Pacira Pharmaceuticals, Inc.
EXPAREL

Document:	Clinical Study Protocol
Official Title:	A Multicenter Study to Evaluate the Pharmacokinetics and Safety of EXPAREL for Postsurgical Analgesia in Pediatric Subjects Aged 6 to Less Than 17 years (PLAY)
NCT Number:	NCT03682302
Document Date:	October 1, 2018

CLINICAL STUDY PROTOCOL

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

Protocol No.:	402-C-319
EudraCT No.:	Not applicable
IND No.:	69,198
Study Phase:	Phase 3
Study Drug:	EXPAREL® (bupivacaine liposome injectable suspension)
Date:	01-OCT-2018
Study Sites:	Multicenter study in the United States
Sponsor:	Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, New Jersey 07054 Telephone: (973) 254-3560

1. SIGNATURE PAGE

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2. SYNOPSIS

Name of Sponsor/Company: Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 (973) 254-3560	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: EXPAREL		
Name of Active Ingredient: Bupivacaine, 1.3%, 13.3 mg/mL		

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

Principal Investigators: To be determined

Study Centers: Multicenter study in the United States (US)

Publications (Reference): None

Objectives:

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.

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.

Methodology:

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 PK and safety in subjects aged 6 to less than 17 years, while Part 2 will assess safety in subjects aged 6 to less than 17 years.

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 complete enrollment 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).

	Surgery Type, Dose, and Number of Subjects [n]	
	Part 1 (PK and Safety)	Part 2 (Safety)
Group 1 (subjects aged 12 to <17 years)	Spine Surgery EXPAREL 4 mg/kg [15] bupivacaine HCl 2 mg/kg [15]	Spine Surgery EXPAREL 4 mg/kg [15] bupivacaine HCl 2 mg/kg [15]
Group 2 (subjects aged 6 to <12 years)	Spine or Cardiac Surgery EXPAREL 4 mg/kg [15]	Spine or Cardiac Surgery EXPAREL 4 mg/kg [15]

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

Part 1 is a multicenter, randomized, open-label study in subjects aged 6 to less than 17 years undergoing spine or cardiac surgeries. There will be two treatment groups: Group 1 will include subjects aged 12 to less than 17 years, while Group 2 will include subjects aged 6 to less than 12 years. Safety will be assessed as a secondary objective.

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Name of Active Ingredient: Bupivacaine, 1.3%, 13.3 mg/mL		

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 sample size is a total of 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-labeled, PK evaluation study in subjects aged 6 to less than 12 years undergoing spine or cardiac surgery. The sample size is a total of 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.

The total sample size for Part 1 is 45 subjects aged 6 to less than 17 years, with 30 subjects in Group 1 and 15 subjects in Group 2.

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

Part 2 is a multicenter, randomized, open-label, safety study in subjects aged 6 to less than 17 years undergoing spine or cardiac surgeries. There will be two treatment groups: Group 1 will include subjects aged 12 to less than 17 years, while Group 2 will include subjects aged 6 to less than 12 years.

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 sample size is a total of 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 2, Group 2, is a single-arm (EXPAREL 4 mg/kg), open-labeled study in subjects aged 6 to less than 12 years undergoing spine or cardiac surgery. The sample size is a total of 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.

The total sample size for Part 2 is 45 subjects aged 6 to less than 17 years, with 30 subjects in Group 1 and 15 subjects in Group 2.

The overall safety assessment will include all 45 subjects from Part 1 and all 45 subjects from Part 2, with a total of 90 subjects.

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, urine pregnancy test for females of childbearing potential, urine drug screen and alcohol breath test will be conducted.

On Day 1, eligible subjects will receive the study drug intraoperatively at the end of surgery via local infiltration to

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produce local analgesia. Use of intraoperative opioids, acetaminophen, ketorolac, or other non-steroidal anti-inflammatory drugs (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 judgment of the treating physician. For subjects discharged from the hospital before all protocol-specified assessments till 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 till 96 hours.

A follow-up phone call will be scheduled for all subjects on Day 7. For the assessment of adverse events (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 till the hospital discharge. Avoid additional use of local anesthetics within 96 hours following the administration EXPAREL.

Postsurgical Assessments

Postsurgical assessments to be done till 96 hours include pain intensity using the 11-point Numeric Rating Scale at Rest (NRS-R; Appendix 1) for subjects aged 12 to less than 17 years and the Color Analog Scale (CAS; Appendix 2) for subjects aged 6 to less than 12 years; neurological assessment (Appendix 3); clinical laboratory tests (Appendix 4); and vital signs.

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

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 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 (NCI) Common Terminology Criteria for Adverse Events (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 persists

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beyond 72 hours post dose.

Cardiac or neurological AEs that do not meet one of these three criteria for AESI should be reported as described in Section 14.1 (Adverse Events) and captured in the database as an AE.

Pharmacokinetic Assessment **(Part 1 only)**

A population PK sampling scheme will be used to limit the number of blood draws for each individual subject. On Day 1, eligible subjects will be assigned to one of the two PK sampling groups shown below based on surgery type (see the table below for PK sample collection schedule). 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. Having two separate PK sampling sequences for spine and cardiac surgeries will help to guard against clustering of PK samples.

Table: PK Sample Collection

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

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 treatments.

Note that a new needle stick may not be necessary for each blood draw. The subject may be fitted with a peripheral venous line at the discretion of the investigator to facilitate the collection of blood for PK assessment.

In the situation where PK blood draws and other assessments coincide with 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 other assessments.

Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be set up to monitor the safety and dosing data on an ongoing basis for all treatment groups.

Number of Subjects (Planned):

Approximately 90 subjects are planned for this study: 45 in Part 1 and 45 in Part 2. Overall, 60 subjects will receive EXPAREL and 30 subjects will receive immediate release bupivacaine.

Eligibility Criteria:

Inclusion Criteria

1. Subjects whose parent(s) or guardian(s) has/have signed and dated the ICF for the subject to participate in the study, and subjects who have provided written assent to participate in the study (if capable).
2. American Society of Anesthesiologists (ASA) Class 1-3.

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3. Male or female subjects 6 to less than 17 years of age on the day of surgery.
4. Body mass index (BMI) at screening within the 5th to 95th percentile for age and sex (see Appendix 5).
5. A negative pregnancy test for female subjects of childbearing potential must be available prior to the start of surgery. The pregnancy test must be conducted in the preoperative holding area according to the study site's standard of care.
6. Subjects and their parent(s)/guardian(s) must be able to speak, read, and understand the language of the ICF and any instruments used for collecting subject-reported outcomes to enable accurate and appropriate responses to study assessments, and provide informed consent/assent.
7. Subjects must be able to adhere to the study visit schedule and complete all study assessments.

Exclusion Criteria

1. Currently pregnant, breastfeeding, or planning to become pregnant during the study or within 1 month after study drug administration.
2. History of hypersensitivity or idiosyncratic reactions to amide-type local anesthetics or to opioid medication.
3. Contraindication to bupivacaine HCl or other amide-type local anesthetics or to opioid medication.
4. Administration of EXPAREL or bupivacaine HCl within 30 days prior to study drug administration.
5. Subjects with coagulopathies or immunodeficiency disorders.
6. History of, suspected, or known addiction to or abuse of drugs or alcohol within the past 2 years.
7. Clinically significant medical or psychiatric disease that, in the opinion of the investigator, indicates an increased vulnerability to study drugs and/or procedures.
8. Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study.

In addition, the subject will be ineligible to receive study drug if he or she meets the following criterion during surgery:

9. Any clinically significant event or condition uncovered during the surgery (e.g., excessive bleeding, acute sepsis) that might render the subject medically unstable or complicate the subject's postsurgical course.

Test Product, Dose, Mode of Administration, and Lot Number:
Name: EXPAREL (bupivacaine liposome injectable suspension).
Active ingredient: Bupivacaine 1.3%, 13.3 mg/mL
Dosage: Single dose of EXPAREL 4 mg/kg
Lot number: To be determined
Mode of administration: Intraoperative local infiltration

Reference Product, Dose, Mode of Administration, and Lot Number:
Name: Bupivacaine HCl
Active ingredient: Bupivacaine HCl
Dosage: 2 mg/kg, not to exceed a maximum dose of 175 mg
Lot number: Commercial product to be provided by Pacira
Mode of administration: Intraoperative local infiltration

Duration of Subject Participation in the Study:
Participation will begin at the signing of the ICF/obtaining written assent. No more than 30 days should pass between signing of the ICF/obtaining written assent and the administration of study drug. The time from study drug administration till the end of participation is 30 ± 3 days. Therefore, subjects may participate in the study for

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up to 63 days.

Pharmacokinetic Analysis (Part 1 only):
A total of 8 blood samples will be collected from each subject at specific time windows for the determination of plasma bupivacaine concentrations. Population PK modeling will be performed using all PK data collected during the study. The population PK model will characterize overall PK of bupivacaine from EXPAREL and will also characterize the PK of immediate release bupivacaine.

Pharmacokinetic Endpoints (Part 1 only):
The following PK endpoints will be predicted from the model:

- Area under the plasma concentration-versus-time curve (AUC)
- Maximum plasma concentration (C_{max})
- The apparent terminal elimination half-life ($t_{1/2el}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution (Vd/F)

Safety Assessments:
The following safety assessments will be conducted at the time points specified:

- Vital signs (temperature, resting heart rate, respiratory rate, oxygen saturation, and blood pressure) at screening; at baseline (on Day 1 prior to surgery); upon arrival in the post-anesthesia care unit (PACU); at 2, 4, 8, 12, 24, 36, 48, 60, 72, and 96 hours after the end of study drug administration; at hospital discharge; and on Day 30.
- Neurological assessment at screening; at 2, 4, 8, 12, 24, 36, 48, 60, 72, and 96 hours after the end of study drug administration; at hospital discharge; and on Day 30 (Part 1 only, see Appendix 3).
- Clinical laboratory tests (hematology, chemistry, and urinalysis) at screening; at baseline (on Day 1 prior to surgery); and at 96 hours after the end of study drug administration (see Appendix 4).
- AEs from the time the ICF is signed/assent is obtained till Day 30.

Safety Endpoints:
The following safety endpoints will be assessed based on the safety measurements conducted at the specified time points:

- Change from baseline in vital signs (temperature, resting heart rate, respiratory rate, oxygen saturation, and blood pressure).
- Summary of neurological assessments (proportion of subjects who are oriented, and proportion of subjects who have any neurologic events). Note: Events identified during the neurologic assessment should be recorded as AEs.
- Change from baseline in clinical laboratory data.
- Incidence of treatment-emergent AEs (TEAEs) and SAEs till Day 30.

Other Assessments:
The following efficacy measurements will be done for exploratory purposes only:

- Pain intensity scores at screening; at 4, 8, 12, 24, 36, 48, 60, 72, and 96 hours after the end of study drug administration; immediately prior to each administration of postoperative opioid pain management medication till 96 hours; and at hospital discharge. If a subject is too anesthetized at the time of a scheduled pain intensity assessment, the assessment should be skipped. Pain intensity will be measured as follows:

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- 11-point NRS-R for subjects aged 12 to less than 17 years (Appendix 1)
- CAS for subjects aged 6 to less than 12 years (Appendix 2)

- Postsurgical opioid pain management medication use (time, dose) till 96 hours after the end of study drug administration.

Other Endpoints:

Analysis of other endpoints will be conducted for exploratory purposes only. The efficacy endpoints listed below will be assessed based on the efficacy measurements conducted at the time points specified.

- Pain intensity scores.
- Area under the curve (AUC) of pain intensity scores.
- Total opioid consumption in morphine equivalents.
- Time to first postsurgical use of opioid medication.

Statistical Methods:

A comprehensive statistical analysis plan will be developed for this study. Descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) will be provided for continuous data. Tabulations (number and percentage of subjects) by category will be provided for categorical data. This study is not powered for efficacy.

A prospective population PK analysis plan will be developed. Nonlinear mixed-effect modeling will be used to analyze the sparse concentration-versus-time data.

Population and individual PK parameters will be estimated. Individual PK parameters estimated for each subject will be used to compute PK exposures (AUC and C_{max}). All PK parameters will be presented in listings and descriptive summary statistics, including the arithmetic mean, median, range, standard deviation, and coefficient of variation. Details and results of this mixed-effect modeling analysis will be reported separately.

Sample Size

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

Table 1: Time and Events Schedule of Study Procedures

	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**
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.

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4. LIST OF ACRONYMS/ABBREVIATIONS AND DEFINITIONS OF TERMS

4.1. List of Acronyms/Abbreviations

ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ASA	American Society of Anesthesiology
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
CAS	Color Analog Scale
CFR	Code of Federal Regulations
CK	Creatine kinase
CPK	Creatine phosphokinase
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
ER	Emergency room
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
LDH	Lactate dehydrogenase
NCI	National Cancer Institute
NDA	New Drug Application
NRS-R	Numeric rating scale – at rest
NSAID	Non-steroidal anti-inflammatory drug

OR	Operating room
PACU	Post-anesthesia care unit
PCA	Patient-controlled analgesia
PK	Pharmacokinetic
PMR	Post Marketing Requirement
PPD	Premier Perspective™ Database
PTAE	Pre-treatment adverse event
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard Deviation
TIBC	Total iron binding capacity
TEAE	Treatment-emergent adverse event
UIBC	Unsaturated iron binding capacity
US	United States
WHO	World Health Organization

4.2. Definition of Terms

Pharmacokinetic terms are defined in Section 12.2.

5. ETHICS

5.1. Institutional Review Board/Independent ethics committee

Prior to enrolling subjects into this study, each study site will obtain the approval of an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) that complies with the International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) and/or the United States (US) Food and Drug Administration (FDA) Title 21 Code of Federal Regulations (CFR) Part 56. Attention is directed to the basic elements that are required to be incorporated into the informed consent form (ICF) under 21 CFR Part 50.25 and ICH GCP.

5.2. Ethical Conduct of the Study

This study will be conducted in accordance with the clinical research guidelines established by the FDA Title 21 CFR, Parts 50 (including Subpart D regarding additional safeguards for children in clinical investigations), 54, 56, and 312, and the ICH GCP. Study documents will be maintained in accordance with applicable regulations.

5.3. Subject Information, Consent, and Assent

Before a subject undergoes any study-specific screening procedures, the investigator or designee will thoroughly explain to the subject's parent/guardian the purpose of the study, the associated procedures, and any expected effects and potential adverse reactions. A copy of the IRB- or IEC-approved ICF will be provided to the subject's parent/guardian, who will be given sufficient time and opportunity to inquire about the details of the study and decide whether or not to enroll their child. The subject's parent/guardian, and the study staff with whom he or she discusses the ICF, will sign and date the ICF. If the subject is capable of providing assent, he or she will be provided with an explanation of the study and an IRB- or IEC-approved written assent form to read. Once the investigator is assured that the subject understands the concepts involved, the subject will be asked to give assent (if applicable) to participate in the study. The subject's parent/guardian must sign the ICF and the subject must give assent (if applicable) before any study-specific procedures are performed. A copy of the fully signed ICF will be given to the parent/guardian and a copy of the assent form (if applicable) will be given to the subject.

The investigator will explain to the subject's parent/guardian that they are completely free to decline entering their child into the study and to withdraw their child from the study at any time, for any reason, without risking his or her medical care. The subject may also independently withdraw assent to participate in the study. Similarly, the investigator and/or Pacira Pharmaceuticals, Inc. (Pacira) will be free to withdraw the subject at any time for safety or administrative reasons. Any other requirements necessary for the protection of the human rights of the subject will also be explained, according to the current ICH GCP (E6) and the Declaration of Helsinki (1964, and as amended through 2013).

6. INVESTIGATORS AND STUDY ADMINISTRATION STRUCTURE

Information regarding the investigators, sites, laboratories, and other service providers is available upon request to the IRB/IECs and regulatory agencies.

7. INTRODUCTION

With the identification of acute pain by the World Health Organization (WHO) as a problem of global proportions (Gureje 1998) and the publication of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) pain standards, there is increasing acceptance of pain as the fifth vital sign, on par with blood pressure, pulse, temperature, and respiration rate (Lynch 2001).

Postsurgical pain is one of the most common forms of acute pain (Schug 1993; Carr 1999). In contrast to chronic pain, for which no adaptive value has been demonstrated, acute pain is the normal physiological response to tissue insult or injury and has adaptive value by serving as a warning of danger or damage. Most acute pain is either treatable or avoidable, especially when it occurs in a clinical setting. However, if acute pain is poorly or inappropriately treated, it may progress to chronic pain (Perkins 2000; Petersen-Felix 2002). Thus, effectively modulating the response to acute pain may be considered a primary step in the prevention of chronic pain (Stephen 2003). The suboptimal management of acute pain has been recognized as a problem by clinicians for more than 50 years (Papper 1952; Marks 1973) and has been formally identified as a public health concern by various societies and government institutions worldwide.

In 1992, the US Agency for Health Care Policy and Research developed guidelines for the management of postoperative pain in the hopes of increasing awareness of the consequences of poor pain control in the postoperative setting and promoting better pain management techniques (Stephen 2003). These consequences, which include delayed healing, longer hospitalization, and the development of chronic pain, are significant not only from the patient's perspective (decrease in functionality and quality of life) but also from the health economic perspective (increase in healthcare resource utilization and costs).

Each year, more than 5 million children undergo surgery in the US, and it is estimated that up to 75% of these patients experience significant postoperative pain and receive postoperative analgesia (Owen 1990). Opioid use is ubiquitous among hospitalized patients undergoing surgical procedures (Kessler 2013). One consequence is a growing epidemic of opioid use, misuse, and diversion (Morris 2015; Joranson 2006). Specific to the pediatric population, prescription opioid use before the 12th grade is a predictor of future opioid misuse, with a 33% increase in future risk of misuse after high school (Miech 2015).

A multimodal approach to postoperative analgesia, using a combination of agents (e.g., opioids, local anesthetics, non-steroidal anti-inflammatory drugs [NSAIDs]), and delivery techniques (patient-controlled analgesia [PCA], epidural and regional blocks) is currently recognized as

best practice for pain management (Breivik 1995a; Breivik 1995b; American Society of Anesthesiologists [ASA] Task Force 1995; Dahl 2000). EXPAREL® was developed to extend pain relief with a single-dose administration without the use of indwelling catheters and to decrease the requirement for supplemental opioid medications.

A New Drug Application (NDA) for EXPAREL was submitted as a 505(b)(2) application and subsequently approved by the US FDA on October 28, 2011 (NDA 022-496). As part of the approval for EXPAREL, Pacira is required to conduct pediatric studies as a Post Marketing Requirement (PMR).

7.1. Indication

EXPAREL was initially approved by the US FDA in 2011 for single-dose administration into the surgical site to produce postsurgical analgesia. The indication was amended and approved by the US FDA in 2018 to read: "EXPAREL is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus block to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks."

EXPAREL was developed to provide a prolonged period of decreased pain and decreased opioid use with a single-dose administration without the use of indwelling catheters.

Effective postsurgical pain control is a critical element in patient recovery following surgery, as the majority of patients may experience significant pain, particularly in the first few days. Improved postsurgical pain management contributes to better healing, faster patient mobilization, shortened hospital stays, and reduced healthcare costs (ASA Task Force 1995).

7.2. Current Therapies/Treatments

Current modalities of postsurgical analgesic treatment include infiltration and nerve block with local anesthetic agents, usually combined with the systemic administration of analgesics (multimodal therapy). Multimodal therapy usually includes opioid medications, NSAIDs, and/or acetaminophen provided through a variety of routes including intravenous, transdermal patch, and oral administration. Opioids are widely used and considered amongst the most powerful analgesics; however, they also have considerable drawbacks, including time and resources required for monitoring opioid-related side effects. A reduction in the use of postoperative opioids is desirable to decrease the incidence and severity of opioid-induced adverse effects, such as respiratory depression, nausea, vomiting, constipation, somnolence, pruritus, and urinary retention.

With over 70 million surgeries performed annually in the US, postoperative pain is a ubiquitous condition among the US population. While it is a predictable component of the postoperative process, such pain is often poorly managed, resulting in clinical and physiological changes that increase morbidity and mortality (inability to ambulate early, etc.), diminish quality of life, and extend length of stay, thereby increasing hospital expenditures (Oderda 2007) and reducing

patient satisfaction. Effective relief of acute pain with minimal opioid complications, on the other hand, may improve clinical outcomes, avoid complications (like delay in regaining bowel function or an inability to tolerate liquid and solid oral intake), and conserve healthcare resources. As such, the JCAHO requires that all healthcare facilities practice adequate pain management and monitor opioid-related adverse events (AEs) (Apfelbaum 2003).

Opioid analgesics have long been established to be the most effective agents used for the management of moderate to severe postoperative pain, and are currently considered the mainstay of treatment. However, AEs related to opioid administration (e.g., nausea, vomiting, ileus, confusion) represent one important reason to develop opioid-sparing strategies. Indeed, fear of gastrointestinal side effects, such as nausea and vomiting, as well as respiratory depression, present major limitations for the widespread use of opioid analgesics (Chernin 2001 and Viscusi 2009). Furthermore, management of opioid-related events often requires medical attention (e.g., opioid antagonists, antiemetic agents) and increased pharmacy/nursing time, which may raise healthcare expenses (Carroll 1994).

7.3. EXPAREL (bupivacaine liposome injectable suspension)

Bupivacaine is one of the longer-acting local anesthetics, but even so it has a limited duration of action after local administration, usually less than 8 hours. EXPAREL is a bupivacaine liposome injectable suspension. It consists of microscopic spherical, multivesicular liposomes (DepoFoam® drug delivery system), organized in a honeycomb-like structure comprising numerous non-concentric internal aqueous chambers containing a bupivacaine base at a concentration of 13.3 mg/mL. Each chamber is separated from adjacent chambers by lipid membranes. The lipids (phospholipids, cholesterol, and triglycerides) are naturally occurring or close analogs of endogenous lipids. Bupivacaine is slowly released from the DepoFoam particles by a complex mechanism involving reorganization of the barrier lipid membranes and subsequent diffusion of the drug over an extended period of time. EXPAREL has been noted in infiltration studies to have a bimodal curve (Apseloff 2013), with an initial peak occurring at approximately 0 to 2 hours and a second peak at approximately 24 to 48 hours (Hu 2013).

7.4. Summary of Human Clinical Experience with EXPAREL

The EXPAREL clinical development program assessed the efficacy and safety across a wide range of body regions and applications, investigating its use in the management of acute pain when administered as a peripheral nerve block for regional analgesia, and as a field block for local analgesia. Pacira has conducted 31 clinical studies (13 Phase 1, 7 Phase 2, and 11 Phase 3). Across the 31 completed studies in the clinical program, safety data were collected on 3644 subjects (2141 subjects received EXPAREL, 850 subjects received IR bupivacaine alone, and 653 subjects received placebo).

Across these studies, a total of 2141 adult human subjects received EXPAREL at doses ranging from 9 to 665 mg and by various routes, including field block, peripheral nerve block, subcutaneous, and epidural routes of administration. EXPAREL was well tolerated and had a

favourable safety profile when administered as a field block or as an interscalene brachial plexus nerve block in varying degrees of vascularity in subjects undergoing various surgical procedures. The frequency and types of events are consistent with the profile of other local anaesthetics.

At doses up to 665 mg of EXPAREL, no central nervous system or cardiovascular system AEs observed with high doses of bupivacaine HCl solution have been observed with EXPAREL. Two thorough QTc studies have been conducted; EXPAREL did not cause significant QTc prolongation even at the highest dose evaluated.

Across all studies, the types and the incidence rates of treatment-emergent AEs (TEAEs) were similar between the EXPAREL All Doses group (all doses combined) and the bupivacaine HCl group. The incidence rate for each of the three most common TEAEs (nausea, constipation, and vomiting) was lower in the EXPAREL All Doses group than in the bupivacaine HCl group.

In terms of efficacy, three positive Phase 3 studies (402-C-316, 402-C-317, 402-C-331) demonstrated statistically significant improvements in pain intensity scores compared to placebo or bupivacaine HCl in the postoperative period when administered as a field block (infiltration). All three studies also showed a statistically significant reduction compared to placebo or bupivacaine in total opioid consumption; Studies 316, 317 and 331 additionally show a significantly higher percentage of opioid-free patients and a significantly longer time to first opioid use compared to placebo or IR bupivacaine.

EXPAREL was demonstrated to produce statistically significant and clinically meaningful analgesia in adult patients in two pivotal placebo-controlled Phase 3 studies (317 and 316) involving both orthopedic and soft tissue procedures over 36 and 72 hours, respectively. The primary endpoints (area under the curve [AUC] of the numeric rating scale at rest [NRS-R] pain intensity scores till 72 hours [316] and till 24 hours [317]) were met. Key secondary endpoints (percentage of subjects who received no supplementary opioid medication; total amount of postoperative consumption of opioid medication; and time to first use of opioid medication) were also met, demonstrating prolonged analgesia and reduction of opioid use by various measures. Robust nature of the efficacy results in both pivotal studies, 316 and 317, was demonstrated across subgroups of subjects with various prognostic features and across demographic subgroups.

Study 331 was a Phase 3, multicenter, randomized, double-blind, active-controlled trial of EXPAREL in adult subjects undergoing primary unilateral TKA under spinal anesthesia to investigate pain control and total opioid consumption following a field block. Study 331 compared EXPAREL 266 mg admixed with bupivacaine HCl 100 mg to an active comparator of bupivacaine HCl 100 mg alone. Seventy (70) subjects treated with EXPAREL+ bupivacaine and 69 subjects treated with bupivacaine alone were analyzed. The co-primary efficacy endpoints were the AUC of VAS from 12 to 48 hours and the total opioid consumption (in oral morphine equivalents) from 0 to 48 hours. The cumulative pain intensity in the EXPAREL + bupivacaine group (Mean $AUC_{12\text{-}48}$ = 180.8) was statistically significantly lower than the bupivacaine alone group (mean $AUC_{12\text{-}48}$ = 209.3), so the first co-primary efficacy endpoint was met (P = 0.0381).

The LS geometric mean total opioid consumption from 0 to 48 hours after surgery was statistically significantly lower in the EXPAREL + bupivacaine group than the bupivacaine alone group, so the second co-primary efficacy endpoint was met (16.7 mg vs 84.0 mg; P = 0.0029). In addition, EXPAREL was associated with a higher proportion of subjects who were opioid free through 72 hours (10% vs 0%; P < 0.01) and also significantly prolonged the time to first opioid rescue (median 4.1 hours vs 2.9 hours; P = 0.023) compared to bupivacaine HCl.

An analysis was performed to compare the incidence of opioid-related AEs between the EXPAREL and bupivacaine HCl groups in all bupivacaine-controlled, parallel-group infiltration studies in adults (SIMPLE TKA [total knee arthroplasty] 311, SKY0402-C-208, SIMPLE Hemorrhoidectomy 312, SKY0402-C-209, SKY0402-C-207, SKY0402-C-201, and SIMPLE Breast Augmentation 315). There was a statistically significantly lower incidence of opioid-related AEs in the EXPAREL ≤266 mg group compared to the bupivacaine HCl group till 72 hours post dose. This was consistent with the statistically significantly lower total postoperative consumption of opioids in the EXPAREL ≤266 mg group till 72 hours post dose. Fewer subjects in the EXPAREL ≤266 mg group had at least one opioid-related AE compared to the bupivacaine HCl group (25.6% versus 45.6%; p<0.0001). The total opioid medication administered (adjusted geometric mean) till 72 hours post dose was statistically significantly lower in the EXPAREL ≤266 mg group (7.94 mg) compared to the bupivacaine HCl group (15.84 mg); p<0.0001. The EXPAREL >266 mg group did not show a statistically significant advantage favoring EXPAREL; the mean (standard deviation [SD]) of the average number of opioid-related AEs per subject was 0.58 (0.522), and the total opioid medication administered (adjusted geometric mean) till 72 hours post dose was 22.82 mg in the EXPAREL >266 mg group.

Please see the EXPAREL Full Prescribing Information for safety information regarding the use of EXPAREL for the treatment of postsurgical pain in the setting of infiltration.

Please refer to the Investigator's Brochure for additional information regarding the completed studies.

7.5. Postmarketing Exposure in Adults and Children

As of May-2018, more than 4 million patients have received EXPAREL in the postmarketing setting. While EXPAREL is not approved for use in patients less than 18 years of age, there is evidence that it has been widely used off-label in pediatric cases.

The Premier Perspective™ Database (PPD) is the largest inpatient drug utilization database in the US and contains de-identified hospital chargemaster data from approximately 600 hospitals, which accounts for approximately 15% of all hospitalizations nationwide (McDonald 2013). Recent inquiries into the PPD between 01-Jan-2011 and 31-Mar- 2017 found that it contains data for 2461 patients aged less than 18 years who had been exposed to EXPAREL in both inpatient and outpatient settings, including 1796 patients between 6 and <17 years of age.

In addition, The Cleveland Clinic (Cleveland, Ohio) currently uses EXPAREL off-label as part of its postsurgical multimodal analgesia for patients under the age of 18 years across several surgical procedures. A retrospective chart analysis is being conducted to evaluate the safety profile and clinical benefit of EXPAREL in this setting.

8. OBJECTIVES

8.1. Primary Objective

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

8.2. Secondary Objectives

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

9. OVERALL STUDY DESIGN AND PLAN

9.1. Overall Study Design and Plan

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 PK and safety in subjects aged 6 to less than 17 years, while Part 2 will assess safety in subjects aged 6 to less than 17 years.

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 complete enrollment 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).

	Surgery Type, Dose, and Number of Subjects [n]	
	Part 1 (PK and Safety)	Part 2 (Safety)
Group 1 (subjects aged 12 to <17 years)	Spine Surgery EXPAREL 4 mg/kg [15] bupivacaine HCl 2 mg/kg [15]	Spine Surgery EXPAREL 4 mg/kg [15] bupivacaine HCl 2 mg/kg [15]
Group 2 (subjects aged 6 to <12 years)	Spine or Cardiac Surgery EXPAREL 4 mg/kg [15]	Spine or Cardiac Surgery EXPAREL 4 mg/kg [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. There will be two treatment 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 sample size is a total of 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-labeled, PK evaluation study in subjects aged 6 to less than 12 years undergoing spine or cardiac surgery. The sample size is a total of 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.

The total sample size for Part 1 is 45 subjects aged 6 to less than 17 years, with 30 subjects in Group 1 and 15 subjects in Group 2.

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

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

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 sample size is a total of 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 2, Group 2, is a single-arm (EXPAREL 4 mg/kg), open-labeled study in subjects aged 6 to less than 12 years undergoing spine or cardiac surgery. The sample size is a total of 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.

The total sample size for Part 2 is 45 subjects aged 6 to less than 17 years, with 30 subjects in Group 1 and 15 subjects in Group 2.

The overall safety assessments will include all 45 subjects from Part 1 and all 45 subjects from Part 2, with a total of 90 subjects.

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 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, urine pregnancy test for females of childbearing potential, urine drug screen and alcohol breath test will be conducted.

On Day 1, eligible subjects will receive the study drug intraoperatively at the end of surgery via local infiltration to produce local 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 judgment of the treating physician. For subjects discharged from the hospital before all protocol-specified assessments till 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 till 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 till the hospital discharge.

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

Postsurgical Assessments

Postsurgical assessments to be conducted till 96 hours include pain intensity using the 11-point NRS-R (Appendix 1) for subjects aged 12 to less than years and the Color Analog Scale (CAS; Appendix 2) for subjects aged 6 to less than 12 years; neurological assessment (Appendix 3); clinical laboratory tests (Appendix 4); and vital signs.

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

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 AEs that do not meet one of these three criteria for AESI should be reported as described in Section 14.1 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 (NCI) Common Terminology Criteria for Adverse Events (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.

Pharmacokinetic Assessment (Part 1 only)

A population PK sampling scheme will be used to limit the number of blood draws for each individual subject. On Day 1, eligible subjects will be assigned to one of the two PK sampling groups shown below based on surgery type (Table 2). 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. Having two PK sampling sequences for spine and cardiac surgeries will help to guard against clustering of PK samples.

Table 2: PK Sample Collection

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

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 treatments.

Note that a new needle stick may not be necessary for each blood draw. The subject may be fitted with a peripheral venous line at the discretion of the investigator to facilitate the collection of blood for PK assessment.

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 other assessments.

9.2. Duration of the Study and Subject Participation

Participation will begin at the signing of the ICF/obtaining written assent. No more than 30 days should pass between signing of the ICF/obtaining written assent and the administration of study drug. The time from study drug administration till the end of participation is 30 ± 3 days. Therefore, subjects may participate in the study for up to 63 days.

9.3. Data Safety Monitoring Board

If Pacira, the investigator, or officials from regulatory authorities discover conditions during the study that indicate that the study or study site should be terminated, this action may be taken after Pacira has consulted with appropriate regulatory authorities and notified the investigator(s). A Data Safety Monitoring Board (DSMB) will be set up to monitor the safety and dosing data on an ongoing basis for all treatment groups, with additional expedited DSMB review conducted as necessary.

9.4. Discussion of Study Design

This study is designed to formulate specific guidance regarding dose for the safe administration of EXPAREL in the pediatric population aged 6 to less than 17 years. EXPAREL doses recommended for adults are expressed as absolute values or ranges, whereas doses for pediatric subjects will be based on body weight, consistent with general prescription standards used in pediatric practice.

A population PK modeling of the infiltration studies in adults and simulations to support child/adolescent dosing was performed. Predicted values generated by the final model adequately described observed bupivacaine concentrations following administration of EXPAREL. According to this model, a dose of 4 mg/kg would produce bupivacaine concentrations in pediatric patients aged 6 to less than 17 years analogous to those observed in the adult infiltration studies.

In addition, the available data from The Cleveland Clinic (as discussed in Section 7.5) shows that the average dose among 375 pediatric patients was 4.1 ± 1.8 mg/kg, with no significant AEs attributed to EXPAREL use. This study is designed to further characterize the PK profile and to confirm the safety of the 4 mg/kg dose of EXPAREL.

A population PK sampling scheme will be used to limit the number of blood draws. A total of 8 blood samples will be collected from each subject at the specific post-dose time windows shown in Table 2 for the determination of bupivacaine plasma concentrations.

10. STUDY POPULATION

Subjects must meet all eligibility criteria to be enrolled in this study.

10.1. Inclusion Criteria

Subjects eligible for study entry must meet all of the following criteria:

1. Subjects whose parent(s) or guardian(s) has/have signed and dated the ICF for the subject to participate in the study, and subjects who have provided written assent to participate in the study (if capable).
2. American Society of Anesthesiologists (ASA) Class 1-3.
3. Male or female subjects 6 to less than 17 years of age on the day of surgery.
4. Body mass index (BMI) at screening within the 5th to 95th percentile for age and sex (see Appendix 5).
5. A negative pregnancy test for female subjects of childbearing potential must be available prior to the start of surgery. The pregnancy test must be conducted in the preoperative holding area according to the study site's standard of care.
6. Subjects and their parent(s)/guardian(s) must be able to speak, read, and understand the language of the ICF and any instruments used for collecting subject-reported outcomes to enable accurate and appropriate responses to study assessments, and provide informed consent/assent.
7. Subjects must be able to adhere to the study visit schedule and complete all study assessments.

10.2. Exclusion Criteria

A subject will not be eligible for the study if any of the following criteria is met:

1. Currently pregnant, breastfeeding, or planning to become pregnant during the study or within 1 month after study drug administration.
2. History of hypersensitivity or idiosyncratic reactions to amide-type local anesthetics or to opioid medication.
3. Contraindication to bupivacaine HCl or other amide-type local anesthetics or to opioid medication.
4. Administration of EXPAREL or bupivacaine HCl within 30 days prior to study drug administration.
5. Subjects with coagulopathies or immunodeficiency disorders.
6. History of, suspected, or known addiction to or abuse of drugs or alcohol within the past 2 years.

7. Clinically significant medical or psychiatric disease that, in the opinion of the investigator, indicates an increased vulnerability to study drugs and/or procedures.
8. Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study.

In addition, the subject will be ineligible to receive study drug if he or she meets the following criterion during surgery:

9. Any clinically significant event or condition uncovered during the surgery (e.g., excessive bleeding, acute sepsis) that might render the subject medically unstable or complicate the subject's postoperative course.

10.3. Removal of Subjects from Therapy or Assessment

Every reasonable effort should be made to maintain subject compliance and participation in the study. Subjects who withdraw from the study after receiving study drug should undergo safety assessments till the end of the study (Day 30).

If a subject who withdraws from the study has an ongoing AE, every effort must be made to follow such events until satisfactory resolution is obtained, or further follow-up is otherwise no longer warranted.

10.3.1. Withdrawal Secondary to Adverse Events

If a subject experiences an AE that renders him or her incapable of continuing with the remaining study assessments, then he or she will be discontinued from further participation in the study. A final evaluation visit should be performed so that the subject's study participation can be terminated in a safe and orderly manner. Otherwise, the subject's parent or guardian will be instructed to notify the study personnel of any abnormalities during the intervals between study visits and to come to the study site if medical evaluation is needed and the urgency of the situation permits. Any subject exhibiting undesirable AEs will receive appropriate treatment at the discretion of the investigator.

This study involves a single administration of the study drug; therefore, subjects should not be terminated from the ongoing study assessments as long as they are willing and able to continue with the follow-up schedule according to the protocol. For emergencies and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the investigator.

10.3.2. Voluntary or Study Investigator Withdrawal

Subjects (or their parent or guardian) are free to discontinue participation in the study at any time, without prejudice to future treatment. Nevertheless, subjects will be encouraged to complete at least the study safety assessments. In addition, a subject may be discontinued from

the study if he or she refuses to comply with study procedures. Reasons for discontinuation from the study will be recorded.

If a subject is discontinued by the investigator or voluntarily withdraws from the study after receiving study drug, the subject will be asked to complete a final evaluation so that he or she can be withdrawn in a safe and orderly manner. In the final evaluation, vital signs (temperature, resting heart rate, respiratory rate, oxygen saturation, and blood pressure) and any changes in the subject's health status will be recorded.

After termination from the study, the subject may be followed for safety including monitoring of AEs till Day 30.

11. TREATMENTS

11.1. Treatments to be Administered

Study Drug

Dosing of EXPAREL for this study will be based on body weight, with a starting dose of 4 mg/kg. This weight-based dosing applies to Part 1 and Part 2 of the study.

The study drug will be administered prior to wound closure. The investigator must document the size of the incision. Each infiltration site should be spaced 1.0 to 1.5 cm apart and approximately 1 to 1.5 mL should be delivered into both deep and superficial areas. Following infiltration, the tissue should visibly expand with minimal leakage.

All eligible subjects will receive a single dose of EXPAREL intraoperatively at the end of surgery via local infiltration into the surgical site. EXPAREL can be administered as is or may be expanded with normal (0.9%) saline to increase the volume up to a final concentration of 0.89 mg/mL (i.e., 1:14 dilution by volume). The total volume of expansion will be dependent on the incision length. Details regarding the expansion of EXPAREL are provided in the Study Drug Infiltration Guide.

Total Volume of Expansion

The investigator must document the total volume used for each surgery.

- EXPAREL 4 mg/kg + normal saline (20–60 mL based on the incision size) = total volume.

  For example: If the infiltration sites are 1.5 cm apart, then a 10 cm incision would be 10 × 2 sides × 3 layers = 60 cm. If there is 1 mL infiltrated every 1.5 cm, the total volume would be 40 mL.

In Part 1, all eligible subjects will receive a single dose of EXPAREL intraoperatively at the end of surgery via local infiltration. EXPAREL can be administered as is or expanded to increase volume up to a final concentration of 0.89 mg/mL (i.e., 1:14 dilution by volume) with normal

saline (0.9% sodium chloride solution). The total volume of expansion will be dependent on the size of the wound.

In Part 2, all eligible subjects randomized to EXPAREL will receive a single dose of EXPAREL intraoperatively at the end of surgery via local infiltration. Dosing will be informed by the results of Part 1 and any recommendations based on the complete safety review.

Subjects randomized to the active control group will receive bupivacaine HCl 2 mg/kg, with a maximum dose of 175 mg.

Postsurgical Pain Management

The use of postsurgical pain medication in cases of insufficient analgesia is permitted according to the institution's standard of care. The investigator must record all pain management medications administered during hospitalization. Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL

11.2. Administration Instructions/Procedures

All injections must be performed with an infiltrative moving needle technique, with frequent aspirations to reduce the chance for accidental intravascular injection. If an aspiration draws blood, the needle must be moved and placed in a different location until the aspiration is negative. The study drug should be infiltrated in small increments into both deep and superficial layers to ensure uniform distribution along the entire length of the surgical wound.

11.2.1. Study Drug Administration Considerations

As there is a potential risk of severe adverse effects associated with the administration of local anesthetics, the study site must be equipped to treat subjects with evidence of cardiac toxicity.

EXPAREL may not be administered to a subject if the vial has been open for more than 4 hours. In order to prevent the study drug from settling, gently inverting and re-inverting the syringe several times prior to administration is recommended. No agents should be admixed with EXPAREL.

11.3. Identity of Investigational Products

11.3.1. Description of EXPAREL

EXPAREL is formulated as a sterile, non-pyrogenic, white to off-white, preservative-free, homogeneous suspension of bupivacaine encapsulated into multivesicular lipid-based particles (the DepoFoam drug delivery system).

Bupivacaine is present at a nominal concentration of 13.3 mg/mL. EXPAREL will be provided in 20 mL, 1.3% (13.3 mg/mL) single-use, clear glass vials.

EXPAREL vials should be stored refrigerated between 2°C and 8°C (36°F to 46°F).

11.3.2. Description of Reference Product

The reference product will be bupivacaine HCl. All information on the drug administered, dose, frequency, and duration will be captured in the electronic case report form (eCRF).

11.3.3. Description of Diluents

Normal saline (0.9% sodium chloride solution) for injection will be used for the expansion of study drug.

11.4. Method of Assigning Subjects to Treatment

11.4.1. Randomization Scheme

Approximately 90 subjects are planned for this study: 45 in Part 1 and 45 in Part 2. The randomization code will be generated by a centralized randomization system, which will also be used to communicate subject randomizations to study sites. All randomized subjects will have both a unique subject identifier and a unique random code identifier. No subject or random code identifiers will be reused once assigned.

11.4.2. Randomization Procedures for Treatment Assignment

Once a subject is identified as being qualified to participate in the study (see Section 10), and is at the study site for surgery, the authorized site staff or designee will obtain a randomization assignment. The subject will be considered randomized into the study once the study treatment assignment is received.

11.4.3. Replacement of Subjects

Subjects who are withdrawn from the study before receiving study drug may be replaced. Once assigned, subject numbers will not be reused; subjects enrolled to replace those who withdraw will be assigned a unique subject number.

11.5. Selection of Doses in the Study

The dose of EXPAREL (4 mg/kg) was selected to provide similar exposure in pediatric subjects as was seen in adults. A Population PK model was developed using all data obtained from the infiltration studies in adult subjects (SKY0402-C-201, SKY0402-C-208, SKY0402-C-316, SKY0402-C-317, and SKY0402-C-401). Simulations from this model were performed to predict bupivacaine plasma concentrations in pediatric subjects aged 6 to less than 17 years. The dose of EXPAREL administered will not exceed 266 mg, regardless of the weight of the subject.

The selection of the 4 mg/kg dose is also supported by real world evidence collected at the Cleveland Clinic, where 375 pediatric patients have received EXPAREL at a mean dose of 4.1 ± 1.8 mg/kg, with no significant AEs attributed to EXPAREL use.

11.6. Prior and Concomitant Therapy and Medications

All medications taken within 30 days prior to study drug administration till Day 30 after study drug administration or until the subject is withdrawn from the study, whichever is sooner, will be

recorded on the eCRF. Additionally, any medications administered in association with an AE will be recorded till Day 30.

11.6.1. Before Study Drug Administration

Permitted Prior Medications and Therapy

- Prophylactic antibiotics are permitted according to the surgeon's preference.

Restricted Prior Medications and Therapy

- Use of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study is not permitted.

11.6.2. During Surgery

Permitted

- Use of intraoperative opioids, acetaminophen, ketorolac, or other NSAIDs.

Restricted

- No drugs should be admixed with the study drug (e.g., epinephrine, dexamethasone, clonidine).
- Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL.

11.6.3. After Surgery

Permitted

- Postsurgical pain management will consist of institution's standard of care in case of insufficient analgesia.
- Parenteral antiemetic medication may be administered, as needed.

Restricted

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

All postsurgical analgesics administered must be documented till 96 hours after surgery.

11.7. Treatment Compliance

Study drug will be administered intraoperatively by the study staff and, thus, compliance is ensured.

11.8. Accountability of Study Drug

Any shipment of EXPAREL for the study will contain an investigational drug transmittal and receipt form to assist the investigator or designee (e.g., pharmacist) in maintaining current and accurate inventory records. At a minimum, the pharmacist or designee will maintain accurate records demonstrating dates and units of drug received, lot numbers, subjects to whom drug was administered, and accounts of any drug destroyed accidentally or deliberately. The investigator must retain vials containing used, unused, or expired EXPAREL for return or destruction, as instructed by Pacira, following confirmation of drug accountability data by an unblinded study monitor. A record of drug return or destruction will be maintained and provided to Pacira. Inventory records must be readily available for inspection by the unblinded study monitor and appropriate regulatory authorities at any time. A copy of the inventory records, drug accountability information, and notice of return or destruction will be returned to Pacira at the end of the study. Only authorized personnel identified by the investigator will have the ability to access and administer the drug.

12. STUDY ENDPOINTS AND MEASUREMENTS

12.1. Pharmacokinetic Analysis

A total of 8 blood samples will be collected per subject at specific time windows (Table 2) for the determination of plasma concentrations. Population PK modeling will be performed using all PK data collected during the study. The population PK model will estimate EXPAREL individual and population PK parameters and exposure, inter-individual variability of PK parameters, and intra-individual variability of bupivacaine concentrations.

12.2. Pharmacokinetic Endpoints

A population PK analysis will be performed. The following model-predicted PK endpoints will be determined:

- Area under the plasma concentration-versus-time curve (AUC)
- Maximum plasma concentration (C_{max})
- The apparent terminal elimination half-life ($t_{1/2el}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution (Vd/F)

12.3. Safety Assessments

The following safety measurements will be conducted at the time points specified:

- Vital signs (temperature, resting heart rate, respiratory rate, oxygen saturation, and blood pressure) at screening; upon arrival in the post-anesthesia care unit (PACU); at 2, 4, 8, 12, 24, 36, 48, 60, 72, and 96 hours after the end of study drug administration; at hospital discharge; and on Day 30.

- Neurological assessment at screening; at 2, 4, 8, 12, 24, 36, 48, 60, 72, and 96 hours after the end of study drug administration; at hospital discharge; and on Day 30 (Part 1 only, Appendix 3).
- Clinical laboratory tests (hematology, chemistry, and urinalysis) at screening; at baseline (on Day 1 prior to surgery) and at 96 hours after the end of study drug administration (see Appendix 4).
- AEs from the time the ICF is signed/assent is obtained till Day 30.

12.4. Safety Endpoints

The following safety endpoints will be assessed based on the safety measurements conducted at the specified time points:

- Change from baseline in vital signs (temperature, resting heart rate, respiratory rate, oxygen saturation, and blood pressure).
- Summary of neurological assessments (proportion of subjects who are oriented, and proportion of subjects who have any neurologic events). Note: Events identified during the neurologic assessment should be recorded as AEs.
- Change from baseline in clinical laboratory data.
- Incidence of TEAEs and SAEs till Day 30.

12.5. Other Measurements

The following efficacy measurements will be done for exploratory purposes only:

- Pain intensity scores at screening; at 4, 8, 12, 24, 36, 48, 60, 72, and 96 hours after the end of study drug administration; immediately prior to each administration of postoperative opioid pain management medication till 96 hours; and at hospital discharge. If a subject is too anesthetized at the time of a scheduled pain intensity assessment, the assessment should be skipped. Pain intensity scores will be collected using the following instruments:
    - 11-point NRS-R for subjects aged 12 to less than 17 years (Appendix 1)
    - CAS for subjects aged 6 to less than 12 years (Appendix 2)
- Postoperative opioid pain management medication use (time, dose) till hospital discharge.

12.6. Other Endpoints

Analysis of these other endpoints will be conducted for exploratory purposes only. The efficacy endpoints listed below will be assessed based on the efficacy measurements conducted at the time points specified.

- Pain intensity scores
- The AUC of pain intensity scores

- Total opioid consumption in morphine equivalents
- Time to first postsurgical use of opioid medication.

12.7. Appropriateness of Measures

The endpoints selected for this study were based on well-established clinical measurements used in peer-reviewed studies.

13. STUDY PROCEDURES

A time and events schedule for study procedures is provided in Table 1. PK Sampling times are provided in Table 2.

13.1. Instructions for Conducting Procedures and Measures

All post-dose assessments will be timed from the end of study drug administration.

Day 1 is defined as the day on which study drug is administered. The beginning of surgery is defined as the time of the first incision. The end of surgery is defined as the time of the last suture/staple. Postsurgical is defined as after the end of surgery.

13.1.1. Pain Intensity Assessment

Pain intensity will be assessed using age-specific tools at screening; at 4, 8, 12, 24, 36, 48, 60, 72, and 96 hours after the end of study drug administration; immediately prior to each administration of postoperative opioid pain management medication till 96 hours; and at hospital discharge. Pain intensity scores will be collected using the following instruments:

- 11-point NRS-R for subjects aged 12 to less than 17 years (Appendix 1)
- CAS for subjects aged 6 to less than 12 years (Appendix 2)

13.1.2. Neurological Examination

A neurological assessment will be conducted during Part 1 only at the following time points: at screening; at 2, 4, 8, 12, 24, 36, 48, 60, 72, and 96 hours after the end of study drug administration; at hospital discharge; and on Day 30. The examination will include the subject's orientation. Additionally, subjects aged 6 years or older will be asked whether he or she is experiencing any numbness of the lips, the tongue, or around the mouth; hearing problems; or muscle twitching (see Appendix 3). If the subject answers "yes" to any of these questions, the event should be recorded as an AE and additional safety procedures should be conducted as appropriate (see Section 13.1.7).

13.1.3. Clinical Laboratory Tests

The scheduled clinical laboratory tests (hematology, chemistry, and urinalysis) will be conducted at screening; baseline (on Day 1 prior to surgery); and at 96 hours after the end of study drug administration (see Appendix 4). Clinical laboratory tests, as appropriate, may also be conducted if a subject experiences an AESI, or an SAE (see Section 13.1.7).

13.1.4. Vital Signs

The scheduled 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 at screening; upon arrival at the PACU; at 2, 4, 8, 12, 24, 36, 48, 60, 72, and 96 hours after the end of study drug administration; at hospital discharge; and on Day 30. Vital signs may also be measured if a subject experiences an AESI or an SAE (see Section 13.1.7). The subject will remain in a supine position during the assessment.

13.1.5. Physical Examination

A full physical examination will be conducted at screening. Superficial abnormalities that may interfere with participation in the study will be noted. A follow-up physical examination will be conducted on Day 30 and will include examination of the surgical site.

13.1.6. Electrocardiograms

A 12-lead ECG will be conducted at screening or on Day 1 before surgery. A 12-lead ECG according to the study site's standard of care may also be conducted if a subject experiences an AESI or an SAE (see Section 13.1.7).

13.1.7. Adverse Events of Special Interest

All AEs will be recorded from the time the ICF is signed/assent is given till Day 30. 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 Appendix 6 for additional information on handling of AESIs.

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 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 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.

Cardiac or neurological AEs that do not meet one of these three criteria for AESI should be reported as described in Section 14.1 and captured in the database as an AE.

13.2. Screening Procedures

- Explain study purpose and procedures.
- Obtain written informed consent/assent before performing any study-related procedures.
- Assess eligibility.
- Record relevant medical/surgical history, demographics, and baseline characteristics.
- Conduct urine pregnancy test for females of childbearing potential (Part 1 only).
- Perform physical examination.
- Perform neurological assessment (see Appendix 3; Part 1 only).
- Conduct clinical laboratory tests (hematology, chemistry, and urinalysis) (see Appendix 4).
- Conduct a urine drug screen and alcohol breath test at the investigator's discretion. Subjects with a positive result will be excluded from the study.
- Measure vital signs (temperature, resting heart rate, respiratory rate, oxygen saturation, and blood pressure) after subject has rested in a supine position.
- Conduct 12-lead ECG after subject has rested in a supine position.
- Record a pain intensity score using one of the following instruments:
    - 11-point NRS-R for subjects aged 12 to less than 17 years (Appendix 1)
    - CAS for subjects aged 6 to less than 12 years (Appendix 2)
- Record concomitant medications.
- Record AEs starting at the signing of the ICF/assent.

All subjects who are screened for enrollment, but do not meet eligibility criteria, who decline to participate, or whose parent or guardian decline the subject's participation, will be documented on a screening log with the reason for non-participation.

13.3. Baseline Procedures (Day 1 Prior to Surgery)

- Confirm eligibility.
- Update relevant medical and surgical history.
- Conduct urine pregnancy test for females of childbearing potential. A negative pregnancy test result must be available before surgery.
- Measure vital signs (temperature, resting heart rate, respiratory rate, oxygen saturation, and blood pressure) after subject has rested in a supine position.

- Conduct 12-lead ECG after subject has rested in a supine position.
- Conduct clinical laboratory tests (hematology, chemistry, and urinalysis; Appendix 4).
- Conduct a urine drug screen and alcohol breath test at the investigator's discretion (Part 1 only). Subjects with a positive result will be excluded from the study.
- Record changes to concomitant medications since screening.
- Record AEs and any treatment(s) for the events.

13.4. Intraoperative Procedures

- Confirm eligibility based on exclusion criterion 9 (i.e., verify that no significant intraoperative events have occurred).
- Prepare study drug.
- Administer study drug at the end of surgery.
- Record start and stop times of study drug administration.
- Record dosage of study drug administered and expansion volume if applicable.
- Record use of intraoperative opioids.
- Record surgery start and stop times.
- Record size of incision.
- Record concomitant medications.
- Record AEs and any treatment(s) for the events.

Refer to Section 13.1.7 for additional procedures in the event a cardiac or neurological AE of special interest or SAE occurs.

13.5. Postoperative Assessments till 96 Hours

- Record age-specific pain intensity score at 4, 8, 12, 24, 36, 48, 60, 72, and 96 hours after the end of study drug administration; and immediately prior to each administration of postoperative opioid pain management medication. Pain assessments should be obtained before blood draws at the overlapping time points. If a subject is too anesthetized at the time of a scheduled pain intensity assessment, the assessment should be skipped. Pain intensity scores will be collected using the following instruments:
  - 11-point NRS-R for subjects aged 12 to less than 17 years (Appendix 1)
  - CAS for subjects aged 6 to less than 12 years (Appendix 2)
- Perform neurological assessment at 2, 4, 8, 12, 24, 36, 48, 60, 72, and 96 hours after the end of study drug administration (see Appendix 3).

- Measure vital signs (temperature, resting heart rate, respiratory rate, oxygen saturation, and blood pressure) at 2, 4, 8, 12, 24, 36, 48, 60, 72, and 96 hours after the end of study drug administration.
- Collect blood sample for PK analysis at the procedure-specific time windows shown in Table 2; record the date and time each sample is collected.
- Collect blood sample for clinical laboratory testing (hematology, chemistry, and urinalysis) at 96 hours after the end of study drug administration (see Appendix 4).
- Record supplemental pain medications and concomitant medications used by the subject.
- Administer postoperative opioid pain management medication upon request, as needed. Record pain score prior to administration of such medication.
- Record date, time, and amount of all opioid pain management medication administered.
- Record other concomitant medications.
- Record AEs and any treatment(s) for the events.

Refer to Section 13.1.7 for additional procedures in the event a cardiac or neurological AE of special interest or SAE occurs.

Note: Subjects will be discharged from the hospital as indicated by their physician, and a nurse will perform follow-up visits at the subject's home to perform postsurgical assessments and collect PK samples till 96 hours.

13.6. Hospital Discharge

- Record age-specific pain intensity score
- Perform neurological assessment (see Appendix 3; Part 1 only).
- Measure vital signs (temperature, resting heart rate, respiratory rate, oxygen saturation, and blood pressure)
- Record AEs and any treatment(s) for the events
- Record concomitant and discharge medications
- Record date and time of discharge

13.7. Day 7 Phone Call

- Document any unscheduled phone calls, unscheduled office visits, or ER visits related to pain.
- Record AEs and any treatment(s) for the events.
- Record concomitant medications.

13.8. Day 30 Visit

- Perform follow-up physical examination.
- Perform neurological assessment (see Appendix 3; Part 1 only).
- Measure vital signs (temperature, resting heart rate, respiratory rate, oxygen saturation, and blood pressure) after subject has rested in a supine position.
- Document any unscheduled phone calls, unscheduled office visits, or ER visits related to pain after discharge.
- Record AEs and any treatment(s) for the events.
- Record concomitant medications.

14. ADVERSE EVENT REPORTING

Consistent with the current regulatory guidance provided by the US FDA CFR Part 312 and the ICH GCP, AE and SAE are defined in Section 14.1.1 and Section 14.2.1, respectively.

The concepts of AEs and SAEs represent regulatory instruments used to evaluate and monitor the safety of clinical study subjects. Therefore, these terms only apply in light of their regulatory definition. The term serious, in a regulatory sense, does not necessarily mean severe. The SAE concept is used primarily to identify, during the conduct of the study, those SAEs that may require expedited reporting to regulatory authorities.

See Section 13.1.7 for a description of AESIs.

14.1. Adverse Events

14.1.1. Definitions

Adverse Event (AE)*:* Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

An AE can be any unfavorable and unintended change in a body structure or body function. AEs include any clinically significant deterioration of a subject's medical status. The AE may involve any organ or system and can be represented by the new onset or deterioration of a disease, a syndrome, a symptom, a physical sign, as well as by findings and results of instrumental examinations and laboratory tests. Any medically relevant and untoward change after the subject signs the ICF, including frequency or pattern changes for a fluctuating condition (e.g., migraine) is considered an AE.

An AE that occurs after the ICF is signed and before the start of the study drug administration is identified as a pre-treatment AE (PTAE). An AE that occurs after the administration of the study treatment is considered a TEAE.

Adverse Reaction: Any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is a reason to conclude that the drug caused the event.

Suspected Adverse Reaction: Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug. Suspected adverse reactions are a subset of all AEs for which there is a reasonable possibility that the drug caused the event.

14.1.2. Recording Adverse Events

It is the responsibility of the investigator to document all AEs (i.e., PTAEs and TEAEs), with an onset after the subject signs the ICF. For the purpose of this study, all AEs that occur till Day 30 must be recorded regardless of whether or not they are considered related to the study drug. Whenever feasible, AE terms should be documented as medical diagnoses (highest possible level of integration); otherwise, the AEs should be reported separately as individual signs or symptoms. Only one AE per line should be recorded in the AE case report form (CRF); for example, an AE of nausea and vomiting should be listed as two separate events: the event of nausea and the event of vomiting. If a diagnosis is established after symptoms are recorded on the AE CRF, the diagnosis should be recorded and the symptoms collapsed (removed; i.e., lined through and initialed). Whenever possible, abnormal laboratory results should be reported as their clinical corollary (e.g., low potassium should be recorded as hypokalemia).

A continuous AE with varying grades of severity should be recorded as one AE. The highest grade of severity experienced by that subject during the course of the continuous AE should be recorded.

Any condition noted before the subject signs the ICF will be listed as medical history and is considered a pre-existing condition. If a pre-existing condition changes (i.e., becomes more severe or more frequent) at any time after the ICF is signed, or after study drug administration, it is considered an AE. Note: A change in treatment for a pre-existing condition (e.g., new high blood pressure medication) does not necessarily indicate an AE.

Information recorded on the AE CRF will include the AE term, the date and time of onset, severity, seriousness, relationship to study drug, action taken with subject due to an AE, and the outcome of the AE, including the date and time of resolution, if applicable.

14.1.3. Severity of Adverse Events

In general, the severity of an AE should be categorized using the following guidelines:

Mild: An AE that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An AE that is discomforting and interferes with normal everyday activities.

Severe: An AE that prevents normal everyday activities.

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

14.1.4. Relationship of Adverse Events to Study Drug

The investigator will assess the relationship of the AE to study drug after careful medical consideration on a case-by-case basis. General guidelines for determining the causality of an AE to the study drug are provided below:

Unrelated: A causal relationship between the study drug and the AE can be easily ruled out (e.g., based on the temporal sequence, absence of a reasonable pathophysiological mechanism, or direct evidence of actual cause).

Unlikely: A clinical event with a temporal relationship to study drug administration which makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide a plausible explanation.

Possible: A clinical event with a reasonable time sequence to administration of the study drug but which could also be explained by a concurrent disease or other drugs or chemicals.

Probable: A clinical event with a reasonable time sequence to administration of the study drug unlikely to be attributed to a concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (dechallenge).

Definite: The pharmacological properties of the study drug(s) or of the substance class, and the course of the AE after dechallenge and, if applicable, after rechallenge, and/or specific test indicate involvement of the study drug(s) in the occurrence/worsening of the AE, and no indication of other causes exists.

14.1.5. Outcome of Adverse Events

The investigator will assess the outcome of the AE after careful medical consideration, on a case-by-case basis. General guidelines are provided below:

Recovered/Resolved:	The event resolved and the subject recovered from the AE.
Recovered/Resolved with Sequelae:	The initial event resolved, but has a continuing abnormal condition as a result of the AE.
Not Recovered/ Not Resolved:	At the time of the last assessment, the event was ongoing, with an undetermined outcome. Note: ongoing AEs are not to be considered resolved as a result of death.
Recovering/Resolving:	At the time of the last assessment, the event was decreasing in frequency, severity, etc., and a resolution was expected.
Fatal:	The AE directly caused death.
Unknown:	There was an inability to access the subject or the subject's records to determine the outcome (e.g., subject withdrew consent or was lost to follow-up).

14.1.6. Action Taken with Subject Because of an Adverse Event

The investigator will provide any actions taken regarding the subject (e.g., treatment, diagnostic tests, laboratory tests, or therapy) for each reported AE.

- None.
- Medication.
- Non-pharmaceutical therapy. (The specific therapy used must be recorded in the CRF.)
- Discontinued from study.
- Other. (The specific action taken must be recorded in the CRF.)

14.2. Serious Adverse Events

14.2.1. Definition of a Serious Adverse Event

Serious Adverse Event (SAE): An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death[1]
- A life-threatening adverse event[2]
- Inpatient hospitalization or prolongation of existing hospitalization[3]
- A persistent or significant incapacity[4]
- Congenital anomaly/birth defect
- Medically significant[5]

[1]**Death:** Any event resulting in a subject's death must be reported as an SAE. However, death, in and of itself, is not an AE; it is an outcome. The cause of death is the AE. Therefore, the investigator should make every effort to obtain and document the cause of death for all subjects who die during the study. If, despite all efforts, the cause of death remains unknown, the AE should be documented as an "unspecified fatal event."

[2]**Life-threatening**: An AE is considered life-threatening if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

[3]**Hospitalization**: It should be noted that hospitalization, in and of itself, does not represent an SAE. It is the AE leading to the subject's hospitalization that becomes "serious" when it requires inpatient care. Consequently, an SAE should not be reported in case of preplanned hospitalizations for a pre-existing condition that did not worsen during the study. However, any medical condition that delays a subject's discharge from the hospital (i.e., prolonged hospitalization) or requires the subject to be readmitted should be reported as an SAE.

[4]**Persistent or significant incapacity**: A substantial disruption of a person's ability to conduct normal life functions.

[5]**Medically Significant**: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medically significant events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

14.2.2. Reporting Serious Adverse Events

Any SAE or death that occurs at any time after the subject signs the ICF through Day 30, whether or not related to EXPAREL, must be reported by the investigator or designee to Pacira Drug Safety within 24 hours of discovery by either email (drugsafety@pacira.com) or fax (973-201-0649). In addition, the investigator or designee is encouraged to contact the medical monitor to discuss the case, as needed.

Investigators should not wait to receive additional information to fully document the event before notifying Pacira Drug Safety or designee of the SAE. The fax or email report should be followed by a full written summary using the SAE Form detailing relevant aspects of the SAE in question. Where applicable, information from relevant hospital records and autopsy reports should be obtained and all subject-identifying information redacted prior to forwarding to Pacira. In the event of a fatal or life-threatening SAE, any required follow-up must be provided to Pacira Drug Safety or designee immediately. The investigator will follow all SAEs until resolved or the condition stabilizes and further follow-up is not warranted.

If the investigator is made aware of any SAEs after Day 30, these should also be reported to Pacira Drug Safety or designee, provided the SAE is considered related to EXPAREL. The site would then provide a completed SAE form within 1 business day and the event would be followed until resolution, or until adequate stabilization is met.

15. STATISTICAL METHODS

A comprehensive statistical analysis plan (SAP) will be developed for this study.

15.1. Study Hypothesis

No formal hypothesis testing will be conducted.

15.2. Study Endpoints

The endpoints to be assessed in this study are listed in Section 12.2 (Pharmacokinetic Endpoints), Section 12.4 (Safety Endpoints), and Section 12.6 (Other Endpoints).

15.3. Determination of Sample Size

The sample size was based on the number of subjects necessary to characterize the PK profile of EXPAREL in pediatric subjects with the precision required by the FDA.

15.4. Analysis Populations

The following study populations are planned:

- The PK population will consist of all subjects who receive study drug and provide at least one quantifiable plasma concentration.
- The safety population will consist of all subjects who underwent the planned surgery and received study treatment.

15.5. Handling Subject Dropouts and Discontinuations

Subjects who discontinue after dosing will not be replaced.

15.6. Statistical Analyses

Continuously valued data will be summarized using descriptive statistics (n [number of subjects contributing data], mean, SD, median, minimum, and maximum). Discretely valued data will be tabulated (n and percentage) by category. The denominator for all percentages will be the number of subjects who underwent the planned surgery.

15.6.1. Baseline Characteristics

Baseline characteristics will be summarized or tabulated as appropriate.

15.6.2. Efficacy Analyses

Pain intensity scores will be summarized by time point.

Area under the pain scale versus time curve will be calculated using the trapezoidal rule and summarized.

15.6.3. Pharmacokinetic Analysis

A prospective population PK analysis plan will be developed. Nonlinear mixed-effect modeling with NONMEM® software (Beal 2011) will be used to analyze the sparse concentration-versus-time data. Population and individual PK parameters will be estimated. Individual PK parameters estimated for each subject will be used to compute PK exposures (AUC and C_{max}). PK parameters will be presented in listings and descriptive summary statistics, including the arithmetic mean, median, range, standard deviation, and coefficient of variation. Details and results of this mixed-effects modeling analysis will be reported separately.

15.6.4. Safety Analyses

The incidence of AEs will be tabulated by system organ class and preferred term. Subjects reporting the same AE more than once will be counted only once within each tabulation category for that AE.

15.7. Significance Testing

Not applicable.

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17. INVESTIGATOR AGREEMENT

Printed Name of Investigator: _____

Printed Title/Position: _____

Printed Institution Address: _____

_____

_____

I have reviewed this protocol (including appendices) and agree:

- To assume responsibility for the proper conduct of the study at this site;
- To conduct the study in compliance with this protocol, with any future amendments, and with any other study conduct procedures provided by Pacira Pharmaceuticals, Inc. or designee. I also agree to comply with Good Clinical Practice and all regulatory requirements;
- Not to implement any changes to the protocol without agreement from Pacira Pharmaceuticals, Inc. or designee and prior review and written approval from the Independent Ethics Committee, except where it is necessary to eliminate an immediate hazard to the subjects or for administrative aspects of the study (where permitted by applicable regulatory requirements);
- That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol, and with other relevant information (e.g., the Investigator's Brochure);
- To ensure that all persons assisting me with the conduct of this study are adequately informed about the investigational product(s) and about their study-related duties and functions as described in this protocol;
- That I am aware that regulatory authorities may require investigators to disclose all information about significant ownership interests and/or financial ties related to the sponsor and/or the investigational product(s). Consequently, I agree to disclose all such significant financial information to Pacira Pharmaceuticals, Inc. and to update this information promptly if any relevant changes occur during the course of the study through 1 year following completion of the study. I also agree that any information regarding my significant financial interest related to Pacira Pharmaceuticals, Inc. and/or the investigational product(s) will be disclosed to the regulatory authorities by Pacira Pharmaceuticals, Inc.

_____ _____

Signature of Investigator

18. APPENDICES

Appendix 1: Numeric Rating Scale at Rest (NRS-R)

Subjects aged 12 to less than 17 years will be evaluated for pain using the NRS-R at screening; at 4, 8, 12, 24, 36, 48, 60, 72, and 96 hours after the end of study drug administration; immediately prior to each administration of postoperative opioid pain management medication till 96 hours; and at hospital discharge. If a subject is too anesthetized at the time of a scheduled pain intensity assessment, the assessment should be skipped.

Pain Intensity Scale

On a scale of 0 to 10, where 0 = no pain and 10 = worst possible pain, circle the number that best describes how much pain are you having right now? (Circle one number only.)

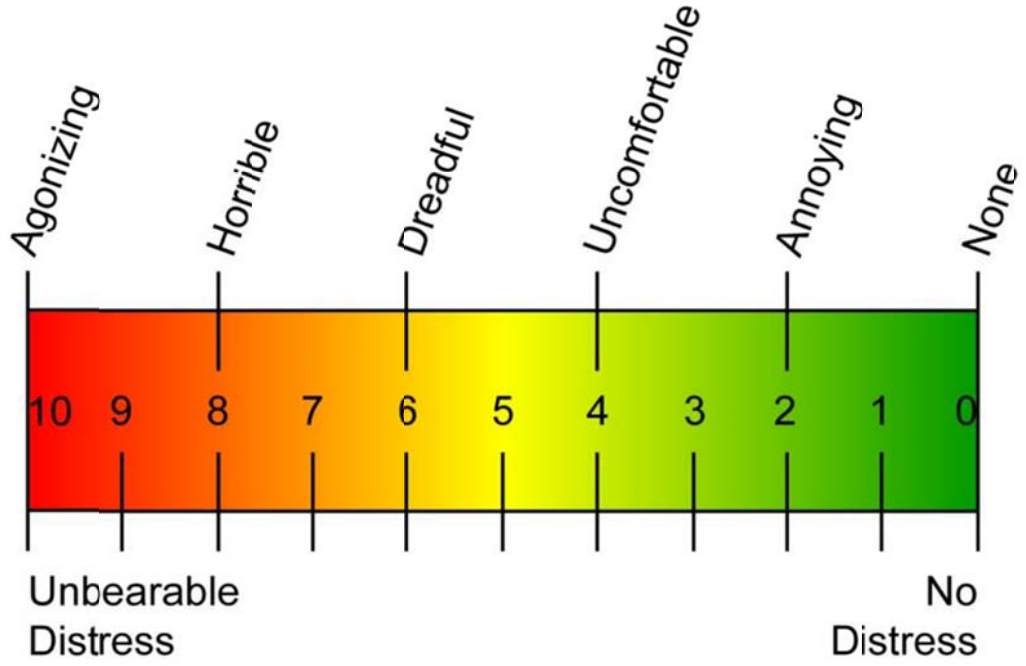
0	1	2	3	4	5	6	7	8	9	10

No pain **Worst possible pain**

Appendix 2: Color Analog Scale (CAS)

Subjects aged 6 to less than 12 years will be evaluated for pain using the CAS at screening; at 4, 8, 12, 24, 36, 48, 60, 72, and 96 hours after the end of study drug administration; immediately prior to each administration of postoperative opioid pain management medication till 96 hours; and at hospital discharge. If a subject is too anesthetized at the time of a scheduled pain intensity assessment, the assessment should be skipped.

Using the color scale of 0 to 10 below, where 0 (green color) means no pain and 10 (red color) means worst possible pain, circle the number that best describes how much pain are you having right now? (Circle one number only.)



Appendix 3: Neurological Assessment

The neurological assessment will be conducted at screening; at 2, 4, 8, 12, 24, 48, 60, 72, and 96 hours; at hospital discharge; and on Day 30.

The examination will include the subject's orientation.

- Is the subject oriented?
  ☐ Yes ☐ No ☐ Not Assessable

If the subject is not oriented, the event should be recorded as an AE.

Additionally, the subject will be asked the following questions:

- Since your last assessment have you had numbness of the lips, the tongue, or around the mouth? ☐ Yes ☐ No
- Since your last assessment have you had a metallic taste in your mouth?
  ☐ Yes ☐ No
- Since your last assessment, have you had problems with your hearing not related to the use of a hearing aid? ☐ Yes ☐ No
- Since your last assessment, have you had problems with your vision not related to the use of eye glasses? ☐ Yes ☐ No
- Since your last assessment, have your muscles been twitching?
  ☐ Yes ☐ No

If the subject answers “yes” to any of these questions, the event should be recorded as an AE and additional safety procedures should be conducted (see Section 13.1.7).

Appendix 4: Clinical Laboratory Tests

The scheduled clinical laboratory tests (hematology, chemistry, and urinalysis) will be conducted at screening; at baseline (on Day 1 prior to surgery); and at 96 hours.

Additionally, appropriate clinical laboratory tests should be conducted if a subject experiences a cardiac or neurological AE of special interest or an SAE (see Section 13.1.7).

General Chemistry Analysis	General Hematology (CBC with Differential) Components	Urinalysis
Albumin	White blood cells	Color
Alkaline phosphatase	Red blood cells	Appearance
Alanine transaminase (ALT)	Hemoglobin	Specific gravity
Amylase	Hematocrit	pH
Aspartate transaminase (AST)	Mean corpuscular volume	Protein
Bilirubin, direct	Mean corpuscular hemoglobin	Glucose
Bilirubin, total	Mean corpuscular hemoglobin concentration	Ketones
Blood urea nitrogen		Bilirubin
Calcium	Red cell distribution width	Blood
Carbon dioxide (bicarbonate)	Platelets	Urobilinogen
Chloride	Mean platelet volume	Nitrite
Cholesterol	Absolute/percent neutrophil count	Leukocyte esterase
Creatine kinase (CK), total (or creatine phosphokinase [CPK])	Absolute/percent lymphocyte count	
	Absolute/percent monocyte count	
Creatinine, serum	Absolute/percent eosinophil count	
Gamma-glutamyl transpeptidase (GGT)	Absolute/percent basophil count	
Glucose		
Iron		
Unsaturated/Total Iron binding capacity (UIBC/TIBC)		
Lactate dehydrogenase (LDH)		
Lipase		
Magnesium		
Phosphorus		
Potassium		
Sodium		
Total protein		
Transferrin		
Triglycerides		
Uric acid		

Appendix 5: BMI Normal Ranges (5th to 95th Percentile)

Age (years)	Males	Females
2	14.7 – 19.3	14.4 – 19.1
3	14.3 – 18.2	14.0 – 18.3
4	14.0 – 17.8	13.7 – 18.0
5	13.8 – 18.0	13.5 – 18.2
6	13.8 – 18.4	13.4 – 18.8
7	13.7 – 19.2	13.4 – 19.6
8	13.8 – 20.0	13.5 – 20.7
9	14.0 – 21.0	13.8 – 21.8
10	14.2 – 22.1	14.0 – 22.9
11	14.5 – 23.2	14.4 – 24.1
12	15.0 – 24.2	14.8 – 25.2
13	15.4 – 25.2	15.3 – 26.2
14	16.0 – 26.0	15.8 – 27.2
15	16.5 – 26.8	16.3 – 28.1
16	17.1 – 27.6	16.8 – 28.9

Adapted from: Centers for Disease Control and Prevention, National Center for Health Statistics, http://www.cdc.gov/growthcharts/clinical_charts.htm

Appendix 6: Flow Diagram for Handling of AESIs