurely, the last follow-up time will be defined as the maximum of the last pain or any other study assessment, the last concomitant medication start or end datetime, and the last adverse event start or end datetime.

5. ANALYSIS POPULATIONS

The Safety Population will consist of all subjects who underwent the planned surgery and received study treatment. All analyses based on the safety population will be by actual treatment received.

The PK Population will consist of subjects who received study drug and provided at least one quantifiable plasma concentration. All analyses will be by actual treatment received.

All analyses of data collected for exploratory purposes (i.e., data related to pain intensity scores and opioid consumption) will be conducted using the safety population, and analyzed according to the actual treatment received.

6. STATISTICAL METHODS OF ANALYSIS

6.1 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, with the exception that pharmacokinetics descriptive statistics will be performed using Sigmastat and Microsoft Excel. Continuous variables will be summarized using descriptive statistics [sample size (n), mean, standard deviation (SD), minimum, median, and maximum]. Categorical variables will be tabulated with number and percentage of subjects. Unless otherwise noted, percentages will be based on the number of subjects in the treatment group or group within the analysis population.

Individual subject data will be provided in listings. All listings will be sorted by group, treatment (Group 1), surgery type (Group 2), site, subject and, if applicable, collection date and time.

Unless otherwise stated, summaries will present data pooled from all sites.

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

For tables presenting summaries of pain intensity scores, if more than one score is presented for a specific timeframe/timepoint of interest, the highest score within that specific timeframe/timepoint should be used.

Unless otherwise stated, separate summaries and data listings will be presented for each age group (Group 1, Group 2). Unless otherwise noted, summaries for Group 1 will be presented by treatment group and summaries for Group 2 will be presented by type of surgery (Spine or Cardiac).

6.1.1 Handling Missing Values

6.1.1.1 Exposure, Surgery, and Rescue Opioid 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 opioid rescue pain medication taken on Day 1 has no time of administration recorded, the imputed time will be the end of surgery.

6.1.1.2 Postsurgical Opioid Medication

Opioid rescue pain medication usage will be summarized based on oral morphine equivalent dosage (MED mg).

If a subject is discontinues the study early (e.g., dies, withdraws consent, is withdrawn from the study, or is lost to follow-up) before the end of the analyses time interval (e.g., 72 hours after end of surgery), his or her total opioid rescue pain medication usage through the time interval will be a projected amount.

For the calculation of the total amount of opioid medication used from the end of surgery through, for example, 72 hours, if a subject is discharged at x<36 hours after end of surgery, the total postsurgical opioid consumption through 72 hours will be calculated as $72 * \frac{D_{0,x}}{x}$, where $D_{0,x}$ is the opioid consumption during the initial x hours (inclusive) postsurgery. If a subject is discharged at $36 \leq x < 72$ hours, the total postsurgical opioid consumption through 72 hours will be calculated as $D_{0,x}+D_{2x-72,x}$, where $D_{2x-72,x}$ is the opioid consumption from $2x-72$ hours (exclusive) through x hours (inclusive). For example, if a subject is discharged at x=70 hours, the postsurgical 0 to 72 hours opioid consumption will be calculated as the consumption during the first 70 hours plus the consumption between 70 and 72 hours, which is imputed by the consumption between 68 and 70 hours.

If an opioid medication is taken on the discharge day, but the 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 day of discharge, and the time of dosing is missing, it will be imputed as12:00 pm.

6.1.1.3 Adverse Event or Concomitant Medications Dates or Times

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

For partial start date/time:

- If the year is unknown, then the date will be assigned the year of the first dose of study treatment. If the entire study is conducted within the same year, then that year will be the imputed year.
- If the month is unknown, then, if the year matches the year of the dose of study drug date, then the month and day of the dose of study drug date will be used to impute the missing month and corresponding day. Otherwise, 'January' will be assigned.
- If the day is unknown, then, if the month and year match the month and year of the dose of study drug date, then the day of the dose of study drug date will be imputed. Otherwise, '01' will be assigned.
- If the time is unknown, then, if the date (day, month, and year) matches the date of the administration of study drug, then the end time of the study drug administration will be imputed. Otherwise, '00:00' will be assigned.

For partial stop date/time:

- If the year is unknown, then the date will be assigned the year that subject discontinued from study, and time will be set to the last time of the day ('23:59').
- If the month is unknown, then month subject discontinued from study will be assigned.
- If the day is unknown, then the last day of the month will be assigned.
- If the time is unknown, then the last time of the day will be assigned ('23:59'), with the exception of end times for epoch in any CDISC dataset, where next day and '00:00' would be assigned.

6.1.1.4 Adverse Event Severity or Relationship to Study Drug

If severity of an AE is not reported, then for tables of AEs by severity, the event will be classified as 'Severe'. If relationship to study drug is not reported for an AE, then for tables of study-drug related treatment emergent AEs, the event will be assigned the relationship 'definite'. If the AE starts before study drug administration, then the relationship 'unrelated' is presumed. Tables presenting related AEs will include all AEs with relationships of 'possible', 'probable' or 'definite' as assessed by the investigator.

If severity or relationship is missing, then a sub-row will be added in the summary tables for imputed vs. severe or imputed vs. related.

6.1.1.5 Time of Events

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

6.2 Subject Disposition

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

- Screened
- Randomized
  - Randomized, not treated
  - Randomized and treated
- In the safety population

- In the PK population
- Completed the study as planned
- Discontinued from the study, and
  - Reasons for discontinuation from the study

Percentages will be based on the number of subjects randomized.

6.3 Description of Demographics and Baseline Characteristics

6.3.1 Demographics

The summary of demographic data will present:

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

Demographics in the PK Population and the Safety Population will be summarized by treatment group (EXPAREL or Bupivacaine HCl) for Group 1 and by surgery type (cardiac or spine) for Group 2.

6.3.2 Baseline Characteristics

The summary of baseline characteristic data will present:

- American Society of Anesthesiologists (ASA) Classification
- Baseline pain intensity scores
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m^2)

The formula for BMI is $w/(h^2)$, where w is weight in kilograms and h is height in meters. Weight in pounds will be converted to kilograms using the conversion factor of 2.2046 pounds to 1 kilogram. Height in inches will be converted to centimeters using the conversion factor of 2.54 centimeters to 1 inch. Height in centimeters will be converted to meters using the conversion factor of 100 centimeters to 1 meter.

Baseline characteristics summaries will be summarized by treatment group for Group 1 and by surgery type for Group 2.

Descriptive statistics (n, mean, SD, median, minimum and maximum) will be provided for pain scores, height, weight, and BMI at baseline. The number and percent of subjects will be tabulated for the various categories of ASA classification.

6.4 Surgery Characteristics

Surgery characteristics include duration of surgery and total incision length. Duration of surgery is calculated as the difference between the end of surgery and start of surgery times and reported in hours. Descriptive statistics will be provided for the duration of surgery and total incision length using the safety population, by treatment group for Group 1, and by surgery type for Group 2. Surgical characteristics will be included in data listings.

6.5 Intraoperative, Prior, and Concomitant Medications

Intraoperative, Prior, and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) and will be classified according to the default anatomical therapeutic chemical (ATC 4) classification term and preferred term (PT).

Intraoperative medications are medications collected on Intraoperative Medication eCRF page. Intraoperative medications are defined as medications given as part of the surgical procedure. These may include anesthesia, opioids or other medications with start and stop dates on the day of surgery and start times overlapping within the surgery start and stop times.

Prior medications are defined as medications with a stop date and time prior to the start of surgery. Prior medications are recorded on the prior/concomitant medication eCRF page.

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) and recorded on the prior/concomitant or post surgical pain medication CRF page.

Intraoperative, prior and concomitant medications will be summarized separately using the number and percentage of subjects within each age group and treatment group of the study by ATC class and PT for the safety population. Subjects may have more than one medication per ATC category and PT. At each level of subject summarization, a subject will be counted once if one or more medications are reported by the subject at that level.

A data listing will be created for all medications, with a flag variable identifying intraoperative, prior, and concomitant medications.

A listing mapping the ATC class and PT to verbatim term will be presented.

6.6 Measurements of Treatment Compliance

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

6.7 Pharmacokinetic Analysis

6.7.1 Sample Collections for Pharmacokinetic Analysis

A sparse PK sampling scheme is used to limit the number of blood draws from individual subjects. On Day 1, eligible subjects will be assigned to one of two PK sampling groups shown in **Table 2** based on surgery type. A total of 8 blood samples will be collected from each subject at the specific time windows shown for the determination of bupivacaine plasma concentrations.

Table 2 PK Sampling Times

Surgery Type	PK Sample Timing (Based on the End of Study Drug Administration)							
	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Sample 7	Sample 8
Spine	15±5 min	30±5 min	45±5 min	1-1.25 h	2-3 h	10-18 h	24-36 h	42-60 h
Cardiac	15±5 min	30±5 min	45±5 min	1-1.25 h	15-25 h	30-40 h	45-55 h	64-72 h

Abbreviations: h = hour; min = minutes; PK = pharmacokinetic

These sampling time points will not only characterize overall PK of bupivacaine from EXPAREL, but will also characterize the PK of immediate release bupivacaine and thoroughly characterize the early peak for both surgery types.

6.7.2 Pharmacokinetic Parameters Calculation Methods

Nonsterospecific assay is used for the measurement of bupivacaine concentration. Pharmacokinetic parameters will be calculated by noncompartmental analysis (NCA) method from concentration-time data following these guidelines:

- Actual sampling times relative to study drug administration will be used for all calculations of the PK parameters. If there is any doubt as to the actual time a sample was taken, then the scheduled time will be used.
- Concentrations from unscheduled PK blood samples will be used in the analysis of the parameters.
- There will be no imputation of missing concentration data.
- For the summaries of concentrations and for calculation of area under the curve (AUC) from bupivacaine plasma concentrations, concentrations below the limit of quantification (BLOQ) will be handled as follows:
    - Pre-dose values will be set to zero.
    - BLOQ values between the dosing time and the first time point above lower limit of quantification (LLOQ) will be set to 0.
    - BLOQ values at time points between two measurable concentration values will be set to ½ of LLOQ (lower limit of quantification).
    - All remaining BLOQ values will be set to missing.

The following PK endpoints will be determined using non-compartmental methods:

- Area under the plasma concentration-versus-time curve (AUC0-∞ and AUC0-last). The AUC0-last from the time of dosing to the time of the last quantifiable concentration will be calculated using the linear trapezoidal method. The AUC0-∞ from the time of dosing (zero) to infinity will be calculated as sum of AUC0-last and residual area Ct/λz.
- Maximum plasma concentration (Cmax) and time of Cmax (Tmax).
- The apparent terminal elimination half-life (t1/2el). t1/2el will be calculated as $\log_e(2)/\lambda_z$.The apparent terminal elimination rate constant (λ_z) will be estimated at terminal phase by linear regression after log-transformation of the concentrations:
    - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression.
    - A minimum number of three data points in the terminal phase will be used in calculating λ_z with the line of regression starting post the Cmax data point (Cmax will not be part of the regression slope) and including the last point above LLOQ value (Ct).
    - An appropriate number of decimal places will be used for λ_z to enable the reported value of terminal half-life (t1/2el) to be calculated.
- Apparent clearance (CL/F) will be estimated as Dose/AUC0-∞.
- Apparent volume of distribution (Vd/F) will be estimated based on the teriminal phase as Dose/(λ_z· AUC0-∞).

In addition, a population PK modeling will be performed using all PK data collected during the study. The population PK analysis plan will be developed separately.

6.7.3 Pharmacokinetic Concentrations and Variables

A complete data listing will be provided for all PK bupivacaine concentration data. Concentrations that are BLOQ will be indicated in the listing.

A plot of bupivacaine concentration-time data, with original scale and semi-log scale overlain on the same page will be created for each individual subject.

If different than the preceding plot, a plot of dose-normalized concentration-time data, with the original scale and semi-log scale overlaid on same page, will also be created for each individual subject.

Plasma bupivacaine concentrations for each formulation will be summarized at each nominal time window (any out-of-window results would be shown only in a listing). The following descriptive statistics

will be presented: n, geometric mean, arithmetic mean, SD, %CV, median, minimum and maximum. Results will be summarized by treatment group (EXPAREL or bupivacaine HCl) for Group 1 and by surgery type (cardiac or spine) for Group 2. Plots of mean bupivacaine concentration over time will be created with the original scale and semi-log scale overlain on the same page. If the number of subjects in a group is less or equal to 3, then individual concentration over time curves will be plotted instead of the mean concentration. For group 1, there will be two plots overlain for the two treatments. For group 2, there will be two separate plots for the two types of surgery.

Pharmacokinetics parameters will be presented in the data listings and descriptive summary statistics, including the arithmetic mean, median, minimum, maximum, standard deviation, %CV of mean, geometric mean, %CV of geometric mean. Differences will be compared between the two formulations using single factor ANOVA.

6.8 Safety Analyses

Safety assessments in this study consist of vital signs, 12-lead ECGs, neurological assessments, and AEs. Vital signs, ECGs, and neurological assessments will be serially collected (see Time and Events Schedule of Study Procedures, **Section 9**). Adverse events will be collected from the time of informed consent through to the final Day 30 visit.

6.8.1 Vital Signs

Vitals signs are resting heart rate (bpm), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), temperature (ºC), oxygen saturation (%), and respiratory rate (breaths/min). Vital signs will be summarized by treatment group (Group 1), and by surgery type (Group 2) at each assessment timepoint. Summaries will present both observed results by timepoint and change-from-baseline results. Baseline is defined as the last measurement on prior to the end of study drug administration . Baseline statistics will be presented at each assessment timepoint for those subjects reporting data at that timepoint.

Time windows will be derived for each post baseline visit using the time intervals for the study time windows detailed in Table 3.

Table 3 Analysis Study Time Windows for Vital Signs Assessments

Study Time	Time Interval for Study Time Window
Baseline	≥ 0 minutes prior to dose
Post-dose 2 hours	1.75 – 2.25 hours after end of study drug administration
Post-dose 4 hours	3.75 – 4.25 hours after end of study drug administration
Post-dose 8 hours	7.5 – 8.5 hours after end of study drug administration
Post-dose 12 hours	11 – 13 hours after end of study drug administration
Post-dose 24 hours	23 – 25 hours after end of study drug administration
Post-dose 36 hours	34 – 38 hours after end of study drug administration
Post-dose 48 hours	46 – 50 hours after end of study drug administration
Post-dose 60 hours	58 – 62 hours after end of study drug administration
Post-dose 72 hours	70 – 74 hours after end of study drug administration
Post-dose 96 hours	92 – 100 hours after end of study drug administration
Day 30	27 – 33 days after end of study drug administration

If there are multiple vital sign values for the same parameter prior to the end of study drug administration, the last value will be chosen for Baseline. If there are multiple vital sign values in a post-end of study drug administration window, the value closest to the target time point will be chosen for analysis. Unscheduled visits can be mapped to a study time only if the scheduled assessment for that time was not done and an unscheduled visit falls into the time interval for the visit window. Data from both scheduled and unscheduled visits will be listed.

6.8.2 Electrocardiograms

Investigators will classify ECG tracings as 'normal, 'abnormal not clinically significant' or 'abnormal clinically significant'. ECGs are assessed only at screening or on Day 1 prior to surgery, and a listing of ECG data will be provided.

6.8.3 Neurological Assessments

Neurological assessments include orientation (orientated, disoriented, not assessable), numbness (of lips, tongue, or around mouth), metallic taste, hearing problems, vision problems, and muscle twitching. The number and percentage of subjects will be tabulated for each neurological assessment by treatment group for Group 1 and by surgery type for Group 2, at any time after baseline and at each assessment timepoint.

Time windows will be derived for each post baseline visit using the time intervals for the study time windows detailed in Table 4.

Table 4 Analysis Study Time Windows for Neurological Assessments

Study Time	Time Interval for Study Time Window
Baseline	≥ 0 minutes prior to dose
Post-dose 2 hours	1.75 – 2.25 hours after end of study drug administration
Post-dose 4 hours	3.75 – 4.25 hours after end of study drug administration
Post-dose 8 hours	7.5 – 8.5 hours after end of study drug administration
Post-dose 12 hours	11 – 13 hours after end of study drug administration
Post-dose 24 hours	23 – 25 hours after end of study drug administration
Post-dose 36 hours	34 – 38 hours after end of study drug administration
Post-dose 48 hours	46 – 50 hours after end of study drug administration
Post-dose 60 hours	58 – 62 hours after end of study drug administration
Post-dose 72 hours	70 – 74 hours after end of study drug administration
Post-dose 96 hours	92 – 100 hours after end of study drug administration
Day 30	27 – 33 days after end of study drug administration

If there are multiple neurological assessment values for the same parameter prior to the end of study drug administration, the last value will be chosen for Baseline. If there are multiple neurological assessment values in a post-end of study drug administration window, the value closest to the target time point will be chosen for analysis. Unscheduled visits can be mapped to a study time only if the scheduled assessment for that time was not done and an unscheduled visit falls into the time interval for the visit window. Data from both scheduled and unscheduled visits will be listed.

6.8.4 Adverse Events

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

An AE will be considered TEAE if the onset date and time is between the start time of study drug administration and the final Day 30 visit.

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

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

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

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

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

- Any TEAE
  - Maximum severity: Mild
  - Maximum severity: Moderate
  - Maximum severity: Severe
- At least one related TEAE
- At least one serious TEAE
- At least one TEAE of special interest
- Subjects discontinued due to a TEAE
- Died on study (i.e., within 30 days of study drug administration)

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

Adverse event tables will present the data within each age group of the study. Incidence tables will be created for the following groups of TEAEs:

- All TEAEs by System Organ Class (SOC) and Preferred term (PT) sorted in descending order of frequency
- All TEAEs by relationship to study drug
- All TEAEs by severity
- All TEAEs of special interest
- All serious TEAEs

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

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

investigator assessment of relationship to study treatment is either 'unrelated', 'unlikely related'. All AE summaries based on related AEs will be produced based on the investigator assessment of relatedness.

Table 5 are the MedDRA terms for the adverse events of special interest according to the protocol. All AEs reported by investigators are based on this definition along with their clinical judgement.

Table 5. MedDRA Terms for AEs of Special Interest

Group	Protocol term	MedDRA 21.1 Dictionary Terms	
		Term Level	Term
Cardiac	Chest pain	Preferred term	Chest Pain
	Abnormal/irregular heart rate	Preferred term	Heart Rate Irregular
	Shortness of breath requiring intervention	Preferred term	Dyspnoea
Neurologic	Seizure	Preferred term	Seizure
	Altered mental status	Preferred term	Mental Status Changes
	Altered sensorium	Preferred term	Depressed level of consciousness
	Rigidity	Preferred term	Muscle Rigidity
	Dysarthria	Preferred term	Dysarthria
	Tremors	Preferred term	Tremor
	Tinnitus	Preferred term	Tinnitus
	Visual disturbance	Preferred term	Visual Impairment
	Dizziness*	Preferred term	Dizziness
Other	Dizziness#	Preferred term	Dizziness
	Hyperesthesia#	Preferred term	Hyperaesthesia
	Muscular twitching#	Preferred term	Muscle Twitching
	Tingling#	Preferred term	Paresthesia
	Paresthesia#	Preferred term	Paresthesia

* if severe or worsening
\# if event persists or occurs after 72 hours after start of study treatment dose

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

6.8.5 Laboratory Parameters

Clinical laboratory assessments (hematology, chemistry, and urinalysis) are collected at screening, baseline (prior to the end of study drug administration) and 96 hours after the end of study drug administration. Laboratory results will be summarized by treatment group (Group 1), and by type of surgery (Group 2) at each assessment timepoint. Summaries will present both actual and change-from-baseline results. Baseline statistics will be presented at each assessment timepoint for those subjects reporting data at that timepoint.

Tabulations of the number and percentage of subjects with value of below normal, normal, or above normal will be provided by treatment group (Group 1), and type of surgery (Group 2), at each assessment timepoint.

Time windows will be derived for each post baseline visit using the time intervals for the study time windows detailed in Table 6

Table 6 Analysis Study Time Windows for Clinical Laboratory Assessments

Study Time	Time Interval for Study Time Window
Baseline	≥ 0 minutes prior to dose
Post-dose 96 hours	92 – 100 hours after end of study drug administration

If there are multiple clinical laboratory assessment values for the same parameter prior to the end of study drug administration, the last value will be chosen for Baseline. If there are multiple clinical laboratory assessment values in a post-end of study drug administration window, the value closest to the target time point will be chosen for analysis. Unscheduled visits can be mapped to a study time only if the scheduled assessment for that time was not done and an unscheduled visit falls into the time interval for the visit window. Data from both scheduled and unscheduled visits will be listed.

6.9 Efficacy Analysis

For exploratory efficacy analyses, descriptive statistics that are appropriate for the efficacy variable will be shown within each age group and treatment group (Group 1), type of surgery (Group 2), for the safety population.

6.9.1 Pain Intensity Score

Summary statistics will be presented for pain intensity scores at each assessment timepoint. These summaries will be based on the observed values at the scheduled time points. Data listings of pain intensity scores will also be provided.

Time windows will be derived for each post baseline visit using the time intervals for the study time windows detailed in Table 7.

Table 7 Analysis Study Time Windows for Pain Intensity Scores

Study Time	Time Interval for Study Time Window
Baseline	≥ 0 minutes prior to dose
Post-dose 4 hours	3.75 – 4.25 hours after end of study drug administration
Post-dose 8 hours	7.5 – 8.5 hours after end of study drug administration
Post-dose 12 hours	11 – 13 hours after end of study drug administration
Post-dose 24 hours	23 – 25 hours after end of study drug administration
Post-dose 36 hours	34 – 38 hours after end of study drug administration
Post-dose 48 hours	46 – 50 hours after end of study drug administration
Post-dose 60 hours	58 – 62 hours after end of study drug administration
Post-dose 72 hours	70 – 74 hours after end of study drug administration
Post-dose 96 hours	92 – 100 hours after end of study drug administration

If there are multiple pain intensity score values for the same parameter prior to the end of study drug administration, the last value will be chosen for Baseline. If there are multiple pain intensity score values in a post-end of study drug administration window, the value closest to the target time point will be chosen for analysis. Unscheduled visits can be mapped to a study time only if the scheduled assessment for that time was not done and an unscheduled visit falls into the time interval for the visit window. Data from both scheduled and unscheduled visits will be listed.

6.9.1.1 Area under the Curve

Area under the pain-time curve (AUC) is derived using the linear trapezoidal rule (see formula below) on the pain scores. AUC will start with the first pain assessment obtained after surgery and use all following pain assessments including those collected prior to administration of opioid medication and unscheduled assessments. Actual assessment times will be used in deriving AUC.

$$AUC = [\sum_{i=4}^{n}(p_i + p_{(i-1)})(t_i - t_{(i-1)})]/2$$

Where p_i is the pain intensity score at time i, and t_i is the time, in hours, from end of surgery. Note that i starts at 4 as this represents the first measurement post-surgery.

Summary statistics will be presented for the following pain intensity AUCs: $AUC_{Adjusted(4-24)}$, $AUC_{Adjusted\ (4-48)}$, $AUC_{Adjusted\ (4-72)}$, $AUC_{Adjusted\ (4-96)}$ and $AUC_{Adjusted\ (4\text{-Hospital Discharge})}$.

6.9.2 Opioid Consumption

Opioid medications will be converted to oral morphine equivalent dose (MED mg) using the appropriate conversion factor from Table 8 for all summaries. Opioids are collected on the Post Surgical Pain Medication and Prior/Concomitant Medications eCRF pages. The amount of total opioid dose will be calculated as the sum of the oral morphine equivalent of all opioids taken after surgery up to the timepoint of interest. Subjects with no opioid use during the period in question will be assigned a dose of 0 for summaries and changed to the lesser of 0.1 or half of the smallest total amount observed in the study, whichever is smaller, prior to being transformed with the natural logarithm for analysis. Total postsurgical opioid dose will be calculated through 24, 48, and 72 hours. In addition to the descriptive statistics for continuous data, geometric mean (GM) and coefficient of variation (CV) will also be included and mean and SD will be excluded.

For the calculation of the total dose through 72 hours, if a subject's last follow-up time is 72-x hours, then the approach described in Section 6.1.1.2 is used.

Table 8 Oral Morphine Equivalents

Medication	Unit	Route	Oral Morphine Conversion Multiplication Factor
Morphine, Morphine Sulfate	mg	IV,IM,SC	3
Morphine	mg	PO	1
Morphine	mg	R	1
Buprenorphine	mcg	IM	75
Buprenorphine	mcg	SL	37.5
Codeine (Tylenol 3, acetaminophen-coedine, Paracetamol Forte, Tylenol 4, …)	mg	PO	0.15
Codeine Phosphate	mg	IM	0.24
Demerol, Meperidine, Pethidine	mg	IV,SC	0.3
Demerol, Meperidine, Pethidine	mg	PO	0.1
Fentanyl, Remifentanil	mcg	IV,PO,IM,TD	300
Hydromorphone	mg	R	4
Hydromorphone (Dilaudid)	mg	IV,IM,SC	20
Hydromorphone (Dilaudid)	mg	PO	4
Hydromorphone (Dilaudid)	mg	EP	45
Ketobemidone, Oxycodone	mg	IV	3
Methadone	mg	IM	3
Methadone	mg	PO	1.5
Methadone	mg	IV	6
Nalbuphine/Nallouphine (Nubain/Manfine)	mg	IV,IM,SC	3
Oxycodone, Oxycocet, Percocet, acetaminophen-oxycodone, Oxycodone HCl	mg	PO	1.5
Oxymorphone	mg	PO	3
Oxymorphone	mg	IM,SC	30
Pentazocine/Acetaminophen	mg	PO	0.2
Pentazocine/Naloxone	mg	PO	0.2

Pentazocine	mg	IM	1
Tapentadol	mg	PO	0.3
Ultram, Tramadol, Tramacol hydrochloride	mg	PO,IM	0.25
Vicodin, Norco, Lorcet, Lortab, hydrocodone-acetaminophen, Ketobemidone	mg	PO	1

Key: EP = Epidural; IM = Intramuscular; IV = Intravenous; INS = Intra Nasal Spray; NA = Not Applicable; PO = Oral; R = Rectal; SC = Subcutaneous; SL = Sublingual; TBD = To Be Determined; TD = Transdermal
If other rescue medications are given, then the conversion to oral Morphine Equivalent will be determined post-hoc. If a combination opioid product is given, then the oral Morphine Equivalent will be determined by the opioid part of the medication. Opioids given post surgically with an indication such as 'anesthesia maintenance' will not be included.

6.9.2.1 Time to First Postsurgical Use of Opioid Medication

Time to first postsurgical use of opioid rescue medication will be computed in hours as the date and time of the first opioid rescue medication minus the date and time of the end of surgery. If a subject is not administered an opioid rescue medication, the time to first administration will be censored at 72 hours after surgery or at the time of last follow-up, whichever is earliest. Time to first opioid consumption will be summarized by the quartiles (25th, 50th, and 75th), minimum and maximum estimated using Kaplan-Meier methods within age group and part of the study. The quartile and the 95% confidence limits (CONFTYPE=LOGLOG) for each quartile will be presented.

A Kaplan-Meier plot of the time from end of surgery to first opioid rescue medication use will be presented within age group and part of the study, and a log-rank test p-value of treatment difference shown for group 1.

6.10 Interim Analysis

Not Applicable.

6.10.1 Sample Size Review

The sample size was based on the number of subjects necessary to characterize the PK of EXPAREL in pediatric subjects with the precision required by the Food and Drug Administration.

6.11 Deviations from the Protocol

This SAP has an additional analysis that was not specified in the Protocol. Pharmacokinetic parameters will be calculated with a NCA method as specified in Section 6.7.2.

7. REFERENCES

1. US Federal Register. International Conference on Harmonisation; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. 16 September 1998.
2. American Statistical Association. Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, 07 August 1999. http://www.amstat.org/profession/ethicalstatistics.html
3. Royal Statistical Society. The Royal Statistical Society: Code of Conduct, August 1993. http://www.rss.org.uk/about/conduct.html.

8. SAS CODE

Endpoint	SAS Code

AUC of Pain Intensity Score	* AUC calculations;
	%macro AUC(st,en);
	
	data auc;
	set adre(where=(&st.<=atptn<=&en.));
	by usubjid paramcd base avisitn adt ady t anl01fl;
	retain prevval prevt;
	if first.ady then do;
	prevval=.;
	prevt=.;
	end;
	else trapez=(aval+prevval)/2*(t-prevt);
	prevval=aval;
	prevt=t;
	run;
	proc means data=auc noprint;
	by usubjid paramcd base avisitn adt ady
	/*pftsfl*/;
	var aval trapez t;
	output out=a&st.&en. sum(aval)=singl
	sum(trapez)=aval min(t)=mint max(t)=maxt;
	run;
	data a&st.&en.;
	set a&st.&en.;
	if .<mint<maxt then aval=aval;
	else if 0<mint=maxt then aval=singl;
	drop _: mint maxt singl;
	run;
	
	%mend AUC;
	
	%AUC(4,24); /* AUC 4-24 */
	%AUC(4,48); /* AUC 4-48 */
	%AUC(4,72); /* AUC 4-72 */
	%AUC(4,96); /* AUC 4-96 */
	*** AUC 4-Hospital Discharge: ***;
	*** For this run, make a subset of the data ***;
	*** first with only assessments taken on or ***;
	*** before hospital discharge ***;
	%AUC(4,96); /* AUC 4-96 */

9. TIME AND EVENTS SCHEDULE OF STUDY PROCEDURES

Time Window	Screen Visit Within 30 days	D1 Preop	OR	15 min ±5 min	30 min ±5 min	1 h ±15 min	2 h ±15 min	4 h ±15 min	8 h ±30 min	12 h ±1 h	24 h ±1 h	36 h ±2 h	48 h ±2 h	60 h ±2 h	72 h ±2 h	96 h ±4 h	Hosp Dis	D7 Call ±1 d	D30 Visit ±3 d
Obtain signed informed consent/assent	X																		
Assess/confirm eligibility	X	X	X																
Record medical history and surgical history	X	X																	
Record demographics and baseline characteristics	X																		
Urine pregnancy test (for females of childbearing potential; Part 1 only)	X	X																	
Urine drug screen and alcohol breath test at the investigator's discretion (Part 1 only).	X	X																	
Physical examination	X																		X
12-lead ECG[1]	X[2]																		
Clinical laboratory tests (hematology, chemistry, urinalysis)[3]	X	X														X			
Perform neurological assessment	X						X	X	X	X	X	X	X	X	X	X	X		X
Measure and record vital signs[4]	X	X					X	X	X	X	X	X	X	X	X	X	X		X
Record age-specific pain intensity score[5]	X							X	X	X	X	X	X	X	X	X	X		
Collect PK blood samples per time windows in Table 2				◄	-	-	-	-	-	-	-	-	-	-	-	►			
Prepare study medication			X																
Administer study medication; record dosage, volume, size of incision, and administration start and stop times			X																
Record intraoperative opioids administered and doses			X																
Record surgery start and stop times			X																
Record times and doses of all pain management medication administered			◄	-	-	-	-	-	-	-	-	-	-	-	-	►			
Record date and time of discharge																	X		

	Screen Visit	D1 Preop	OR	15 min	30 min	1 h	2 h	4 h	8 h	12 h	24 h	36 h	48 h	60 h	72 h	96 h	Hosp Dis	D7 Call	D30 Visit
Time Window	Within 30 days			±5 min	±5 min	±15 min	±15 min	±15 min	±30 min	±1 h	±1 h	±2 h	±2 h	±2 h	±2 h	±4 h		±1 d	±3 d
Document any unscheduled phone calls, unscheduled office visits, or ER visits related to pain after discharge																		X	X
Record prior and concomitant medications[6]	←	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	→ X
Record AEs beginning at the time the ICF or assent is signed[1,3,4,7]	←	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	→ X

Note: Postsurgical assessments will be conducted at the time points specified after the end of study drug administration.

In the situation where PK blood draws and other assessments coincide or occur at about the same time, the blood draw for PK analysis must be conducted first, and the pain intensity assessment conducted second, as applicable, followed by any other assessments.

1 ECG abnormalities that are clinically significant should be recorded as AEs. May also conduct a 12-lead ECG if a subject experiences an AESI (i.e., cardiac AE or neurological AE), or an SAE; see footnote 7.

2 A baseline 12-lead ECG must be recorded prior to surgery and may be performed either at the screening visit or in the preoperative holding area on Day 1.

3 May also conduct clinical laboratory tests if a subject experiences an AESI or an SAE; see footnote 7.

4 Vital signs (temperature, resting heart rate, respiratory rate, oxygen saturation and blood pressure) will be measured after the subject has rested in a supine position for at least 5 minutes. May also measure vital signs if a subject experiences an AESI (i.e., cardiac AE or neurological AE), or an SAE; see footnote 7.

5 Pain intensity will be measured using the 11-point NRS-R for subjects aged 12 to less than 17 years (Appendix 1) and CAS for subjects aged 6 to less than 12 years (Appendix 2). The preoperative pain intensity assessment should be conducted immediately prior to each administration of postoperative opioid pain management medication till 96 hours. If a subject is too anesthetized at the time of a scheduled pain intensity assessment, the assessment should be skipped.

6 Instruct subject to discontinue prohibited medications. Record date/time of all medications starting at least 30 days prior to study drug administration till 96 hours after study drug administration. Record medications administered for treatment of an AE till Day 30.

7 In case a cardiac or neurological AE of special interest (AESI) or serious AE (SAE) occurs during the study, if the investigator or medical monitor considers that the event may be related to study treatment or suggests the possible occurrence of local anesthetic systemic toxicity (LAST; with or without the need for treatment [e.g., intralipids]), or if a plausible etiology for the event cannot be found, an unscheduled PK blood sample must be collected and a 12-lead ECG, vital signs, and clinical laboratory tests (hematology and complete metabolic profile [CMP]) according to the study site's standard of care may be conducted. See Section 13.1.7 and Appendix 6 for additional information on handling of AESIs. Cardiac or neurological events that do not meet one of these three criteria should be reported as described in Section 14.1.

Cardiac AESIs include chest pain, abnormal/irregular heart rate, and shortness of breath requiring intervention. Neurologic AESIs include seizure, altered mental status/altered sensorium, rigidity, dysarthria, tremors, tinnitus, visual disturbance, and severe or worsening dizziness. Additionally, the following events may be of special interest if they persist or occur beyond 72 hours post dose: dizziness, hyperesthesia, muscular twitching, and tingling/paresthesia. Severity of dizziness will be assessed based on NCI CTCAE (Version 5.0). Dizziness will be captured as an AESI if it is severe or worsens or persist beyond 72 hours post dose (see Section 13.1.7).

Abbreviations:

AE: adverse event; AESI: AE of special interest; CAS: Color Analog Scale; CTCAE: Common Terminology Criteria for Adverse Events; d: day(s); ECG: electrocardiogram; ER: emergency room; h: hour; Hosp Dis: hospital discharge; ICF: informed consent form; min: minutes; NCI: National Cancer Institute; NRS-R: Numeric Rating Scale at Rest; OR: operating room; PK: pharmacokinetic; SAE: serious adverse event.

10. LAYOUT OF TABLES, LISTINGS AND FIGURES

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

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

Percentages should not appear if the count is zero.

Italicized text in the TLF mock-ups indicate notes to programmers and 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 14.1-1 the title in the mock-up appears as:

```
Table 14.1-1.1.1: Summary of Subject Disposition (Part 1, Group 1) – All
Screened Subjects
```

but should appear as follows on the final TLF:

```
                    Table 14.1-1.1.1
        Summary of Subject Disposition (Part 1, Group 1)
                    Safety Population
```

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

Always insert a page break between parts of the study.

Sort all listings within study part and age group by site, subject with further sorts dependent on listing.

Table and listing shells follow.

For categorical variables, if subjects are missing data for a certain category (example Race), a missing subcategory should be added under the respective category.

For any subjects who are enrolled in the incorrect group for their age, add a footnote to all TFL's for that group: "Subject XXXX is XX years old but was incorrectly enrolled in Group X."

11. TABLE OF CONTENTS FOR TABLE MOCK-UPS

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-319

Table 14.1-1.1.1: Summary of Subject Disposition (Group 1: 12 to <17 years) – All Screened Subjects

	EXPAREL 4 mg/kg [N=xx]	Bupivacaine HCl 2 mg/kg [N=xx]	Total [N=xx]
Screened [1]			xx
Randomized	xx	xx	xx
Not Treated	xx	xx	xx
Treated	xx	xx	xx
Safety Population – n (%) [2]#	xx (xx.x)	xx (xx.x)	xx (xx.x)
PK Population – n (%) [3]@	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Study – n (%)@	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued from Study – n (%)@	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reasons for Discontinuation – n (%)@	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death – n (%)@	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse Event – n (%)@	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of Efficacy – n (%)@	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to Follow-up – n (%)@	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal by Subject – n (%)@	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other – n (%)@	xx (xx.x)	xx (xx.x)	xx (xx.x)

= as treated; @ = as randomized;
[1] Signed the informed consent form; [2] Received study drug and surgery; [3] Received study drug and provide at least one quantifiable plasma concentration
Percentages based on number randomized.
Source: *list SAS datasets used to create table* *ddmmmyyyyThh:mm*
SAS X.Y *program_name*

Note to programmer: *For reasons for discontinuation only those reasons that appear in the data will appear on the table. Use this template also for tables:*

Table 14.1-1.1.2: Summary of Subject Disposition (Group 2: 6 to < 12 years) – All Screened Subjects

Note to programmer: *Replace treatment columns by Spine Surgery and Cardiac Surgery for this table.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-319

Table 14.1-2.1.1: Summary of Subject Demographics (Group 1: 12 to <17 years) - PK Population

	Statistic	EXPAREL 4 mg/kg [N=xx]	Bupivacaine HCl 2 mg/kg [N=xx]	Total [N=xx]
Age (yrs)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
Sex				
Female	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Male	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity				
Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race				
American Indian/Alaska Native	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black/African American	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian/Pacific Islander	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Reported	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
White	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

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

Note to programmer: *If subjects are missing data for a category (example Race), a missing subcategory should be added under the respective category. Use this template also for tables:*

Table 14.1-2.1.2: Summary of Subject Demographics (Group 2: 6 to < 12 years) - PK Population

Note to programmer: *Replace treatment columns by Spine Surgery and Cardiac Surgery for this table*.

Table 14.1-2.2.1: Summary of Subject Demographics (Group 1: 12 to <17 years) - Safety Population

Table 14.1-2.2.2: Summary of Subject Demographics (Group 2: 6 to < 12 years) - Safety Population

Note to programmer: *Parts 1 and 2 combined. Replace treatment columns by Spine Surgery and Cardiac Surgery for this table*.

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Table 14.1-3.1.1: Summary of Subject Baseline Characteristics (Part 1, Group 1) - PK Population

	Statistic	EXPAREL 4 mg/kg [N=xx]	Bupivacaine HCl 2 mg/kg [N=xx]	Total [N=xx]
Neurological Assessments				
Subject oriented				
Yes	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
No	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not assessable	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Numb lips, tongue, mouth				
Yes	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
No	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Metallic taste				
Yes	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
No	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Problems hearing				
Yes	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
No	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Problems with vision				
Yes	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
No	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Muscle twitch				
Yes	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
No	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
ECG				
Normal	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Abnormal, NCS	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Abnormal, CS	n (%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

NCS = Not clinically significant CS = Clinically significant

Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Pacira Pharmaceuticals (Page 2 of 4) Protocol: 402-C-319

Table 14.1-3.1.1: Summary of Subject Baseline Characteristics (Group 1: 12 to <17 years) - PK Population

	Statistic	EXPAREL 4 mg/kg [N=xx]	Bupivacaine HCl 2 mg/kg [N=xx]	Total [N=xx]
Baseline NRS Pain Score	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
ASA Classification				
1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Height (cm)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
Weight (kg)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx

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

Pacira Pharmaceuticals (Page 3 of 4) Protocol: 402-C-319

Table 14.1-3.1.1: Summary of Subject Baseline Characteristics (Group 1: 12 to <17 years) - PK Population

	Statistic	EXPAREL 4 mg/kg [N=xx]	Bupivacaine HCl 2 mg/kg [N=xx]	Total [N=xx]
Body Mass Index (kg/m^2)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
Heart Rate (bpm)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
Systolic Blood Pressure (mmHg)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
Diastolic Blood Pressure (mmHg)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx

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

Pacira Pharmaceuticals (Page 4 of 4) Protocol: 402-C-319

Table 14.1-3.1.1: Summary of Subject Baseline Characteristics (Group 1: 12 to <17 years) - PK Population

	Statistic	EXPAREL 4 mg/kg [N=xx]	Bupivacaine HCl 2 mg/kg [N=xx]	Total [N=xx]
Temperature (°C)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
Oxygen Saturation (%)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
Respiratory Rate (breaths/min)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Minimum	xx	xx	xx
	Median	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx

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

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

Table 14.1-3.1.2: Summary of Subject Baseline Characteristics (Group 2: 6 to < 12 years) - PK Population

Note to programmer: *Replace treatment columns by Spine Surgery and Cardiac Surgery, replace Baseline NRS Pain Score by Baseline CAS Pain Sore for this table.*

Table 14.1-3.2.1: Summary of Subject Baseline Characteristics (Group 1: 12 to <17 years) - Safety Population

Note to programmer: *Parts 1 and 2 combined.* Exclude neurological assessments.

Table 14.1-3.2.2: Summary of Subject Baseline Characteristics (Group 2: 6 to < 12 years) - Safety Population

Note to programmer: *Parts 1 and 2 combined. Replace treatment columns by Spine Surgery and Cardiac Surgery, replace Baseline NRS Pain Score by Baseline CAS Pain Sore for this table.*

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Table 14.1-4.1.1: Summary of Surgery Characteristics (Group 1: 12 to <17 years) - Safety Population

Characteristic	Statistic	EXPAREL 4 mg/kg [N=xx]	Bupivacaine HCl 2 mg/kg [N=xx]	Total [N=xx]
Duration of Surgery (hours)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx	xx	xx
	Minimum	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx
Total Incision Length (cm)	n	xx	xx	xx
	Mean	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx
	Median	xx	xx	xx
	Minimum	xx.x	xx.x	xx.x
	Maximum	xx	xx	xx

Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Note to programmer: *Parts 1 and 2 combined. First page will present overall sites; subsequent pages will present each site – one site per page. For individual sites the label should be the site number. Use this template also for following table:*

Table 14.1-4.1.2: Summary of Surgery Characteristics (Group 2: 6 to < 12 years) - Safety Population

Note to programmer: *Replace treatment columns by Spine Surgery and Cardiac Surgery for this table.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-319

Table 14.1-5.1.1: Tabulation of Incidence of Intraoperative Medications (Group 1: 12 to <17 years) - Safety Population

Anatomical Therapeutic Class (ATC) Preferred Name	EXPAREL 4 mg/kg n (%)	Bupivacaine HCl 2 mg/kg n (%)	Total n (%)
Subjects taking at least one medication	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PN1.1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PN1.2	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC2	xx (xx.x)	xx (xx.x)	xx (xx.x)
PN2.1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PN2.2	xx (xx.x)	xx (xx.x)	xx (xx.x)
ETC.			

Medications are coded using World Health Organization Drug Dictionary (WHO-DD) September 2018.

Sorted by descending total incidence by ATC for Total column. Subjects using the same intraoperative medication (PT) more than once or multiple medications within an ATC class are counted only once at each ATC summary level.

Intraoperative medications are those indicated as such by the investigator.

Subjects using the same medication more than once are counted only once at each summary level.

Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Note to programmer: *Parts 1 and 2 combined. Use this template also for table following.*

Table 14.1-5.1.2: Tabulation of Incidence of Intraoperative Medications (Group 2: 6 to < 12 years) - Safety Population

Note to programmer: *Parts 1 and 2 combined. Replace treatment columns by Spine Surgery and Cardiac Surgery for this table.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-319

Table 14.2-1.1.1: Summary of Numeric Rating Scale Pain Intensity Scores (Group 1: 12 to <17 years) - Safety Population

Time Point	Statistic	EXPAREL 4 mg/kg [N=xx]	Bupivacaine HCl 2 mg/kg [N=xx]
Screening	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx
4 hours	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx
8 hours	n	xx	xx
	Mean	xx.x	xx.x
	SD	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx

Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS *X.Y* *program_name*

Note to programmer: *Other timepoints for this table are: 12 hours, 24 hours, 36 hours, 48 hours, 60 hours, 72 hours, 96 hours, and Hospital Discharge. Use this template also for tables:*

Table 14.2-1.1.2: Summary of Color Analog Scale Pain Intensity Scores (Group 2: 6 to < 12 years) - Safety Population

Note to programmer: *Replace treatment columns by Spine Surgery and Cardiac Surgery for this table.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-319

Table 14.2-2.1.1: Summary of AUC of Pain Intensity Scores (Group 1: 12 to <17 years) – Safety Population

Parameter	Statistic	EXPAREL 4 mg/kg [N=xx]	Bupivacaine HCl 2 mg/kg [N=xx]
AUC(4-24)	N	xx	xx
	Mean	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x
	Minimum	xx	xx
	Maximum	xxx	xxx

AUC = area under the curve calculated using the trapezoidal method;

Source: *list SAS datasets used to create table* *ddmmmyyyyThh:mm*

SAS *X.Y* *program_name*

Note to programmer: *Other parameters to include in this table: AUC(4-48), AUC(4-72), AUC(4-96) and AUC(4-Hospital Discharge). Use this template also for:*

Table 14.2-2.1.2: Summary of AUC of Pain Intensity Scores (Group 2: 6 to < 12 years) – Safety Population

Note to programmer: *Replace treatment columns by Spine Surgery and Cardiac Surgery for this table.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-319

Table 14.2-3.1.1: Summary of Total Opioid Consumption (MED mg) (Group 1: 12 to <17 years) - Safety Population

Time Period [1]	Statistic	EXPAREL 4 mg/kg [N=xx]	Bupivacaine HCl 2 mg/kg [N=xx]
0-24 hrs	n	xx	xx
	Geometric Mean	xx.x	xx.x
	%CV	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx
0-48 hrs	n	xx	xx
	Geometric Mean	xx.x	xx.x
	%CV	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx
0-72 hrs	n	xx	xx
	Geometric Mean	xx.x	xx.x
	%CV	x.xx	x.xx
	Minimum	xx	xx
	Median	xx.x	xx.x
	Maximum	xx	xx

[1] Time 0 is defined as the time of the end of surgery.

Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Table 14.2-3.1.2: Summary of Total Opioid Consumption (MED mg) (Group 2: 6 to < 12 years) - Safety Population

Note to programmer: *Use preceding Table as template. Replace treatment columns by Spine Surgery and Cardiac Surgery for this table.*

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Table 14.2-4.1.1: Analysis of Time to First Postsurgical Opioid Medication Use (Group 1: 12 to <17 years) - Safety Population

	Statistic	EXPAREL 4 mg/kg [N=xx]	Bupivacaine HCl 2 mg/kg [N=xx]
Number of Subjects on			
Rescue Medication (Opioid)	n (%)	xx (xx.x)	xx (xx.x)
No Rescue Medication (Censored)	n (%)	xx (xx.x)	xx (xx.x)
Time to First Rescue [1]			
Quartiles [2]			
First (25% rescued)	Estimate	xx.xx	xx.xx
	(95% CI)	(xx.xx,xx.xx)	(xx.xx,xx.xx)
Median (50% rescued)	Estimate	xx.xx	xx.xx
	(95% CI)	(xx.xx,xx.xx)	(xx.xx,xx.xx)
Third (75% rescued)	Estimate	xx.xx	xx.xx
	(95% CI)	(xx.xx,xx.xx)	(xx.xx,xx.xx)
Minimum	Observed	xx.xx	xx.xx
Maximum	Observed	xx.xx*	xx.xx

* indicates censored observation CI = confidence interval
Subjects who are not administered an opioid rescue medication by 72 hours are censored at 72 hours after surgery or at the time of last follow-up, whichever is earliest.
[1] Time 0 is defined as the time of the end of surgery.
[2] Estimates from Kaplan-Meier analysis.
Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Table 14.2-4.1.3: Analysis of Time to First Postsurgical Opioid Medication Use (Group 2: 6 to < 12 years) - Safety Population

Note to programmer: *Use preceding Table as template. Replace treatment columns by Spine Surgery and Cardiac Surgery for this table.*

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Table 14.3-1.1.1: Summary of Vital Signs (Group 1: 12 to <17 years) – Safety Population

Vital Sign	Timepoint	Value	Statistic	EXPAREL 4 mg/kg [N=xx]	Bupivacaine HCl 2 mg/kg [N=xx]
Resting Heart Rate (bpm)	Baseline	Actual	n	xx	xx
			Mean	xx.x	xx.x
			SD	x.xx	x.xx
			Minimum	xx	xx
			Median	xx.x	xx.x
			Maximum	xx	xx
	2 hours	Actual	n	xx	xx
			Mean	xx.x	xx.x
			SD	x.xx	x.xx
			Minimum	xx	xx
			Median	xx.x	xx.x
			Maximum	xx	xx
		Change from Baseline	n	xx	xx
			Mean	xx.x	xx.x
			SD	x.xx	x.xx
			Minimum	xx	xx
			Median	xx.x	xx.x
			Maximum	xx	xx

[1] Baseline (Day 1 prior to surgery) for subjects with data at the timepoint.
Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Note to programmer: *Vital signs are 'Resting Heart Rate (bpm)', 'Systolic Blood Pressure (mmHg)', 'Diastolic Blood Pressure (mmHg)', 'Temperature (°C)', 'Oxygen Saturation (%) and Respiratory rate (breaths/min)'. Timepoints to appear on this table are, in order of appearance, 2, 4, 8, 12, 24, 36, 48, 60, 72, and 96 hours, Hospital Discharge, and Day 30. Don't split timepoint across pages.*

Table 14.3-1.1.2: Summary of Vital Signs (Group 2: 6 to < 12 years) – Safety Population

Note to programmer: *Use preceding Table as template. Replace treatment columns by Spine Surgery and Cardiac Surgery for this table.*

Table 14.3-1.1.3: Summary of Vital Signs (Both Groups: 6 to < 17 years) – Spine Surgery – Safety Population

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-319

Table 14.3-2.1.1: Summary of Neurological Assessments by Timepoint (Group 1: 12 to <17 years) - Safety Population

Timepoint	Assessment	Score	EXPAREL 4 mg/kg [N=xx] n (%)	Bupivacaine HCl 2 mg/kg [N=xx] n (%)
Screening	Oriented?	No	xx (xx.x)	xx (xx.x)
		Yes	xx (xx.x)	xx (xx.x)
		Not Assessable	xx (xx.x)	xx (xx.x)
	Numbness of lips, tongue or mouth	No	xx (xx.x)	xx (xx.x)
		Yes	xx (xx.x)	xx (xx.x)
	Metallic taste	No	xx (xx.x)	xx (xx.x)
		Yes	xx (xx.x)	xx (xx.x)
	Hearing problems	No	xx (xx.x)	xx (xx.x)
		Yes	xx (xx.x)	xx (xx.x)
	Vision problems	No	xx (xx.x)	xx (xx.x)
		Yes	xx (xx.x)	xx (xx.x)
	Muscle twitching	No	xx (xx.x)	xx (xx.x)
		Yes	xx (xx.x)	xx (xx.x)
Etc.				

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

Note to programmer: *Timepoints to appear on this table are, in order of appearance, Screening, and 2, 4, 8, 12, 24, 36, 48, 60, 72, and 96 hours, Hospital Discharge, and Day 30. Do not split a timepoint across pages. Do not split timepoints across pages.*

Use Table 14.3-2.1.1 as template. Replace treatment columns by Spine Surgery and Cardiac Surgery for these tables:

Table 14.3-2.1.2: Summary of Neurological Assessments by Timepoint (Group 2: 6 to < 12 years) - Safety Population

Table 14.3-2.1.3: Summary of Neurological Assessments by Timepoint (Both Groups: 6 to < 17 years) – Spine Surgery - Safety Population

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-319

Table 14.3-3.1.1.1: Summary of Clinical Laboratory Data by Timepoint (Group 1: 12 to <17 years) - Hematology - Safety Population

Laboratory parameter (units)

Timepoint	Value	Statistic	EXPAREL 4 mg/kg [N=xx]	Bupivacaine HCl 2 mg/kg [N=xx]
Baseline [1]	Actual	n	xx	xx
		Mean	xx.x	xx.x
		SD	x.xx	x.xx
		Minimum	xx	xx
		Median	xx.x	xx.x
		Maximum	xx	xx
96 hours	Actual	n	xx	xx
		Mean	xx.x	xx.x
		SD	x.xx	x.xx
		Minimum	xx	xx
		Median	xx.x	xx.x
		Maximum	xx	xx
	Change	n	xx	xx
		Mean	xx.x	xx.x
		SD	x.xx	x.xx
		Minimum	xx	xx
		Median	xx.x	xx.x
		Maximum	xx	xx

[1] Baseline (Day 1 prior to surgery) for subjects with data at the timepoint.
Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Note to programmer: *See protocol for list of lab analytes. Analytes should be sorted in alphabetical order. Use as template for following tables.*

Table 14.3-3.1.1.2: Summary of Clinical Laboratory Data by Timepoint (Group 2: 6 to < 12 years) – Hematology - Safety Population

Note to programmer: *Replace treatment columns by Spine Surgery and Cardiac Surgery for this table.*

Table 14.3-3.1.1.3: Summary of Clinical Laboratory Data by Timepoint (Both Groups: 6 to < 17 years) - Spine Surgery – Hematology - Safety Population

Table 14.3-3.2.1.1: Summary of Clinical Laboratory Data by Timepoint (Group 1: 12 to <17 years) – Chemistry - Safety Population

Table 14.3-3.2.1.2: Summary of Clinical Laboratory Data by Timepoint (Group 2: 6 to < 12 years) – Chemistry - Safety Population

Note to programmer: *Replace treatment columns by Spine Surgery and Cardiac Surgery for this table.*

Table 14.3-3.2.1.3: Summary of Clinical Laboratory Data by Timepoint (Both Groups: 6 to < 17 years) – Spine Surgery – Chemistry - Safety Population

Table 14.3-3.3.1.1: Summary of Clinical Laboratory Data by Timepoint (Group 1: 12 to <17 years) – Urinalysis - Safety Population

Table 14.3-3.3.1.2: Summary of Clinical Laboratory Data by Timepoint (Group 2: 6 to < 12 years) – Urinalysis - Safety Population

Note to programmer: *Replace treatment columns by Spine Surgery and Cardiac Surgery for this table. For urinalysis results only numeric results will appear.*

Table 14.3-3.3.1.3: Summary of Clinical Laboratory Data by Timepoint (Both Groups: 6 to < 17 years) - Spine Surgery – Urinalysis - Safety Population

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Table 14.3-3.4.1.1: Tabulation of Clinical Laboratory Data by Timepoint (Group 1: 12 to <17 years) – Urinalysis - Safety Population

Analyte	Timepoint	Category	Statistic	EXPAREL 4 mg/kg [N=xx]	Bupivacaine HCl 2 mg/kg [N=xx]
Analyte 1	Baseline [1]	*Cat 1*	n (%)	xxx (xx.x%)	xxx (xx.x%)
		Cat 2	n (%)	xxx (xx.x%)	xxx (xx.x%)
		Etc.	n (%)	xxx (xx.x%)	xxx (xx.x%)
	96 hours	*Cat 1*	n (%)	xxx (xx.x%)	xxx (xx.x%)
		Cat 2	n (%)	xxx (xx.x%)	xxx (xx.x%)
		Etc.	n (%)	xxx (xx.x%)	xxx (xx.x%)
Analyte 2	Baseline [1]	*Cat 1*	n (%)	xxx (xx.x%)	xxx (xx.x%)
		Cat 2	n (%)	xxx (xx.x%)	xxx (xx.x%)
		Etc.	n (%)	xxx (xx.x%)	xxx (xx.x%)
	96 hours	*Cat 1*	n (%)	xxx (xx.x%)	xxx (xx.x%)
		Cat 2	n (%)	xxx (xx.x%)	xxx (xx.x%)
		Etc.	n (%)	xxx (xx.x%)	xxx (xx.x%)
Etc.					

[1] Baseline (prior to surgery) for subjects with data at the timepoint.
Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Note to programmer: *Do not split timepoint statistics across pages, if possible. Present all available lab analytes. Categories are the superset of those reported in the data for both timepoints combined. All categories should appear for both timepoints with zeros (0) as counts where needed. Use as template for following table.*

Table 14.3-3.4.1.2: Tabulation of Clinical Laboratory Data by Timepoint (Group 2: 6 to < 12 years) – Urinalysis - Safety Population

Note to programmer: *Replace treatment columns by Spine Surgery and Cardiac Surgery for this table.*

Table 14.3-3.4.1.3: Tabulation of Clinical Laboratory Data by Timepoint (Both Groups: 6 to < 17 years) – Spine Surgery – Urinalysis - Safety Population

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Table 14.3-3.5.1.1: Tabulation of Clinical Laboratory Range by Timepoint (Group 1: 12 to <17 years) – Hematology - Safety Population

Laboratory parameter (units)

Timepoint	Normal Range	Statistic	EXPAREL 4 mg/kg [N=xx]	Bupivacaine HCl 2 mg/kg [N=xx]
Baseline	Below	n (%)	xxx (xx.x%)	xxx (xx.x%)
	Normal	n (%)	xxx (xx.x%)	xxx (xx.x%)
	Above	n (%)	xxx (xx.x%)	xxx (xx.x%)
96 hours	Below	n (%)	xxx (xx.x%)	xxx (xx.x%)
	Normal	n (%)	xxx (xx.x%)	xxx (xx.x%)
	Above	n (%)	xxx (xx.x%)	xxx (xx.x%)

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

Note to programmer: *Do not split timepoint statistics across pages. Present all available analytes. Analytes should be sorted in alphabetical order. Use this template also for tables:*

Table 14.3-3.5.1.2: Tabulation of Clinical Laboratory Range by Timepoint (Group 2: 6 to < 12 years) – Hematology - Safety Population

Note to programmer: *Replace treatment columns by Spine Surgery and Cardiac Surgery for this table.*

Table 14.3-3.5.1.3: Tabulation of Clinical Laboratory Range by Timepoint (Both Groups: 6 to < 17 years) – Spine Surgery – Hematology - Safety Population

Table 14.3-3.6.1.1: Tabulation of Clinical Laboratory Range by Timepoint (Group 1: 12 to <17 years) – Chemistry - Safety Population

Table 14.3-3.6.1.2: Tabulation of Clinical Laboratory Range by Timepoint (Group 2: 6 to < 12 years) – Chemistry - Safety Population

Note to programmer: *Replace treatment columns by Spine Surgery and Cardiac Surgery for this table.*

Table 14.3-3.6.1.3: Tabulation of Clinical Laboratory Range by Timepoint (Both Groups: 6 to < 17 years) - Spine Surgery – Chemistry - Safety Population

Table 14.3-3.7.1.1: Tabulation of Clinical Laboratory Range by Timepoint (Group 1: 12 to <17 years) – Urinalysis - Safety Population

Table 14.3-3.7.1.2: Tabulation of Clinical Laboratory Range by Timepoint (Group 2: 6 to < 12 years) – Urinalysis - Safety Population

Note to programmer: *Replace treatment columns by Spine Surgery and Cardiac Surgery for this table. For urinalysis results only numeric results will appear on this table.*

Table 14.3-3.7.1.3: Tabulation of Clinical Laboratory Range by Timepoint (Both Groups: 6 to < 17 years) – Spine Surgery – Urinalysis - Safety Population

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Table 14.3-4.1.1: Overview of Treatment-Emergent Adverse Events (TEAEs) (Group 1: 12 to <17 years) - Safety Population

Number of	EXPAREL 4 mg/kg [N=xx] n (%)	Bupivacaine HCl 2 mg/kg [N=xx] n (%)
Subjects with Any TEAE	xx (xx.x)	xx (xx.x)
Maximum Severity of Mild	xx (xx.x)	xx (xx.x)
Maximum Severity of Moderate	xx (xx.x)	xx (xx.x)
Maximum Severity of Severe	xx (xx.x)	xx (xx.x)
At least one Related	xx (xx.x)	xx (xx.x)
At least one Serious	xx (xx.x)	xx (xx.x)
At least one TEAE of Special Interest	xx (xx.x)	xx (xx.x)
Subjects Discontinued due to TEAE	xx (xx.x)	xx (xx.x)
Died on Study	xx (xx.x)	xx (xx.x)

Related TEAEs are those AEs indicated as 'possible', 'probable' or 'definite' related by the investigator on the AE CRF.

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

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

Table 14.3-4.1.2: Overview of Treatment-Emergent Adverse Events (TEAEs) (Group 2: 6 to < 12 years) - Safety Population

Note to programmer: *Table 14.3.5.1.1 as template. Change columns to Spine Surgery and Cardiac Surgery*.

Table 14.3-4.1.3: Overview of Treatment-Emergent Adverse Events (TEAEs) - Safety Population

Note to programmer: *Combine Table 14.3.5.1.1 and 14.3-5.1.2. Show as 4 columns in one Table*

Table 14.3-4.1.4: Overview of Treatment-Emergent Adverse Events (TEAEs) (Both Groups: 6 to < 17 years) – Spine Surgery - Safety Population

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Table 14.3-4.2.1: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) (Group 1: 12 to <17 years) - Safety Population

System Organ Class Preferred Term	EXPAREL 4 mg/kg [N=xx] n (%)	Bupivacaine HCl 2 mg/kg [N=xx] n (%)
Subjects with at least one TEAE	xx (xx.x)	xx (xx.x)
SOC1	xx (xx.x)	xx (xx.x)
PT1.1	xx (xx.x)	xx (xx.x)
PT1.2	xx (xx.x)	xx (xx.x)
SOC2	xx (xx.x)	xx (xx.x)
PT2.1	xx (xx.x)	xx (xx.x)
PT2.2	xx (xx.x)	xx (xx.x)
	xx (xx.x)	xx (xx.x)
ETC.		

Adverse events coded using the Medical Dictionary for Regulatory Activities (MedDRA 21.1).
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.
Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Note to programmer: *For tables presenting severity or related, if the severity or relationship is missing, then a sub-row will be added into the table for imputed versus severe or imputed versus related. Use this template also for following tables:*

Table 14.3-4.2.2: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) (Group 2: 6 to < 12 years) - Safety Population

Note to programmer: *Replace treatment columns by Spine Surgery and Cardiac Surgery for this table*.

Table 14.3-4.2.3: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) (Both Groups: 6 to < 17 years) - Spine Surgery - Safety Population

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Table 14.3-4.3.1: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) by Severity (Group 1: 12 to <17 years) - Safety Population

System Organ Class Preferred Term	Severity	EXPAREL 4 mg/kg [N=xx] n (%)	Bupivacaine HCl 2 mg/kg [N=xx] n (%)
Subjects with at least one TEAE	Mild	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)
	Severe	xx (xx.x)	xx (xx.x)
SOC1	Mild	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)
	Severe	xx (xx.x)	xx (xx.x)
PT1.1	Mild	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)
	Severe	xx (xx.x)	xx (xx.x)

Adverse events coded using the Medical Dictionary for Regulatory Activities (MedDRA 21.1).
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.
Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm
SAS X.Y program_name

Table 14.3-4.3.2: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) by Severity (Group 2: 6 to < 12 years) - Safety Population

Note to programmer: *Use preceding Table as template. Replace treatment columns by Spine Surgery and Cardiac Surgery for this table.*

Table 14.3-4.3.3: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) by Severity (Both Groups: 6 to < 17 years) – Spine Surgery - Safety Population

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Table 14.3-4.4.1: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) by Relationship to Study Drug (Group 1: 12 to <17 years) - Safety Population

System Organ Class Preferred Term	Relation	EXPAREL 4 mg/kg [N=xx] n (%)	Bupivacaine HCl 2 mg/kg [N=xx] n (%)
Subjects with at least one TEAE	Unrelated	xx (xx.x)	xx (xx.x)
	Unlikely	xx (xx.x)	xx (xx.x)
	Possible	xx (xx.x)	xx (xx.x)
	Probable	xx (xx.x)	xx (xx.x)
	Definite	xx (xx.x)	xx (xx.x)
SOC1	Unrelated	xx (xx.x)	xx (xx.x)
	Unlikely	xx (xx.x)	xx (xx.x)
	Possible	xx (xx.x)	xx (xx.x)
	Probable	xx (xx.x)	xx (xx.x)
	Definite	xx (xx.x)	xx (xx.x)
PT1.1	Unrelated	xx (xx.x)	xx (xx.x)
	Unlikely	xx (xx.x)	xx (xx.x)

Adverse events coded using the Medical Dictionary for Regulatory Activities (MedDRA 21.1).
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.
Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm
SAS X.Y program_name

Note to programmer: *For tables presenting severity or related, if the severity or relationship is missing, then a sub-row will be added into the table for imputed versus severe or imputed versus related. For related tables add the following footnote to the table, "Related TEAEs are those AEs indicated as 'possible', 'probable' or 'definite' related by the investigator on the AE CRF."*

Table 14.3-4.4.2: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) by Relationship to Study Drug (Group 2: 6 to < 12 years) - Safety Population

Note to programmer: *Use preceding Table as template. Replace treatment columns by Spine Surgery and Cardiac Surgery for this table.*

Note to programmer: *Replace treatment columns by Spine Surgery and Cardiac Surgery for all Tables ending in "2".*

Table 14.3-4.4.3: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) by Relationship to Study Drug (Both Groups: 6 to < 17 years) – Spine Surgery - Safety Population

Note to programmer: Use mock-up 14.3-4.2.1 for the following:

Table 14.3-5.1.1: Summary of Incidence of Serious Treatment-Emergent Adverse Events (TEAEs) (Group 1: 12 to <17 years) - Safety Population

Table 14.3-5.1.2: Summary of Incidence of Serious Treatment-Emergent Adverse Events (TEAEs) (Group 2: 6 to < 12 years) - Safety Population

Table 14.3-5.1.3: Summary of Incidence of Serious Treatment-Emergent Adverse Events (TEAEs) (Both Groups: 6 to < 17 years) – Spine Surgery - Safety Population

Note to programmer: Use mock-up 14.3-4.2.1 for the following:

Table 14.3-6.1.1: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) of Special Interest (Group 1: 12 to <17 years) - Safety Population

Table 14.3-6.1.2: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) of Special Interest (Group 2: 6 to < 12 years) - Safety Population

Table 14.3-6.1.3: Summary of Incidence of Treatment-Emergent Adverse Events (TEAEs) of Special Interest (Both Groups: 6 to < 17 years) – Spine Surgery - Safety Population

Note to programmer: Use mock-up 14.1-5.1.1 for the following:

Table 14.3-7.1.1: Tabulation of Incidence of Prior Medications (Group 1: 12 to <17 years) - Safety Population

Table 14.3-7.1.2: Tabulation of Incidence of Prior Medications (Group 2: 6 to < 12 years) - Safety Population

Note to programmer: *On these tables 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 14.3-7.1.3: Tabulation of Incidence of Prior Medications (Both Groups: 6 to < 17 years) – Spine Surgery - Safety Population

Table 14.3-8.1.1: Tabulation of Incidence of Concomitant Medications (Group 1: 12 to <17 years) – Safety Population.

Table 14.3-8.1.2: Tabulation of Incidence of Concomitant Medications (Group 2: 6 to < 12 years) – Safety Population.

Note to programmer: *On these tables change the footnote 'Intraoperative medications are those indicated as such by the investigator' to read 'Concomitant medications are those taken between the start of study drug administration and discharge from study and are not designated intraoperative medications.' Note that a concomitant medication can start prior to start of study drug and be ongoing.*

Table 14.3-8.1.3: Tabulation of Incidence of Concomitant Medications (Both Groups: 6 to < 17 years) – Spine Surgery – Safety Population.

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Table 14.4-1.1: Summary of EXPAREL Pharmacokinetic Parameters (Group 1: 12 to <17 years) – PK Population

	Statistic	EXPAREL [N=xx]	Bupivacaine HCl [N=xx]
AUC(0-inf) (hr*ng/mL)	n	xx	xx
	Mean (%CV)	xx.x (xx.x)	xx.x (xx.x)
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Geometric Mean (%CV)	xx.x	xx.x
	Minimum, Maximum	xx, xx	xx, xx
	p-value *	0.xxx	
AUC(0-last) (hr*ng/mL)	n	xx	xx
	Mean (%CV)	xx.x (xx.x)	xx.x (xx.x)
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Geometric Mean (%CV)	xx.x	xx.x
	Minimum, Maximum	xx, xx	xx, xx
	p-value *	0.xxx	

* 2-sided t-test
Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm
SAS X.Y program_name

Note to programmer: *Other Pharmacokinetic parameters to appear on this table are, in order of appearance: Cmax (ng/mL), Tmax, t1/2el (hr), CL/F (L/hr), and Vd (L). Use this template also for tables:*

Table 14.4-1.2: Summary of EXPAREL Pharmacokinetic Parameters (Group 2: 6 to < 12 years) – Spine Surgery – PK Population

Table 14.4-1.3: Summary of EXPAREL Pharmacokinetic Parameters (Group 2: 6 to < 12 years) – Cardiac Surgery – PK Population

Table 14.4-1.4: Summary of EXPAREL Pharmacokinetic Parameters (Both Groups: 6 to < 17 years) – Spine Surgery – PK Population

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Table 14.4-3.1: Summary of EXPAREL Pharmacokinetic Plasma Concentrations (ng/mL) (Group 1: 12 to <17 years) – PK Population

	Statistic	EXPAREL [N=xx]	Bupivacaine HCl [N=xx]
15 Minutes	n	xx	xx
	Mean (%CV)	xx.x (xx.x)	xx.x (xx.x)
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Geometric Mean (%CV)	xx.x (xx.x)	xx.x (xx.x)
	Minimum, Maximum	xx, xx	xx, xx
30 Minutes	n	xx	xx
	Mean (%CV)	xx.x (xx.x)	xx.x (xx.x)
	SD	x.xx	x.xx
	Median	xx.x	xx.x
	Geometric Mean (%CV)	xx.x (xx.x)	xx.x (xx.x)
	Minimum, Maximum	xx, xx	xx, xx

Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Note to programmer: *Other Pharmacokinetic Plasma Concentration timepoints to appear on this table are, in order of appearance: 45 Minutes, 1 – 1.25 Hours, 2 – 3 Hours, 10 – 18 Hours, 24 – 36 Hours, and 42 – 60 Hours. Use this template also for tables:*

Table 14.4-3.2: Summary of EXPAREL Pharmacokinetic Plasma Concentrations (ng/mL) (Group 2: 6 to < 12 years) – Spine Surgery - PK Population

Table 14.4-3.3: Summary of EXPAREL Pharmacokinetic Plasma Concentrations (ng/mL) (Group 2: 6 to < 12 years) – Cardiac Surgery - PK Population

Note to programmer: *Change timepoints to: 15 Minutes, 30 Minutes, 45 Minutes, 1 – 1.25 Hours, 15 – 25 Hours, 30 – 40 Hours, 45 – 55 Hours, and 64 – 72 Hours.*

Table 14.4-3.4: Summary of EXPAREL Pharmacokinetic Plasma Concentrations (ng/mL) (Both Groups: 6 to < 17 years) – Spine Surgery - PK Population

12. TABLE OF CONTENTS FOR LISTING MOCK-UPS

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Listing 16.2-1.1.1: Subject Disposition (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

Site	Subject	Part	Date of Last Visit	End of Study Status	Specify
xxx	yyyy	Part 1	ddmmmyyyy		
		Part 2			

Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

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

Listing 16.2-1.1.2: Subject Disposition (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

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Listing 16.2-1.1.3: Screen Failures

Site	Subject	Date of Screening	Reason(s) for Screen Failure
xxx	yyyy	ddmmmyyyy	

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

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Listing 16.2-2.1.1: Randomization and Populations (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

			Randomization		Population	
Site	Subject	Part	Date and Time	Number	Safety	PK
xxx	yyyy	Part 1	ddmmmyyyyThh:mm	xxxxx	X	X
		Part 2				

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

Note to programmer: *Population will by 'Y' if subject in set, blank otherwise. Use this template also for listing:*

Listing 16.2-2.1.2: Enrollment and Populations (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Change "Randomization" column header to "Enrollment".*

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Listing 16.2-3.1.1: Demographics (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

Site	Subject Number	Subject Init.	Birth Date	Age(yrs)	Sex	Race	Ethnicity	ASA Class
xxx	yyyy	AMZ	ddmmmyyyy	xx	X	xxxxxxxxxxx	xxxxxxxxx	X

The following subjects were not placed in the correct group according to their age: xxxx, xxxx, .

Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Note to programmer: *If race is 'other' then race should be 'Other: other-specify-text'. Use this template also for listing:*

Listing 16.2-3.1.2: Demographics (Group 2: 6 to < 12 years) – All Subjects

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Listing 16.2-4.1.1: Height and Weight (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

Site	Subject	Collection Date	Height (cm)	Weight (kg)	Body Mass Index (kg/m^2)
xxx	yyyy	ddmmmyyyyThh:mm	xxx.X	xxx.X	xx.X

Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Note to programmer: *Use this template also for listing:*

Listing 16.2-4.1.2: Height and Weight (Group 2: 6 to < 12 years) – All Subjects

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Listing 16.2-5.1.1: Surgery (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

Site	Subject	Date	Start Time	Stop Time	Duration (hrs)	Procedure Name	Incision Length (cm)	Intraoperative Medications Administered?
xxx	yyyy	ddmmmyyyy	HH:MM	HH:MM	X.X	xxxxx	xx.X	xxx

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

Note to programmer: *If anesthesia type is 'other' then text should read 'other: specify-text'. Procedure Name is 'Cardiac' or 'Spine'. Use this template also for listing:*

Listing 16.2-5.1.2: Surgery (Group 2: 6 to < 12 years) – All Subjects

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Listing 16.2-6.1.1: Numeric Rating Scale at Rest Pain Intensity Score (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

Site	Subject	Date and Time	Time From Dose			Pain Score
			Scheduled(hr)	Actual(hr)	Deviation(hrs)	
xxx	yyyy	ddmmmyyyyThh:mm	xx.xx	xx.xx	xxxx	xx.x
		ddmmmyyyyThh:mm	Day 1 Pre-op	xx.xx	xxxx	xx.x
		ddmmmyyyyThh:mm *	4 hours	xx.xx	xxxx	xx.x
		ND	8 hours			
		ddmmmyyyyThh:mm	12 hours	xx.xx	xxxx	xx.x
		ddmmmyyyyThh:mm	Unscheduled	xx.xx	xxxx	xx.x
		ddmmmyyyyThh:mm	…	xx.xx	xxxx	xx.x
		ddmmmyyyyThh:mm	Hospital discharge	xx.xx	xxxx	xx.x

ND=Not Done;
* = out of window
Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm
SAS X.Y program_name

Note to programmer: *Sort by collection date and time. If Pain Intensity Score 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. An asterisk (*) will be placed next to the deviation if an assessment is out of window. See Table of Time and Events for windows. Use this template also for listing:*

Listing 16.2-6.1.2: Color Analog Scale Pain Intensity Score (Group 2: 6 to < 12 years) – All Subjects

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Listing 16.2-7.1.1.1: Opioid Medication Total Dose (MED mg) and Opioid-free Status (Group 1: 12 to <17 years) - All Subjects

TREATMENT: *treatment-name*

Site	Subject	0-24 hrs [1]	0-48 hrs [1]	0-72 hrs [1]	Opioid-Free
xxx	yyyy	xxxx.x	xxxx.x	xxxx.x	NO
xxx	yyyy	-	-	-	YES

Total dose is dose from end of surgery through timepoint.
[1] Time 0 is defined as the time of the end of surgery.
Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Note to programmer: *Use this template also for listing:*

Listing 16.2-7.1.1.2: Opioid Medication Total Dose (MED mg) and Opioid-free Status (Group 2: 6 to < 12 years) - All Subjects

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Listing 16.2-7.2.1.1: Opioid Medication (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

Site	Subject	Date and Time	Time to Rescue (hr)	Medication	Dose (units)	Conversion Factor	Dose (MED mg)	Route
xxx	yyyy	ddmmmyyyyThh:mm	xxx.x	xxxxxxxxxxx	xx(xxxx)	x.xx	xxx.x	xxxxxxx
		ddmmmyyyyThh:mm	xxx.x	xxxxxxxxxxx	xx(xxxx)	x.xx	xxx.x	xxxxxxx
		ddmmmyyyyThh:mm	xxx.x	xxxxxxxxxxx	xx(xxxx)	x.xx	xxx.x	xxxxxxx
		ddmmmyyyyThh:mm	xxx.x	xxxxxxxxxxx	xx(xxxx)	x.xx	xxx.x	xxxxxxx

Time to rescue is time from end of surgery to rescue medication dose.
Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm
SAS X.Y program_name

Note to programmer: *Medication should be preferred term. If medication or route is 'Other', text should read 'Other: specify-text'. Sort by date and time within subject. Use this template also for listing:*

Listing 16.2-7.2.1.2: Opioid Medication (Group 2: 6 to < 12 years) – All Subjects

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Listing 16.2-8.1.1: Day 7 Phone Call (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

Site	Subject	Date	Day 7 Phone Call			Number of pain-related		Number of ER Visits	AE Assessed
			Schedule (days)	Actual (days)	Deviation (days)	Phone Calls	Office Visits		
XXX	YYYY	DDMONYYYY	7	XX.X	XX.X	XX	XX	XXXX	Yes
XXX	YYYY	DDMONYYYY	7	XX.X	XX.X	XX	XX	XXXX	No
XXX	YYYY	DDMONYYYY	7	XX.X	XX.X	XX	XX	XXXX	No

ER = Emergency Department
Source: *list SAS datasets used to create table* DDMONYYYYTHH:MM

SAS X.Y

Note to programmer: *Sort by date and time within subject. Use this template also for listing:*

Listing 16.2-8.1.2: Day 7 Phone Call (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace treatment columns by Spine Surgery and Cardiac Surgery for this table.*

Listing 16.2-8.1.3: Day 30 Visit (Group 1: 12 to <17 years) – All Subjects

Note to programmer: *Change "Day 7 Phone Call" column to "Day 30 Visit".*

Listing 16.2-8.1.4: Day 30 Visit (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Change "Day 7 Phone Call" column to "Day 30 Visit". Replace treatment columns by Spine Surgery and Cardiac Surgery for this table.*

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Listing 16.2-9.1.1.1: EXPAREL Pharmacokinetic Concentrations (Raw) (Group 1: 12 to <17 years) – All Subjects

Site	Subject	Scheduled Timepoint (hrs)	Date and Time	Actual (hrs)	Deviation (hrs)	Concentration Original (ng/mL)
xxx	yyyy	xx	yyyy-MM-DDThh:mm	-	-	xxxx.x
		xx	yyyy-MM-DDThh:mm	xx.x	xx.x	xxxx.x
		xx	yyyy-MM-DDThh:mm	xx.x	xx.x	xxxx.x
		xx-xx	yyyy-MM-DDThh:mm	xx.x	xx.x	xxxx.x
		xx-xx	yyyy-MM-DDThh:mm	xx.x	xx.x	xxxx.x
		xx-xx	yyyy-MM-DDThh:mm	xx.x	xx.x	xxxx.x
		xx-xx	yyyy-MM-DDThh:mm	xx.x	xx.x	xxxx.x
		xx-xx	yyyy-MM-DDThh:mm	xx.x	xx.x	xxxx.x

BLOQ = Below limit of quantification. ND = Not determined.
Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Note to programmer: *Scheduled time points are different for spine and cardiac surgeries. Sort by date and time within subject. Use this template also for listings:*

Listing 16.2-9.1.1.2: EXPAREL Pharmacokinetic Concentrations (Raw) (Group 2: 6 to < 12 years) – Spine Surgery – All Subjects

Listing 16.2-9.1.1.3: EXPAREL Pharmacokinetic Concentrations (Raw) (Group 2: 6 to < 12 years) – Cardiac Surgery – All Subjects

Listing 16.2-9.3.1.1: Bupivacaine Pharmacokinetic Concentrations (Raw) (Group 1: 12 to <17 years) – All Subjects

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Listing 16.2-9.5.1.1: EXPAREL Pharmacokinetic Parameters (Group 1: 12 to <17 years) – PK Population

Site	Subject	AUC(0-inf) (ng*hr/mL)	AUC(0-last) (ng*hr/mL)	Cmax (ng/mL)	Tmax	t1/2el (hr)	CL/F (L/hr)	Vd (L)
xxx	yyyy	xxxx.xx	xxxx.xx	xxx.x	x.xx	x.xx	xx.xx	xx.xx

ND = Not determined.
Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Note to programmer: *Sort by site and subject. Use this template also for listings:*

Listing 16.2-9.5.1.2: EXPAREL Pharmacokinetic Parameters (Group 2: 6 to < 12 years) – Spine Surgery – PK Population

Listing 16.2-9.5.1.3: EXPAREL Pharmacokinetic Parameters (Group 2: 6 to < 12 years) – Cardiac Surgery – PK Population

Listing 16.2-9.6.1.1: Bupivacaine Pharmacokinetic Parameters (Group 1: 12 to <17 years) – PK Population

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Listing 16.2-10.1.1: Hematology (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

Subject	Visit	Date and Time	Analyte (units)	Normal Range Low	Normal Range High	Result	Change	Flag
yyyy	Screening	ddmmmyyyyThh:mm	xxxxxxxxxxx (units)	xxx.xx	xxx.xx	xxx.xx	-	H
			xxxxxxxxxxx (units)	xxx.xx	xxx.xx	xxx.xx	-	
			Xxxxxxxxxxx (units)	xxx.xx	xxx.xx	xxx.xx	-	L
			Xxxxxxxxxxx (units)	xxx.xx	xxx.xx	xxx.xx	-	
			…					
	Baseline	ddmmmyyyyThh:mm	Xxxxxxxxxxx (units)	xxx.xx	xxx.xx	xxx.xx	-	
			Xxxxxxxxxxx (units)	xxx.xx	xxx.xx	xxx.xx	-	
			Xxxxxxxxxxx (units)	xxx.xx	xxx.xx	xxx.xx	-	L
			Xxxxxxxxxxx (units)	xxx.xx	xxx.xx	xxx.xx	-	
			…					
	96 Hours	ddmmmyyyyThh:mm	xxxxxxxxxxx (units)	xxx.xx	xxx.xx	xxx.xx	xx.X	
			xxxxxxxxxxx (units)	xxx.xx	xxx.xx	xxx.xx	xx.X	
			xxxxxxxxxxx (units)	xxx.xx	xxx.xx	xxx.xx	xx.X	L
			xxxxxxxxxxx (units)	xxx.xx	xxx.xx	xxx.xx	xx.X	

Flag: L=below normal range; H=above normal range.
Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Note to programmer: *Sort by date and time within subject and analyte alphabetically within date. Change is only calculated for Day 10 visit. Use this template also for listings:*

Listing 16.2-10.1.2: Hematology (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

Listing 16.2-11.1.1: Chemistry (Group 1: 12 to <17 years) – All Subjects

Listing 16.2-11.1.2: Chemistry (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

Listing 16.2-12.1.1: Urinalysis – Numeric Results (Group 1: 12 to <17 years)– All Subjects

Listing 16.2-12.1.2: Urinalysis – Numeric Results (Group 2: 6 to < 12 years)– All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

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Listing 16.2-13.1.1: Urinalysis – Character Results (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

Site	Subject	Visit	Date and Time	Analyte	Normal Criteria	Result	Flag
xxx	yyyy	Screening	ddmmmyyyyThh:mm	xxxxxxxxxxxxxxxX	xxxxxxxx	xxxxxxxx	A
				xxxxxxxxxxxxxxxX	xxxxxxxx	xxxxxxxx	
				…			
		Baseline	ddmmmyyyyThh:mm	xxxxxxxxxxxxxxxX	xxxxxxxx	xxxxxxxx	A
				xxxxxxxxxxxxxxxX	xxxxxxxx	xxxxxxxx	
				…			
		Day 10	ddmmmyyyyThh:mm	xxxxxxxxxxxxxxxX	xxxxxxxx	xxxxxxxx	
				xxxxxxxxxxxxxxxX	xxxxxxxx	xxxxxxxx	

Flag: A = abnormal.
Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Note to programmer: *Sort by date and time within subject and analyte alphabetically within date. Use this template also for listing:*

Listing 16.2-13.1.2: Urinalysis – Character Results (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

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Listing 16.2-14.1.1: Vital Signs Assessment (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

Site	Subject	Date and Time	Assessment Schedule (hrs)	Actual (hrs)	Dev. (hrs)	Heart Rate (bpm) Actual (Change)	Temp. (°C) Actual (Change)	SBP (mmHg) Actual (Change)	DBP (mmHg) Actual (Change)	Respiratory rate (breaths /min) Actual (Change)	Oxygen Sat. (%) Actual (Change)
xxx	yyyy	ddmmmyyyyThh:mm	Screening	-	-	xx	xx	xxx	xx	xx	xx
		ddmmmyyyyThh:mm	Baseline	-	-	xx	xx	xxx	xx	xx	xx
		ddmmmyyyyThh:mm	2	xxx.xx	xxx	xx	xx	xxx	xx	xx	xx
						(-xx)	(-xx)	(-xx)	(-xx)	(-xx)	(-xx)
		ddmmmyyyyThh:mm	4	xxx.xx	xxx	xx	xx	xxx	xx	xx	xx
						(xx)	(xx)	(xx)	(xx)	(xx)	(xx)
		ddmmmyyyyThh:mm	8	xxx.xx	xxx	xx	xx	xxx	xx	xx	xx
						(xx)	(xx)	(xx)	(xx)	(xx)	(xx)
		ddmmmyyyyThh:mm	12	xxx.xx	xxx	xx H	xx H	xxx	xx	xx	xx
						(xx)	(xx)	(xx)	(xx)	(xx)	(xx)
		ddmmmyyyyThh:mm	24	xxx.xx	xxx	xx LI	xx LI	xxx	xx	xx	xx
						(xx)	(xx)	(xx)	(xx)	(xx)	(xx)
		ddmmmyyyyThh:mm	36	xxx.xx	xxx	xx	xx	xxx	xx	xx	xx
						(xx)	(xx)	(xx)	(xx)	(xx)	(xx)
		ddmmmyyyyThh:mm	48	xxx.xx	xxx	xx	xx	xxx	xx	xx	xx
						(xx)	(xx)	(xx)	(xx)	(xx)	(xx)
		ddmmmyyyyThh:mm	60	xxx.xx	xxx	xx	xx	xxx	xx	xx	xx
						(xx)	(xx)	(xx)	(xx)	(xx)	(xx)
		ddmmmyyyyThh:mm	72	xxx.xx	xxx	xx	xx	xxx	xx	xx	xx
						(xx)	(xx)	(xx)	(xx)	(xx)	(xx)
		ddmmmyyyyThh:mm	96	xxx.xx	xxx	xx	xx	xxx	xx	xx	xx
						(xx)	(xx)	(xx)	(xx)	(xx)	(xx)
		ddmmmyyyyThh:mm	Hospital Discharge	xxx.xx	xxx	xx	xx	xxx	xx	xx	xx
						(xx)	(xx)	(xx)	(xx)	(xx)	(xx)
		ddmmmyyyyThh:mm	Day 30	xxx.xx	xxx	xx	xx	xxx	xx	xx	xx
						(xx)	(xx)	(xx)	(xx)	(xx)	(xx)

*=out of window; Change is change from baseline.
Source: *list SAS datasets used to create table*
SAS X.Y

ddmmmyyyyThh:mm
program_name

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. Use this template also for listing:*

Listing 16.2-14.1.2: Vital Signs Assessment (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

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Listing 16.2-15-1.1: Electrocardiogram Findings – Investigator Assessment (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

Site	Subject	Assessment Date and Time	Assessment Schedule (hrs)	Finding
xxx	yyyy	ddmmmyyyyThh:mm	Screening	Normal

*=out of window

Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Note to programmer: *Sort by date and time within subject. Use this template also for listing:*

Listing 16.2-15-1.2: Electrocardiogram Findings – Investigator Assessment (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

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Listing 16.2-16.1.1: Neurological Assessment (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

		Assessment				Question					
Site	Subject	Date and Time	Schedule (hrs)	Actual (hrs)	Deviation (hrs)	1	2	3	4	5	6
xxx	yyyy	ddmmmyyyyThh:mm	Screening	-	-	X	X	X	X	X	X
		ddmmmyyyyThh:mm	2	xxx.xx	xxx	NA	X	X	X	X	X
		ddmmmyyyyThh:mm	4	xxx.xx	xxx	X	X	X	X	X	X
		ddmmmyyyyThh:mm	8	xxx.xx	xxx	X	X	X	X	X	X
		ddmmmyyyyThh:mm	12	xxx.xx	xxx	NA	X	X	X	X	X
		ddmmmyyyyThh:mm	24	xxx.xx	xxx	X	X	X	X	X	X
		ddmmmyyyyThh:mm	36	xxx.xx	xxx	X	X	X	X	X	X
		ddmmmyyyyThh:mm	48	xxx.xx	xxx	X	X	X	X	X	X
		ddmmmyyyyThh:mm	60	xxx.xx	xxx	X	X	X	X	X	X
		ddmmmyyyyThh:mm	72	xxx.xx	xxx	X	X	X	X	X	X
		ddmmmyyyyThh:mm	96	xxx.xx	xxx	X	X	X	X	X	X
		ddmmmyyyyThh:mm	Hospital Discharge	xxx.xx	-	X	X	X	X	X	X
		ddmmmyyyyThh:mm	Day 30	xxx.xx	xxx	X	X	X	X	X	X

*=out of window; NA=Not Assessable
1) Is subject oriented?
2) Do you have numbness of the lips, the tongue or around the mouth?
3) Do you have a metallic taste in your mouth?
4) Are you having problems with your hearing not related to the use of a hearing aid?
5) Are you having problems with your vision not related to the use of eye glasses?
6) Are your muscles twitching?

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

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. Use this template also for listing:*

Listing 16.2-16.1.2: Neurological Assessment (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

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Listing 16.2-17.1.1.1: All Adverse Events (Group 1: 12 to <17 years) – All Subjects

Treatment: treatment-name

Site	Subject	TEAE	Data Type	Data
xxx	yyyy	N	Start (Day)	ddmmmyyyyThh:mm (XX)
			Stop (Day)	ddmmmyyyyThh:mm (XX)
			AE Number	X
			System Organ Class	xxxxxxxxxxxxxxxxx
			Preferred	xxxxxxxxxxxxxxxxxxx
			Verbatim	xxxxxxxxxxxxxxxxxxxxX
			Severity	xxxxxxxx
			Relationship to Study Drug	xxxxxxxx
			Action Taken	xxxxxxxxxxxxxxxxxxx
			Outcome	xxxxxxxxxxxxx
			Serious	xxx
			Serious Cause(s)	xxxxxxxxxxxX
				xxxxxxxxxxxxxxxxxxxX

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

Source: *list SAS datasets used to create listing* *ddmmmyyyyThh:mm*

SAS *X.Y* *program_name*

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

Listing 16.2-17.1.1.2: All Adverse Events (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

Listing 16.2-17.2.1.1.1: Treatment-emergent Adverse Events (Group 1: 12 to <17 years) – All Subjects

Listing 16.2-17.2.1.1.2: Treatment-emergent Adverse Events (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

Listing 16.2-17.2.2.1.1: Treatment-emergent Study Drug Related Adverse Events (Group 1: 12 to <17 years) – All Subjects

Listing 16.2-17.2.2.1.2: Treatment-emergent Study Drug Related Adverse Events (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

Listing 16.2-17.3.1.1: All Serious Adverse Events (Group 1: 12 to <17 years) – All Subjects

Listing 16.2-17.3.1.2: All Serious Adverse Events (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

Listing 16.2-17.4.1.1.1: Treatment-emergent Serious Adverse Events (Group 1: 12 to <17 years) – All Subjects

Listing 16.2-17.4.1.1.2: Treatment-emergent Serious Adverse Events (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

Listing 16.2-17.4.2.1.1: Treatment-emergent Study Drug Related Serious Adverse Events (Group 1: 12 to <17 years) – All Subjects

Listing 16.2-17.4.2.1.2: Treatment-emergent Study Drug Related Serious Adverse Events (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

Listing 16.2-17.5.1.1.1: Treatment-emergent Adverse Events of Special Interest, as Reported by Investigators (Group 1: 12 to <17 years) – All Subjects

Listing 16.2-17.5.1.1.2: Treatment-emergent Adverse Events of Special Interest, as Reported by Investigators (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery". For these tables, use the CRF checkbox to identify AEs of Special Interest.*

Listing 16.2-17.5.2.1.1: Treatment-emergent Study Drug Related Adverse Events of Special Interest (Group 1: 12 to <17 years) – All Subjects

Listing 16.2-17.5.2.1.2: Treatment-emergent Study Drug Related Adverse Events of Special Interest (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

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Listing 16.2-17.5.3.1.1: Adverse Events of Special Interest, as Defined in the Protocol (Group 1: 12 to <17 years) – All Subjects

Treatment: treatment-name

Site	Subject	Preferred Term	Start Time (Day)	End Time (Day)
xxx	yyyy	Chest Pain		
		Heart Rate Irregular		
		…		
xxx	yyyy	…		
		…		

Source: *list SAS datasets used to create listing* *ddmmmyyyyThh:mm*

Note to programmer: *Refer to Table 5 for list of AESI's defined in the protocol. Use this template also for listings:*

Listing 16.2-17.5.3.1.2: Adverse Events of Special Interest, as Defined in the Protocol (Group 2: 6 to < 12 years) – All Subjects

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Listing 16.2-18.1.1.1: Prior Medications (Group 1: 12 to <17 years) – All Subjects

Treatment: treatment-name

Site	Subject	Data Type	Date
xxx	yyyy	Start (Day)	ddmmmyyyyThh:mm (XX)
		Stop (Day)	ddmmmyyyyThh:mm (XX)
		Medication Number	X
		ATC Level 1	xxxxxxxxxxxxxxxxx
		ATC Level 2	xxxxxxxxxxxxxxxxxxx
		ATC Level 3	xxxxxxxxxxxxxxxxxxxX
		ATC Level 4	xxxxxxxxxxxxxxxxxxx
		Preferred Name	xxxxxxxxxxxxxxxxxxx
		Verbatim	xxxxxxxxxxxxxxxxxxx
		Dose (Unit)	X (XX)
		Route	xxxxxxxx
		Frequency	xxxxxxxx
		Given for AE or MH?	xxxxxxxxxxxxxxxxxxxx AE # xx *(or MH # xx)*

ATC=Anatomical therapeutic class
Source: *list SAS datasets used to create listing* *ddmmmyyyyThh:mm*

SAS *X.Y* *program_name*

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

Listing 16.2-18.1.1.2: Prior Medications (Group 2: 6 to < 12 years) – All Subjects

Listing 16.2-18.2.1.1: Concomitant Medications (Group 1: 12 to <17 years) – All Subjects

Listing 16.2-18.2.1.2: Concomitant Medications (Group 2: 6 to < 12 years) – All Subjects

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Listing 16.2-19.1.1: Medical/Surgical History (Group 1: 12 to <17 years) – All Subjects

Treatment: treatment-name

Site	Subject	Data Type	Data
xxx	yyyy	Start	ddmmmyyyy
		Stop	ddmmmyyyy
		System Organ Class	xxxxxxxxxxxxxxxxx
		Preferred	xxxxxxxxxxxxxxxxxxx
		History Verbatim	xxxxxxxxxxxxxxxxxxxxX
		Start	ddmmmyyyy
		Stop	ddmmmyyyy
		System Organ Class	xxxxxxxxxxxxxxxxx
		Preferred	xxxxxxxxxxxxxxxxxxx
		History Verbatim	xxxxxxxxxxxxxxxxxxxxX

Source: list SAS datasets used to create listing ddmmmyyyyThh:mm

SAS X.Y program_name

Note to programmer: *Use this template also for the following listing, Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

Listing 16.2-19.1.2: Medical/Surgical History (Group 2: 6 to < 12 years) – All Subjects

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Listing 16.2-20.1.1: Intraoperative Medications (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

Site	Subject	Medication Name	Dose	Unit	Route
xxx	yyyy	*xxx*	xxx.xx	(UNITS)	xxxx
xxx	yyyy	*xxx*	xxx.xx	(UNITS)	xxxx

Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Note to programmer: *Use this template also for listing:*

Listing 16.2-20.1.2: Intraoperative Medications (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

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Listing 16.2-21.1.1: Study Drug Administration (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

Site	Subject	Date	Start Time	Stop Time	Incision Length (cm)	Dose (mg)	Total Volume (mL)
xxx	yyyy	ddmmmyyyy	HH:MM	HH:MM	xx.x	xx.x	xxx

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

Note to programmer: *Use this template for the following listing. Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

Listing 16.2-21.1.2: Study Drug Administration (Group 2: 6 to < 12 years) – All Subjects

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Listing 16.2-22.1.1: Urine Drug Screen, Alcohol Blood Test and Pregnancy Test (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

Site	Subject	Visit	Urine Drug	Blood Alcohol	Pregnancy
xxx	yyyy	Screening	xxxxxxxx	xxxxxxxx	xxxxxxxx
		Day 1 (Preop)	xxxxxxxx	xxxxxxxx	xxxxxxxx
xxx	yyyy	Screening	xxxxxxxx	xxxxxxxx	xxxxxxxx
		Day 1 (Preop)	xxxxxxxx	xxxxxxxx	xxxxxxxx
xxx	yyyy	Screening	xxxxxxxx	xxxxxxxx	xxxxxxxx
		Day 1 (Preop)	xxxxxxxx	xxxxxxxx	xxxxxxxx
xxx	yyyy	Screening	xxxxxxxx	xxxxxxxx	xxxxxxxx
		Day 1 (Preop)	xxxxxxxx	xxxxxxxx	xxxxxxxx

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

Note to programmer: *Use this template also for listing:*

Listing 16.2-22.1.2: Urine Drug Screen, Alcohol Blood Test and Pregnancy Test (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

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Listing 16.2-23.1.1: Admission and Discharge (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

		Date and Time			
		Surgical Facility		PACU	
Site	Subject	Admission	Discharge	Admission	Discharge
xxx	yyyy	ddmmmyyyyThh:mm	ddmmmyyyyThh:mm	ddmmmyyyyThh:mm	ddmmmyyyyThh:mm
xxx	yyyy	ddmmmyyyyThh:mm	ddmmmyyyyThh:mm	ddmmmyyyyThh:mm	ddmmmyyyyThh:mm
xxx	yyyy	ddmmmyyyyThh:mm	ddmmmyyyyThh:mm	ddmmmyyyyThh:mm	ddmmmyyyyThh:mm

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

Note to programmer: *Use this template also for listing:*

Listing 16.2-23.1.2: Admission and Discharge (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

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Listing 16.2-24.1.1: Informed Consent (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

		Met Criteria				
Site	Subject	Screening Visit	Signed Consent	Protocol Version	Inclusion	Exclusion
xxx	yyyy	ddmmmyyyy	ddmmmyyyy	ORIGINAL	YES	YES
xxx	yyyy	ddmmmyyyy	ddmmmyyyy	AMENDMENT 1	NO	YES
xxx	yyyy	ddmmmyyyy	ddmmmyyyy	ORIGINAL	YES	NO

Source: *list SAS datasets used to create table* ddmmmyyyyThh:mm

SAS X.Y program_name

Note to programmer: *Use this template for the following listing. Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

Listing 16.2-24.1.2: Informed Consent (Group 2: 6 to < 12 years) – All Subjects

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Listing 16.2-25.1.1: Subject Eligibility (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

Site	Subject	Date of Informed Consent	Date of Eligibility Assessment	Criteria Failed
xxx	yyyy	ddmmmyyyy	ddmmmyyyy	
xxx	yyyy	ddmmmyyyy	ddmmmyyyy	
xxx	yyyy	ddmmmyyyy	ddmmmyyyy	Inclusion: 1, 4
xxx	yyyy	ddmmmyyyy	ddmmmyyyy	Exclusion: 8, 10, 12

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

Note to programmer: *Include screen failures in this listing.*

Note to programmer: *Use this template also for listing:*

Listing 16.2-25.1.2: Subject Eligibility (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

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Listing 16.2-25a: Subject Eligibility Inclusion Criteria – All Subjects

Inclusion Criteria
xxxxxxxxxxxxxxxxxxxxxxxxxx
Xxxxxxxxxxxxxxxxxxxxxxxxxx
Xxxxxxxxxxxxxxxxxxxxxxxxxx
Xxxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxxxxxxxxxxxxxxxxxxxxxx

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

Note to programmer: *List inclusion criteria from protocol.*

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Listing 16.2-25b: Subject Eligibility Exclusion Criteria – All Subjects

Exclusion Criteria
Xxxxxxxxxxxxxxxxxxxxxxxxx
Xxxxxxxxxxxxxxxxxxxxxxxxx
Xxxxxxxxxxxxxxxxxxxxxxxxx
Xxxxxxxxxxxxxxxxxxxxxxxxx
Xxxxxxxxxxxxxxxxxxxxxxxxx
Xxxxxxxxxxxxxxxxxxxxxxxxx
Xxxxxxxxxxxxxxxxxxxxxxxxx
Xxxxxxxxxxxxxxxxxxxxxxxxx

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

Note to programmer: *List exclusion criteria from protocol.*

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Listing 16.2-26: Unique Adverse Event Terms and Associated Coded Terms

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

Coded using MedDRA

Source: *list SAS datasets used to create listing* *ddmmmyyyyThh:mm*

SAS X.Y *program_name*

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

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Listing 16.2-27: Unique Medication Terms and Associated Coded Terms

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

Coded using Who Drug Dictionary

Source: *list SAS datasets used to create listing* *ddmmmyyyyThh:mm*

SAS X.Y *program_name*

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

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Listing 16.2-28.1.1: Protocol Deviations (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

Site	Subject	Importance	Date	Description
xxx	yyyy	Important	ddmmmyyyyThh:mm	xxxxxxxxxxxxxxxxx
		Minor	ddmmmyyyyThh:mm	xxxxxxxxxxxxxxxxx

Source: *list SAS datasets used to create listing* *ddmmmyyyyThh:mm*

SAS X.Y *program_name*

Note to programmer: *Subjects may have multiple deviations. Sort deviations by importance, then by treatment, site, and subject. Date may or may not include time. Use this template also for listing:*

Listing 16.2-28.1.2: Protocol Deviations (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

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Listing 16.2-29-1.1: Physical Exam (Group 1: 12 to <17 years) – All Subjects

TREATMENT: *treatment-name*

Site	Subject	Not Done	If Not Done, Provide Reason	Date and Time
xxx	yyyy			ddmmmyyyyThh:mm

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

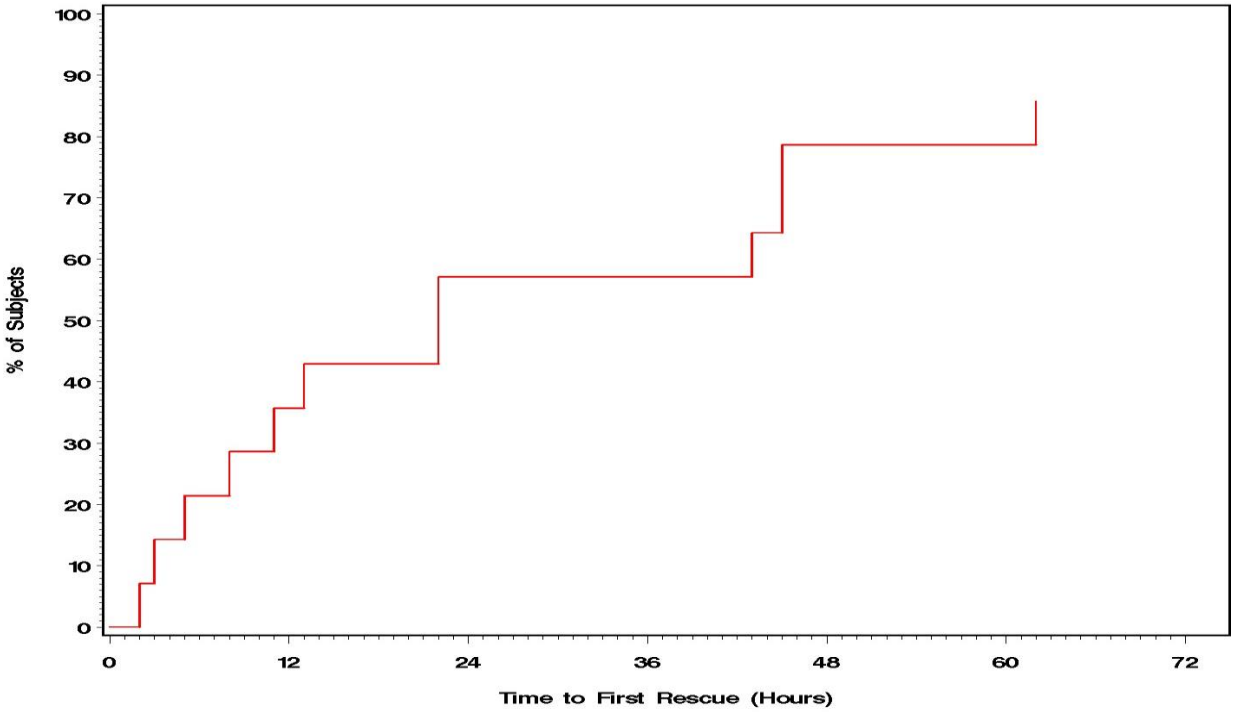
Note to programmer: *Sort by date and time within subject. Use this template also for listing:*

Listing 16.2-29-1.2: Physical Exam (Group 2: 6 to < 12 years) – All Subjects

Note to programmer: *Replace "TREATMENT" with "SURGERY TYPE", followed by "Spine Surgery" or "Cardiac Surgery".*

13. TABLE OF CONTENTS FOR FIGURE MOCK-UPS

Figure 1.1.1 Plot of Time to First Rescue Medication Use (Group 1: 12 to <17 years) – Safety Population



Rescue Time (hrs):	12	24	36	48	60	72
Number (%) of Subjects:	5(36%)	8(57%)	8(57%)	11(79%)	11(79%)	12(86%)
Number of Censored Observations:	0	1	0	0	0	3

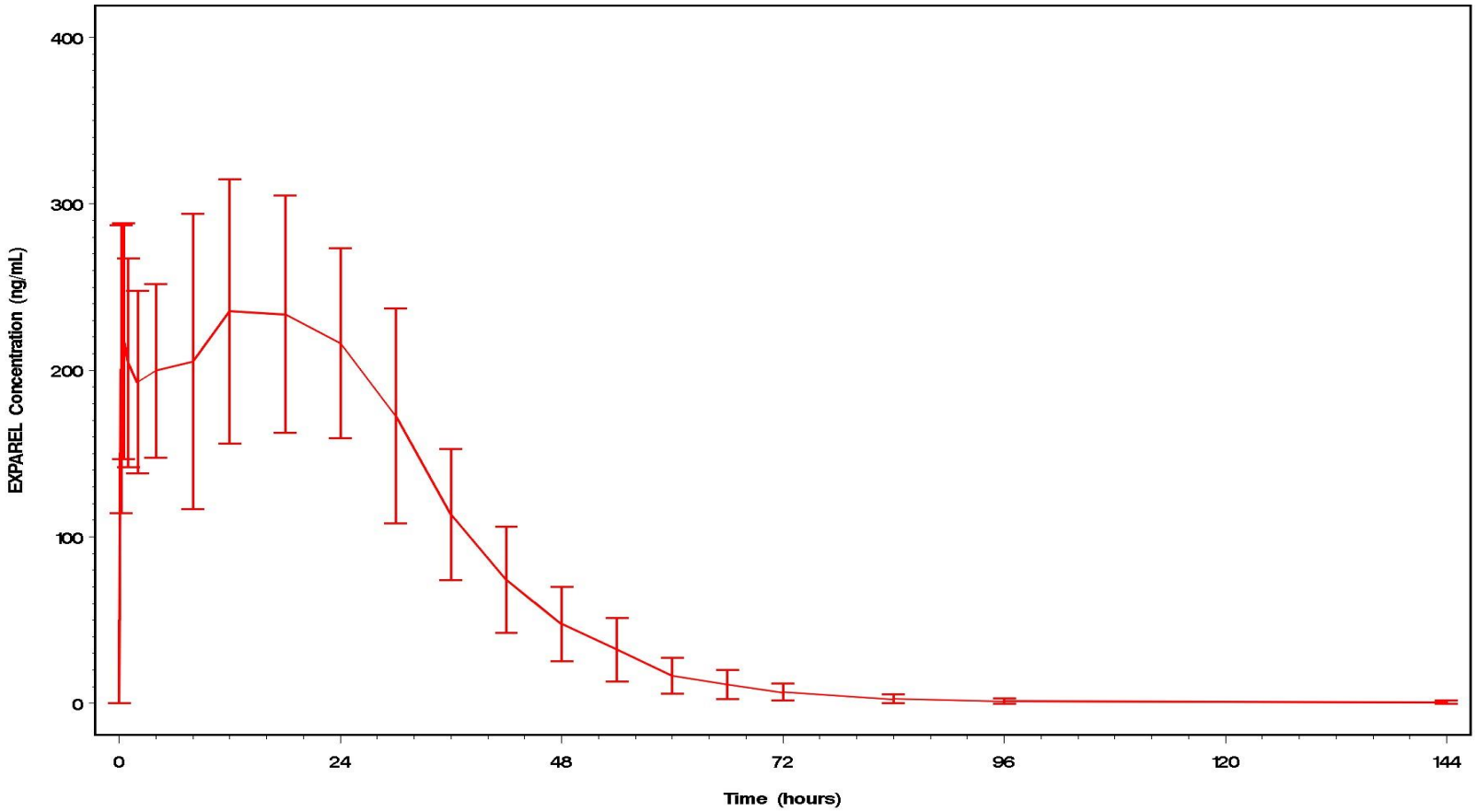
***Note to programmer**: Time to first rescue on x-axis 0-72 Hours by 12. Overlay both treatments for Group 1. For table underneath plot, provide for each treatment in Group 1 with a header for treatment. Add footnote: "Subjects who are not administered an opioid rescue medication by 72 hours are censored at 72 hours after surgery or at the time of last follow-up, whichever is earliest."*

Use this template for the following figure:

Figure 1.1.2 Plot of Time to First Rescue Medication Use (Group 2: 6 to < 12 years) – Safety Population

***Note to programmer**: Time to first rescue on x-axis 0-72 Hours by 12. Overlay both surgery types for Group 2. For table underneath plot, provide for each surgery type in Group 2 with a header for surgery type. Add footnote: "Subjects who are not administered an opioid rescue medication by 72 hours are censored at 72 hours after surgery or at the time of last follow-up, whichever is earliest."*

Figure 2.1.1 Plot of Mean (± SD) Bupivacaine Concentrations (ng/mL) over Time (Group 1: 12 to <17 years) – PK Population – Linear Scale



***Note to programmer**: Overlay both treatments for Group 1. For Samples 4-8, use the midpoint of the collection window for the tick mark (i.e. 1.125 for 1-1.25 window). Label the tick mark with the time window (i.e. "1-1.25 hr"). Change the y-axis label to "Bupivacaine Concentration (mg/mL)".*

Add footnotes: "For concentrations below the limit of quantification (BLOQ), pre-dose values are set to zero, BLOQ values between the dosing time and the first time point above lower limit of quantification (LLOQ) are set to 0, BLOQ values at time points between two measurable concentration values are set to ½ of LLOQ (lower limit of quantification), and all remaining BLOQ values are set to missing. For Samples 4-8, the midpoint of the collection window is used for the tick mark. "

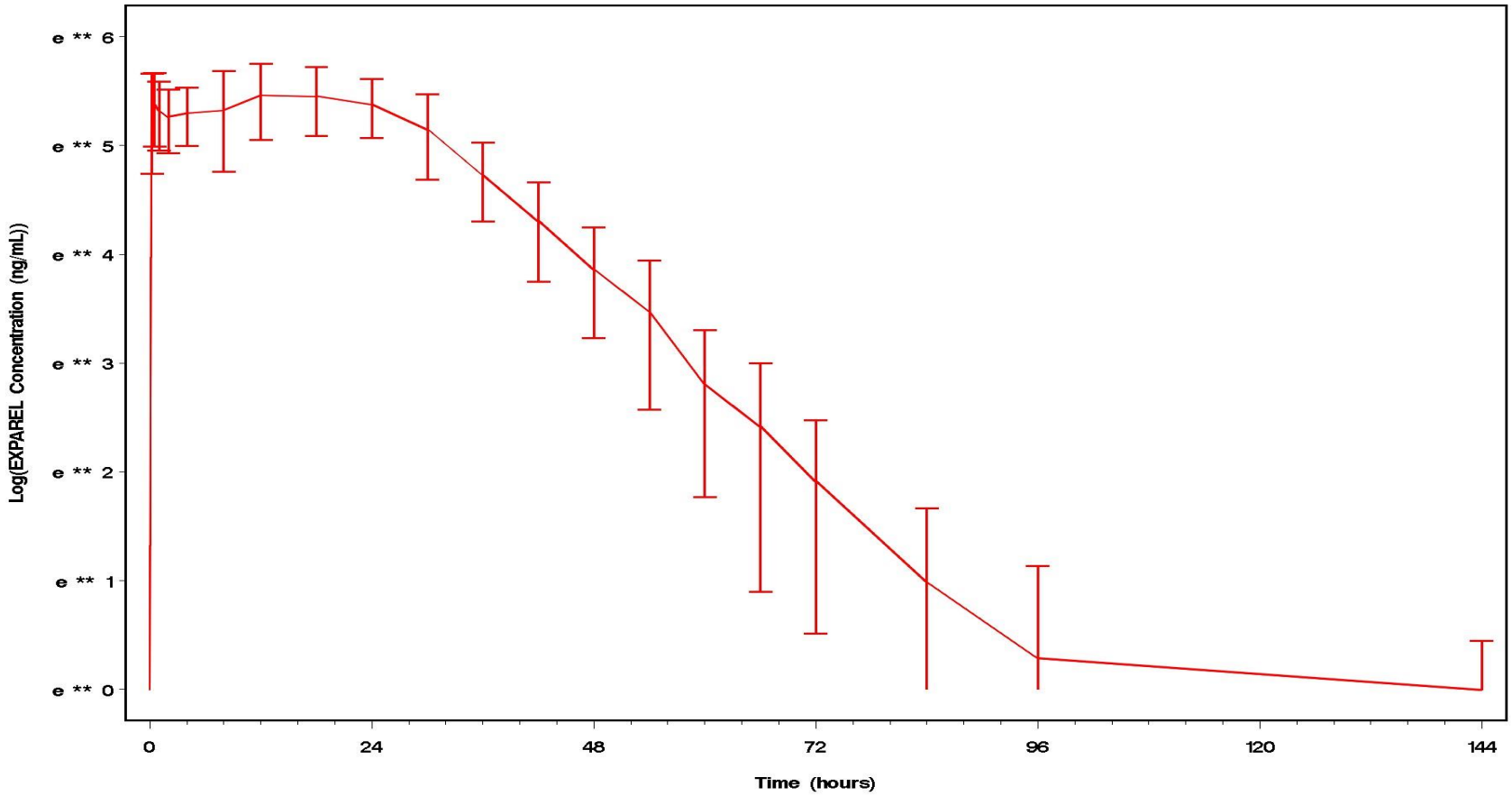
Use this template for the following figures:

Figure 2.1.2 Plot of Mean (± SD) Bupivacaine Concentrations (ng/mL) over Time (Group 2: 6 to < 12 years) – Spine Surgery - PK Population – Linear Scale

Figure 2.1.3 Plot of Mean (± SD) Bupivacaine Concentrations (ng/mL) over Time (Group 2: 6 to < 12 years) – Cardiac Surgery - PK Population – Linear Scale

Figure 2.1.4 Plot of Mean (± SD) Bupivacaine Concentrations (ng/mL) over Time (Both Groups: 6 to < 17 years) – Spine Surgery - PK Population – Linear Scale

Figure 3.1.1 Plot of Mean (± SD) Bupivacaine Concentrations (ng/mL) over Time (Group 1: 12 to <17 years) – PK Population – Semi-logarithmic Scale



***Note to programmer**: Overlay both treatments for Group 1. Change the y-axis label to "Log(Bupivacaine Concentration (mg/mL))".Use this template for the following figure:*

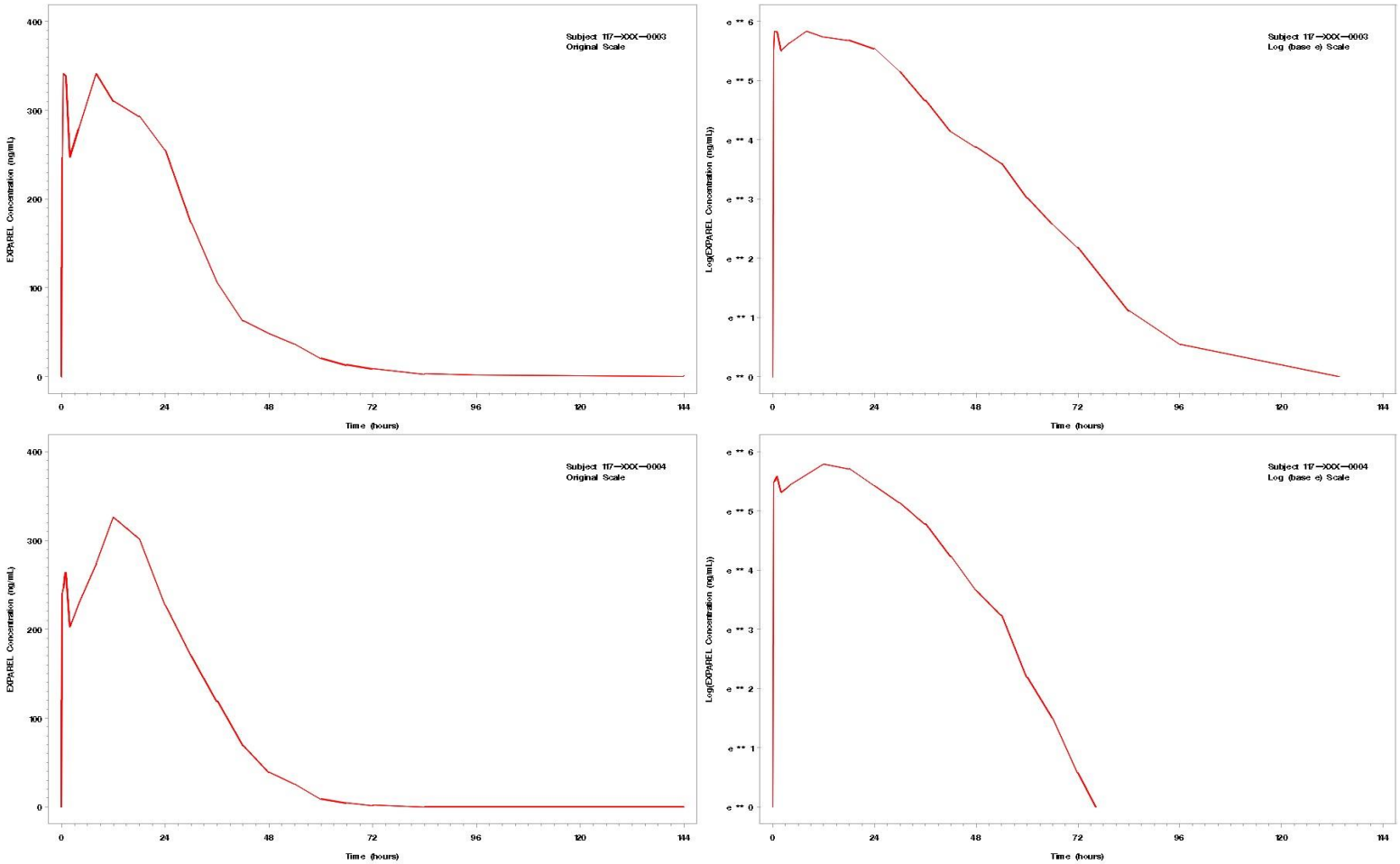
Figure 3.1.2 Plot of Mean (± SD) Bupivacaine Concentrations (ng/mL) over Time (Group 2: 6 to < 12 years) – Spine Surgery - PK Population – Semi-logarithmic Scale

Figure 3.1.3 Plot of Mean (± SD) Bupivacaine Concentrations (ng/mL) over Time (Group 2: 6 to < 12 years) – Cardiac Surgery - PK Population – Semi-logarithmic Scale

Figure 3.1.4 Plot of Mean (± SD) Bupivacaine Concentrations (ng/mL) over Time (Both Groups: 6 to < 17 years) – Spine Surgery - PK Population – Semi-logarithmic Scale

Figure 4.1.1 Plot of Individual Bupivacaine Concentrations (ng/mL) over Time (Group 1: 12 to <17 years) – PK Population – Linear-Linear and Log-Linear

Note to programmer: *Modify the figures below as follows: Combine each pair of figures for individual subjects into one figure. Put log-linear scale on right hand side x-axis. Overlay two lines on one figure.*



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

Figure 4.1.2 Plot of Individual Bupivacaine Concentrations (ng/mL) over Time (Group 2: 6 to < 12 years) – PK Population – Cardiac Surgery – Linear-Linear and Log-Linear

Figure 4.1.3 Plot of Individual Bupivacaine Concentrations (ng/mL) over Time (Group 2: 6 to < 12 years) – PK Population – Spine Surgery – Linear-Linear and Log-Linear

Figure 4.1.4 Plot of Individual Bupivacaine Concentrations (ng/mL) over Time (Group 1: 12 to <17 years) – PK Population – Linear-Linear and Log-Linear

***Note to Programmer:** If there is a lot of dose variation (i.e. a lot of departure from 4 mg/kg EXPAREL or Bupivacaine HCl 2 mg/kg), add figures for dose normalized concentration.*

***Note to programmer**: Use Figure 2.1.1 for the figures below.*

Figure 5.1.1 Plot of Mean (± SD) Numeric Rating Scale at Rest Pain Intensity Scores over Time (Group 1: 12 to <17 years) – Safety Population

***Note to programmer**: Replace label on y-axis with "NRS-R". Overlay both treatments for Group 1.*

Figure 5.1.2 Plot of Mean (± SD) Color Analog Scale Pain Intensity Scores over Time (Group 2: 6 to < 12 years) – Safety Population

***Note to programmer**: Replace label on y-axis with "CAS". Overlay lines for Spine Surgery and Cardiac Surgery for Group 2.*