CLINICAL STUDY REPORT

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)

Protocol No.:	402-C-319
ClinicalTrials.gov No.:	NCT03682302
IND No.:	069,198
Phase:	Phase 3
Study Drug:	EXPAREL (bupivacaine liposome injectable suspension)
Indication:	Analgesia via infiltration after spine or cardiac surgery
Date of Report:	**13-May-2020**
First Subject Screened:	02-APR-2019
Last Subject Observed:	24-SEP-2019
Investigators/Study Sites:	Multicenter study in the United States
Sponsor:	Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 Telephone: (973) 254-3560

1. SIGNATURE PAGE

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Donald Manning
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Donald C. Manning, MD, PhD
Chief Medical Officer

Date

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Julia Yang, MD
Vice President, Clinical Research

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Vincent Yu, PhD
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Michael Rozycki, PhD
Senior Vice President, Regulatory Affairs

Date

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® (bupivacaine liposome injectable suspension)		
Name of Active Ingredient: Bupivacaine		

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 Investigator: Christopher F. Tirotta, MD

Study Center: Multicenter study in the United States

Publications (reference): None

Studied Period: **Date first subject screened**: 02-APR-2019 **Date last subject observed**: 24-SEP-2019	**Phase of Development**: 3

Objectives:

Primary Objective: The primary objective was to evaluate the pharmacokinetics (PK) of EXPAREL in pediatric subjects aged 6 to <17 years undergoing various types of surgeries.

Secondary Objectives: The secondary objective was to evaluate the safety of EXPAREL in pediatric subjects aged 6 to <17 years undergoing various types of surgeries.

Methodology:

This was a multicenter, randomized, open-label, 2-part study to evaluate the PK and safety of EXPAREL in pediatric subjects aged 6 to <17 years who were undergoing spine or cardiac surgeries. Part 1 evaluated PK and safety, while Part 2 assessed safety. Subjects in each part were classified into groups by age: Group 1 enrolled subjects 12 to <17 years of age and Group 2 enrolled subjects 6 to <12 years of age.

Subject enrollment for both age groups was conducted in parallel. Within each age group, enrollment for Part 2 commenced upon complete enrollment of Part 1. The study design is displayed in the table below.

Summary of Study Design for Study 402-C-319

	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]

HCl = hydrochloride; PK = pharmacokinetics

Dosing of EXPAREL was based on body weight, at a dose of 4 mg/kg (up to a maximum total dose of 266 mg). Dosing of bupivacaine hydrochloride (HCl) 2 mg/kg was based on body weight (not to exceed a maximum total dose of 175 mg).

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Group 1 enrolled subjects 12 to <17 years of age. There were 2 study parts within Group 1.

Group 1, Part 1 (PK and safety) was a randomized, multicenter, active-controlled, open-label, PK and safety evaluation in subjects aged 12 to <17 years undergoing spine surgery. Subjects were randomized 1:1 to receive a single dose of either EXPAREL 4 mg/kg or bupivacaine HCl 2 mg/kg via local infiltration at the end of surgery. The planned sample size was 30 subjects (15 subjects per study arm).

Group 1, Part 2 (safety) was a randomized, multicenter, active-controlled, open-label, safety evaluation in subjects aged 12 to <17 years undergoing spine surgery. Subjects were randomized 1:1 to receive either a single dose of EXPAREL 4 mg/kg or bupivacaine HCl 2 mg/kg via local infiltration at the end of surgery. The planned sample size was 30 subjects (15 subjects per study arm).

Group 2 enrolled subjects 6 to <12 years of age. There were 2 study parts within Group 2.

Group 2, Part 1 (PK and safety) was a multicenter, single-arm, open-label, PK and safety evaluation in subjects aged 6 to <12 years undergoing spine or cardiac surgery. Subjects received a single dose of EXPAREL 4 mg/kg via local infiltration at the end of surgery. The planned sample size was 15 subjects.

Group 2, Part 2 (safety) was a single-arm, multicenter, open-label safety evaluation in subjects aged 6 to <12 years undergoing spine or cardiac surgery. Subjects received a single dose of EXPAREL 4 mg/kg via local infiltration at the end of surgery. The planned sample size was 15 subjects.

Screening: Subjects were screened within 30 days prior to study drug administration. After the informed consent form (ICF) was signed by the subject's legal guardian and written assent was provided by the subject (if capable), medical and surgical histories were taken and a 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 were conducted.

Study treatment: On Day 1, eligible subjects received the study drug via local infiltration at the end of surgery to produce local analgesia. Use of intraoperative opioids, acetaminophen, ketorolac, or other non-steroidal anti-inflammatory drugs, was permitted in accordance with each respective study site's standard of care. Additional use of local anesthetics within 96 hours following the administration of EXPAREL was to be avoided (this restriction did not apply to bupivacaine HCl).

Subjects were discharged based on the medical judgment of the treating physician. For subjects discharged from the hospital before all protocol-specified assessments until 96 hours were completed, a nurse performed follow-up visits at the subject's home to ascertain the required postsurgical assessments and collect PK samples until 96 hours after surgery. A follow-up phone call was scheduled on Day 7 (± 1 day) and a follow-up visit was scheduled for Day 30 (-16 days / + 3 days).

Postsurgical Pain Management

Use of postsurgical pain medication in cases of insufficient analgesia was permitted according to each respective study site's standard of care. The investigator recorded all postsurgical pain management medications provided to the subject until the hospital discharge and avoided additional use of local anesthetics within 96 hours following the administration of EXPAREL (but not bupivacaine HCl).

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Postsurgical Assessments

Postsurgical assessments performed up to 96 hours included pain intensity using the 11-point Numeric Rating Scale at Rest (NRS-R) for subjects aged 12 to <17 years and the Color Analog Scale (CAS) for subjects aged 6 to <12 years; neurological assessment; clinical laboratory tests; and vital signs. Adverse events (AEs) were recorded from the time informed consent/assent was obtained up to Day 30.

In case a cardiac or neurological AE of special interest (AESI) or serious AE (SAE) occurred during the study, if the investigator or medical monitor considered that the event may have been related to study treatment or suggested the possible occurrence of local anesthetic systemic toxicity (with or without the need for treatment [eg, intralipids]), or if a plausible etiology for the event could not be found, an unscheduled PK blood sample was collected and a 12-lead ECG, vital signs, and clinical laboratory tests (hematology and complete metabolic profile) may have been conducted according to each respective study site's standard of care.

Cardiac AESIs included chest pain, abnormal/irregular heart rate, and shortness of breath that required intervention. Neurologic AESIs included seizure, altered mental status/altered sensorium, rigidity, dysarthria, tremors, tinnitus, visual disturbance, and severe or worsening dizziness. Additionally, the following events were considered AESIs if they persisted or occurred beyond 72 hours post dose: dizziness, hyperesthesia, muscular twitching, and tingling/paresthesia. Dizziness was captured as an AESI if it was severe (unsteadiness or sensation of movement that limited self-care activities of daily living [based on National Cancer Institute Common Terminology Criteria for Adverse Events]) or worsened or persisted beyond 72 hours post dose.

Data Safety Monitoring Board

A Data Safety Monitoring Board monitored the safety and dosing data on an ongoing basis for all study arms.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 90 subjects (45 in Part 1 and 45 in Part 2) were planned for enrollment. Overall, 60 subjects were to receive EXPAREL and 30 subjects were to receive bupivacaine HCl.

Analyzed:

- Safety population: Group 1 included 31 subjects treated with EXPAREL 4 mg/kg and 30 subjects treated with bupivacaine HCl 2 mg/kg and Group 2 included 5 subjects who underwent spine surgery and 29 subjects who underwent cardiac surgery treated with EXPAREL 4 mg/kg.
- PK population: Group 1 included 16 subjects treated with EXPAREL 4 mg/kg and 15 subjects treated with bupivacaine HCl 2 mg/kg who provided at least 1 quantifiable plasma concentration. Group 2 included 2 subjects who received EXPAREL 4 mg/kg, underwent spine surgery, and provided at least 1 quantifiable plasma concentration, and 21 subjects who received EXPAREL 4 mg/kg, underwent cardiac surgery, and provided at least 1 quantifiable plasma concentration.

Diagnosis and Main Criteria for Inclusion:

Subjects were male or female, 6 to <17 years of age, scheduled to undergo spine or cardiac surgery, had a body mass index within the 5th to 95th percentile for age and sex, and had an American Society of Anesthesiologists (ASA) physical status 1, 2, or 3. Additionally, the subjects' parents/legal guardians and the subjects were willing to provide informed consent and assent (if capable), respectively, and were able to adhere to the study schedule and complete all study assessments.

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Name of Active Ingredient: Bupivacaine		

Test Product, Dose, Mode of Administration, and Lot Number:

Name: EXPAREL (bupivacaine liposome injectable suspension)

Active ingredient: Bupivacaine HCl 1.3%, 13.3 mg/mL

Dosage: Single dose of EXPAREL 4 mg/kg, not to exceed a maximum total dose of 266 mg

Mode of administration: Intraoperative local infiltration

EXPAREL Lot numbers: 18-3125 and 19-4052

Reference Therapy, 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

Mode of administration: Intraoperative local infiltration

Lot number: AD9172

Duration of Treatment:

Participation began at the signing of the ICF/obtaining written assent. No more than 30 days passed between signing of the ICF/obtaining written assent and the administration of study drug. The time from study drug administration until the end of participation was 30 ± 3 days. Therefore, subjects participated in the study for up to 63 days.

Pharmacokinetic Assessment **(Part 1 only)**

A population PK sampling scheme was used to limit the number of blood draws for each individual subject. On Day 1, eligible subjects were assigned to 1 of the 2 PK sampling groups based on surgery type (spine or cardiac surgery). A total of 8 blood samples were collected from each subject at the specified time windows (see table below) for the determination of bupivacaine plasma concentrations. Sparse PK sampling schemes were employed to allow for a comprehensive evaluation of the plasma concentration versus time profiles in each surgery while reducing the burden of blood sample collection on the individual pediatric participants. Population PK modeling was performed using all PK data collected during the study. The population PK model characterized overall PK of bupivacaine from EXPAREL and of bupivacaine HCl.

Summary of PK Sample Collection Times

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

Abbreviations: h=hour(s); min=minutes; PK=pharmacokinetic

Safety Assessments:

Safety was assessed based on AEs from the time the ICF was signed through Day 14 and vital signs at scheduled timepoints.

The following safety assessments were conducted at the timepoints specified:

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- 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; 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.
- 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.
- Adverse events from the time the ICF was signed/assent was obtained until Day 30.

Other Assessments:

Exploratory efficacy assessments included:

- Pain intensity scores measured using the 11-point NRS-R scale (ages 12 to <17 years) or CAS (ages 6 to <12 years) 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.
- Postsurgical opioid pain management medication use (time and dose) through 96 hours after study drug administration and at hospital discharge.

Statistical Methods:

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

Pharmacokinetic parameters were calculated by noncompartmental analysis (NCA) method from concentration-time data. All PK parameters were presented in listings and descriptive summary statistics, including the arithmetic mean, median, range, SD, and coefficient of variation, were presented in tables.

A prospective population PK analysis plan was developed. Nonlinear mixed-effect modeling\population pharmacokinetics method was also used to analyze the data.

Population and individual PK parameters were estimated. Individual PK parameters estimated for each subject were used to compute PK exposures (area under the curve [AUC] and maximum plasma concentration [C_{max}]). Details and results of this mixed-effect modeling analysis were 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.

SUMMARY – CONCLUSIONS
PHARMACOKINETIC RESULTS:

In Group 1 subjects, the mean C_{max} for subjects receiving bupivacaine HCl (564 ng/mL) was higher than that for subjects receiving EXPAREL (357 ng/mL), owing to the lengthy absorption period of EXPAREL. However, EXPAREL had a considerably higher AUC values, which is to be expected given that the administered dosage was over twice that of bupivacaine HCl.

Group 2 subjects were aged 6 to <12 years old given EXPAREL 4 mg/kg only and included 21 cardiac subjects and 2 spine subjects. The exposure of the spine subjects closely matched that of the EXPAREL subjects in Group 1. However, it was apparent that the cardiac subjects had higher exposure than spine subjects, based on C_{max} and AUC. The higher AUC was in line with the reduced CL/F in cardiac vs. spine subjects.

The PK results calculated using NCA stratified by surgery type and formulation are summarized in the table below.

		Group 1		Group 2	
	Formulation	**EXPAREL**	**Bupivacaine HCl**	**EXPAREL**	**EXPAREL**
	Dose mg/kg	3.97±0.14	1.89±0.46[†]	4.00	4.00±0.00
	Age, y	13.6±1.36	14.2±1.26	10.5	8.7±1.79
Parameter	Surgery	Spine	Spine	Spine	Cardiac
$AUC_{0\text{-}tlast}$, ng*h/mL	Mean ±SD	9042.5 ±3762.82	5232.9 ±2538.37	10249.6	16776.4 ±7935.80
	Geomean (CV%)	8296.9 (46.6)	4791.4 (43.7)	-	15316.0 (45.0)
	n	15	15	2	21
$AUC_{0\text{-}\infty}$, ng*h/mL	Mean ±SD	14246.1 ±9118.83	5709.4 ±3281.74	11569.5	26164.0 ±28038.35
	Geomean CV%)	12256.8 (59.0)	5064.2 (51.0)	-	19707.4 (75.1)
	n	15	15	2	18
C_{max}, ng/mL	Mean ±SD	357.3±125.31	563.6±320.93	319.5	447.1±243.41
	Geomean CV%)	336.8 (37.2)	488.2 (60.0)	-	403.4 (46.1)
	n	15	15	2	21
t_{max}, h	Median (range)	1.1 (0.3-26.1)	0.9 (0.3-2.5)	7.4	22.7 (0.2-54.5)
	n	15	15	2	21
C_{max1}, ng/mL	Mean ±SD	321.6±134.28	-	249.0	372.6±271.42
	Geomean CV%)	295.9 (45.3)	-		306.9 (69.2)
	n	15	-	2	21
T_{max1}, h	Median (range)	1.1 (0.3-2.7)	-	2.4	0.4 (0.2-1.2)
	n	15	-	2	21
C_{max2}, ng/mL	Mean ±SD	264.3±105.10	-	303.0	349.0±145.13
	Geomean (CV%)	245.7 (41.5)	-		318.5 (48.2)
	n	15	-	2	21
t_{max2}, h	Median (range)	18.0 (11.1-26.1)	-	15.3	30.1 (15.0-69.3)
	n	15	-	2	21
t½, h	Mean ±SD	26.8±21.26	8.4±6.26	13.4	24.9±20.58
	Geomean CV%)	21.2 (77.3)	7.4 (47.8)	-	20.5 (62.3)
	n	15	15	2	18

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CL/F, L/h	Mean ±SD	17.5±7.47	20.5±8.27	14.5	7.4±3.20
	Geomean CV%)	16.0 (47.7)	18.9 (45.7)	-	6.6 (57.6)
	n	15	15	2	18
Vd/F, L	Mean ±SD	546.4±269.42	226.8±110.63	271.1	216.1±83.77
	Geomean CV%)	488.4 (53.3)	200.9 (56.8)	-	197.1 (50.7)
	n	15	15	2	18

Abbreviations: $AUC_{0-\infty}$ = the area under the plasma concentration-versus-time curve from the time of administration extrapolated to infinity; $AUC_{0-tlast}$ = the area under the plasma concentration-versus-time curve from start of dosing to the time of the last quantifiable plasma concentration; CL/F = total body clearance divided by bioavailability (F); C_{max} = the maximum observed plasma concentration; C_{max1} = the maximum observed plasma concentration before 4 h after the dose of EXPAREL; C_{max2} = the maximum observed plasma concentration beyond 4 h after the dose of EXPAREL; geomean = geometric mean; HCl=hydrochloride; %CV = percent coefficient of variance; SD=standard deviation; t_{max} = the time at which C_{max} was observed; t_{max1} = the time at which C_{max1} was observed; t_{max2} = the time at which C_{max2} was observed; t½ = the apparent terminal elimination half-life determined by dividing 0.693 by the terminal elimination rate constant; Vd/F = the volume of distribution calculated as CL/F divided by the terminal phase rate constant; y=years.

* Median shown because only 2 subjects were included in this group.
† In bupivacaine free base. 0.886 mg bupivacaine free base equivalent = 1.0 mg bupivacaine HCl equivalent.

SAFETY RESULTS:

In Group 1 (12 to <17 years), 19 of 31 subjects (61.3%) who received EXPAREL and 22 of 30 subjects (73.3%) who received bupivacaine HCl experienced a treatment-emergent adverse event (TEAE). In Group 2 (6 to <12 years), 5 of 5 subjects (100%) who underwent spine surgery and 9 of 29 subjects (31.0%) who underwent cardiac surgery experienced a TEAE. No subject discontinued the study due to a TEAE.

The System Organ Class with the highest incidence of TEAEs in both groups was Gastrointestinal Disorders. Only 1 severe TEAE was reported (constipation in a subject who received bupivacaine in Group 1). Possibly treatment-related TEAEs were reported in 7 subjects in Group 1 (2 EXPAREL, 6.5%; and 5 bupivacaine, 16.7%) and 3 subjects in Group 2 (3 spine surgery subjects, 60.0%).

Two subjects, both who were in Group 2 and underwent cardiac surgery experienced at least 1 SAE; none of the SAEs was considered related to study treatment, led to death, or led to discontinuation from the study. Five subjects in Group 1 (2 EXPAREL, 3 bupivacaine subjects) had a TEAE of special interest as reported by investigators; all were mild or moderate and were considered unrelated or unlikely related to study treatment. The incidence of neurologic events was low and these events occurred in both the EXPAREL and bupivacaine arms.

No clinically significant changes in laboratory test results or vital signs were observed.

EFFICACY RESULTS:

This study was not powered to evaluate efficacy; efficacy was examined for descriptive purposes only. Efficacy results are presented below.

Pain Scores

- Mean NRS pain intensity scores for Group 1 (12 to <17 years) are displayed below:

Mean (SD) NRS Pain Intensity Scores, Group 1 (12 to <17 years)						
Timepoint	**EXPAREL**	**Bupivacaine HCl**		**Timepoint**	**EXPAREL**	**Bupivacaine HCl**
Baseline	0.4 (1.04)	0.5 (1.14)		48 hours	3.7 (2.49)	3.0 (2.35)
4 hours	2.9 (2.93)	3.7 (2.66)		60 hours	3.4 (2.75)	4.2 (2.54)
8 hours	4.1 (2.30)	3.3 (2.35)		72 hours	4.5 (2.10)	3.9 (2.10)
12 hours	2.6 (2.40)	3.2 (2.33)		96 hours	4.2 (2.40)	4.3 (2.41)
24 hours	3.4 (1.99)	3.5 (2.37)		Discharge	3.7 (2.32)	3.3 (2.18)
36 hours	3.4 (2.10)	4.0 (2.47)				

- Mean AUC for NRS pain scores for Group 1 (12 to <17 years) are displayed below:

Mean (SD) AUC for NRS Intensity Scores, Group 1 (12 to <17 years)		
Interval	**EXPAREL**	**Bupivacaine HCl**
$AUC_{(4\text{-}24)}$:	51.0 (37.81)	64.7 (41.90)
$AUC_{(4\text{-}48)}$:	139.0 (63.05)	154.6 (83.70)
$AUC_{(4\text{-}72)}$:	232.6 (105.31)	241.4 (126.10)
$AUC_{(4\text{-}96)}$:	306.7 (137.43)	304.2 (162.43)
$AUC_{(4\text{-hospital discharge})}$:	264.9 (124.79)	262.4 (155.45)

- Mean CAS pain scores for Group 2 (6 to <12 years) are displayed below:

Mean (SD) CAS Pain Intensity Scores, Group 2 (6 to <12 years)						
Timepoint	**Spine**	**Cardiac**		**Timepoint**	**Spine**	**Cardiac**
Baseline	0.8 (1.79)	0.0 (0.00)		48 hours	3.4 (3.05)	1.9 (1.92)
4 hours	1.0 (1.41)	2.8 (3.13)		60 hours	2.4 (2.51)	1.2 (1.48)
8 hours	1.4 (1.52)	3.1 (3.09)		72 hours	1.8 (2.36)	1.3 (1.69)
12 hours	1.0 (1.00)	3.6 (3.22)		96 hours	2.0 (3.46)	1.2 (1.37)
24 hours	1.8 (1.92)	2.4 (2.68)		Discharge	3.4 (3.58)	0.8 (1.37)
36 hours	2.2 (1.48)	2.2 (2.41)				

- Mean AUC for CAS pain scores for Group 2 (6 to <12 years) are displayed below:

Mean (SD) AUC for CAS Intensity Scores, Group 2 (6 to <12 years)		
Interval	**Spine Surgery**	**Cardiac Surgery**
$AUC_{(4\text{-}24)}$:	30.2 (21.99)	46.9 (45.04)
$AUC_{(4\text{-}48)}$:	92.7 (64.53)	101.0 (76.35)
$AUC_{(4\text{-}72)}$:	153.5 (113.87)	134.3 (89.09)
$AUC_{(4\text{-}96)}$:	223.5 (184.73)	158.8 (104.26)
$AUC_{(4\text{-hospital discharge})}$:	192.3 (141.43)	155.8 (99.07)

Total Opioid Consumption

- Total opioid consumption data for Group 1(12 to <17 years) are displayed below:

Geometric Mean (%CV) for Total Opioid Consumption (MED mg), Group 1 (12 to <17 years)		
Interval	**EXPAREL**	**Bupivacaine HCl**
0 – 24 hours	46.06 (91.665)	52.66 (70.126)
0 – 48 hours	100.05 (80.116)	113.17 (64.124)
0 – 72 hours	136.61 (66.942)	155.17 (57.9)

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- Total opioid consumption data for Group 2 (6 to <12 years) are displayed below:

Geometric Mean (%CV) for Total Opioid Consumption (MED mg), Group 2 (6 to <12 years)		
Interval	**Spine Surgery**	**Cardiac Surgery**
0 – 24 hours	1.84 (120.869)	16.63 (74.389)
0 – 48 hours	6.48 (82.613)	20.94 (80.100)
0 – 72 hours	10.65 (80.991)	23.53 (88.519)

Time to Rescue Medication

- For Group 1 (12 to <17 years), median time to first rescue medication was 0.82 hours and 0.60 hours in the EXPAREL and bupivacaine HCl groups, respectively.
- For Group 2 (6 to <12 years), median time to first rescue medication was 15.77 hours and 2.43 hours in the spine surgery and cardiac surgery groups, respectively.

CONCLUSION:

Bupivacaine pharmacokinetics of single 4 mg/kg dose of EXPAREL were studied in pediatric subjects of 6 to less than 17 years undergoing spine or cardiac surgeries. For comparison, the pharmacokinetics of single 2 mg/kg doses of bupivacaine HCl were administered to pediatric subjects of 12 to less than 17 years undergoing spine surgeries. The results (geometric mean comparisons for Group 1 spine and Group 2 cardiac, and median for Group 2 spine) indicated that:

- Spine subjects in Group 1 who received bupivacaine HCl had a higher C_{max} (488.2 ng/mL) than matching subjects given an average 1.45-fold higher bupivacaine dose as EXPAREL (336.8 ng/mL).
- In Group 1, bupivacaine overall median t_{max} after Bupivacaine HCl and EXPAREL were short (<1.5 h); however, EXPAREL was associated with a later t_{max2} (median 18.0 h, range 11.1-26.1 h after the dose) and hence more sustained bupivacaine concentrations than seen with the Bupivacaine HCl.
- In Group 1, the AUC of bupivacaine was higher after administration of EXPAREL than when bupivacaine HCl was administered to spine subjects (8296.9 vs. 4791.4 ng×h/mL for $AUC_{0\text{-}tlast}$; 12256.8 vs. 5064.2 ng×h/mL for $AUC_{0\text{-}\infty}$), consistent with a higher bupivacaine dose when given as EXPAREL.
- The AUC of bupivacaine after administration of EXPAREL was higher in cardiac subjects from Group 2 compared with spine subjects from Group 1 (15316.0 vs. 8296.9 ng×h/mL for $AUC_{0\text{-}tlast}$; 19707.4 vs. 12256.8 ng×h/mL for $AUC_{0\text{-}\infty}$).
- The bupivacaine C_{max} was higher in the cardiac subjects (403.4 ng/mL) than in the spine subjects (336.8 ng/mL in Group 1 and 319.5 ng/mL in Group 2 age-matched subjects).
- The time to C_{max} was delayed for the cardiac subjects comparing with spine subjects (median t_{max} over 22.7 vs. < 8 h).
- The CL/F of bupivacaine in Group 2 cardiac subjects given EXPAREL (6.6 L/h) was lower than that after EXPAREL or Bupivacaine HCl when given to spine subjects (14.5 to 18.9 L/h).

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® (bupivacaine liposome injectable suspension)		
Name of Active Ingredient: Bupivacaine		

- The geometric mean estimation of Vd/F yielded a value of 488.4 L for older spine-surgery subjects who received EXPAREL, which was numerically higher than those for other groups (ranging from 197.1 to 271.1 L).

EXPAREL 4 mg/kg was safe and well tolerated in the pediatric subjects (6 to <17 years of age) who participated in this study.

The incidence of SAEs was low and none were considered related to study treatment. EXPAREL was generally well tolerated by the pediatric and adolescent subjects in this study.

The study was not powered to evaluate efficacy; efficacy was examined for descriptive purposes only. In Group 1, mean pain intensity NRS scores tended to be lower through 36 hours in the EXPAREL group; AUC for mean pain intensity NRS scores and total opioid consumption were lower through 72 hours in the EXPAREL group compared with the Bupivacaine HCl group. Median time to first rescue medication was 0.82 hours and 0.60 hours in the EXPAREL and bupivacaine HCl groups, respectively. In Group 2, the mean CAS pain intensity scores, AUC for mean pain intensity CAS scores, and total opioid consumption were generally low for both surgery types. Median time to first rescue medication was 15.77 hours and 2.43 hours in the spine surgery and cardiac surgery groups, respectively.

Date of Report: 13-May-2020

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4. ACRONYMS/ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AESI	Adverse event of special interest
ASA	American Society of Anesthesiology
ATC	Anatomical therapeutic class
AUC	Area under the curve
$AUC_{0\text{-tlast}}$	Area under the plasma concentration vs. time curve from the start of dosing to the time of the last quantifiable plasma concentration
$AUC_{0\text{-}\infty}$	Area under the plasma concentration vs. time curve from the start of dosing extrapolated to infinity
BLQ	Below the level of quantification
BMI	Body mass index
CAS	Color Analog Scale
CFR	Code of Federal Regulations
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
C_{max1}	The maximum observed plasma concentration between 0 hour and 4 h
C_{max2}	The maximum observed plasma concentration beyond 4 h
CRF	Case report form
CV	Coefficient of variance
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Geomean	Geometric mean
ICF	Informed consent form
ICH	International Council for Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
Max	Maximum
MED	Morphine equivalent dose
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
NCA	Noncompartmental analysis
NRS-R	Numeric rating scale – at rest
NSAID	Non-steroidal anti-inflammatory drug

OR	Operating room
PK	Pharmacokinetic
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System Organ Class
$t_{1/2el}$	Apparent terminal elimination half-life
t_{last}	Time of the last temporal quantifiable concentration (Clast)
t_{max}	The time at which C_{max} was observed
t_{max1}	The time at which C_{max1} was observed
t_{max2}	The time at which C_{max2} was observed
TEAE	Treatment-emergent adverse event
US	United States
Vd/F	Apparent volume of distribution

Abbreviations that appear only in tables or figures are defined in the relevant table or figure.

5. ETHICS

5.1. Institutional Review Board/Independent Ethics Committee

Prior to enrolling subjects into this study, each study site obtained the approval of an Institutional Review Board (IRB) that complied with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and/or the United States (US) Food and Drug Administration (FDA) Title 21 Code of Federal Regulations (CFR) Part 56. Attention was directed to the basic elements that were required to be incorporated into the informed consent form (ICF) under 21 CFR Part 50.25 and ICH GCP.

Information pertaining to the IRB used for this study, including the membership list, is provided in Appendix 16.1.3.1.

5.2. Ethical Conduct of the Study

This study was 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 were maintained in accordance with applicable regulations.

5.3. Subject Information, Consent, and Assent

Before a subject underwent any study-specific screening procedures, the Investigator or designee thoroughly explained 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-approved ICF was provided to the subject's parent/guardian, who was 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 discussed the ICF, signed and dated the ICF. If the subject was capable of providing assent, he or she was provided with an explanation of the study and an IRB-approved written assent form to read. Once the Investigator was assured that the subject understood the concepts involved, the subject was asked to give assent (if applicable) to participate in the study. The subject's parent/guardian must have signed the ICF and the subject must have given assent (if applicable) before any study-specific procedures were performed. A copy of the fully signed ICF was given to the parent/guardian and a copy of the assent form (if applicable) was given to the subject.

The Investigator explained to the subject's parent/guardian that they were 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 have independently withdrawn assent to participate in the study. Similarly, the Investigator and/or Pacira Pharmaceuticals, Inc. (Pacira) was 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 were also explained, according to the current ICH GCP (E6) and the Declaration of Helsinki (1964, and as amended through 2013).

A sample ICF is provided in Appendix 16.1.3.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1. Investigators and Study Sites

This study was conducted at 15 sites in the US (Table 1).

Table 1: Study Sites and Principal Investigators

Robert Tracy Ballock, MD (Site 101) The Cleveland Clinic Foundation, 9500 Euclid Avenue, A41, Cleveland, OH 44195
Roger A. Fons, MD (Site 102) Medical College of Wisconsin, 9000 W. Wisconsin Avenue, Milwaukee, WI 53226
Thomas Wesley Templeton, MD (Site 106) Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1009
Gregory B. Hammer, MD (Site 107) Lucille Packard Children's Hospital, 725 Welch Road, Palo Alto, CA 94304
Brad Taicher, DO, MBA (Site 110) Duke University Medical Center, 2301 Erwin Road, 5671 HAFS Building, Durham, NC 27710
Nicole Horn, MD (Site 111) Riley Hospital for Children, 705 Riley Hospital Drive, Indianapolis, IN 46202
Alberto J. de Armendi, MD, PhD, MBA (Site 112) The Children's Hospital at University of Oklahoma Health Sciences Center, 1200 Everett Drive, Oklahoma City, OK 73104
Maria Matuszczak, MD (Site 113) University of Texas McGovern Medical School, 6431 Fannin St, Houston, TX 77030
Sundeep Tumber, DO (Site 115) Shriner's Hospitals for Children Northern California, 2425 Stockton Blvd, Sacramento, CA 95817
Christopher F. Tirotta, MD (Site 116) Variety Children's Hospital db/a Nicklaus Children's Hospital, 3100 SW 62nd Avenue, Miami, FL 33155
Suken A. Shah, MD (Site 118) Nemours Alfred I Dupont Hospital for Children, 1600 Rockland Road, Wilmington, DE 19803
Kumar Belani, MD (Site 123) University of Minnesota Masonic Children's Hospital, 2450 Riverside Avenue, Minneapolis, MN 55454
Ioannis A. Avramis, MD (Site 124) Medical City Dallas, 7777 Forest Lane, Dallas, TX 75230
Michal Szczodry, MD (Site 126) Shriners Hospitals for Children, Chicago, 2211 N Oak Park Avenue, Chicago, IL 60707
Martin J. Morrison, III, MD (Site 128) Loma Linda University Medical Center, 11234 Anderson Street, Loma Linda, CA 92354

The investigators' affiliations and qualifications are presented in their curriculum vitae provided in Appendix 16.1.4.

The principal investigator at each study site was responsible for the validity and accuracy of the data supplied on the case report forms (CRFs). A sample CRF is provided in Appendix 16.1.2.

6.2. Pacira Personnel

The key Pacira personnel who participated in the study are listed below. The signature of the study Principal Investigator, Christopher F. Tirotta, MD, is provided in Appendix 16.1.5.

- Julia Yang, MD, Vice President, Clinical Research
- Vincent Yu, PhD, Vice President, Biometrics
- Alla Nagaev, MD, MD, Associate Medical Director
- Chandni Patel, Clinical Trial Manager, Clinical Operations
- Scott Palfreyman, MS, PA-C, Director of Pharmacovigilance
- Michael Rozycki, PhD, Senior Vice President, Regulatory Affairs

6.3. External Functions

The following external vendors provided services to Pacira during the conduct of this study:

Study conduct and monitoring provided by:
EASi, Inc.
371 Hoes Lane, Suite 201
Piscataway, NJ 08854
732-447-1559

Electronic Data Capture provided by:
TFS, Inc
212 Carnegie Center
Princeton, NJ 08540
609-775-9500

Interactive Response Capture provided by:
Suvoda
Carrer de Pau Claris, 138
7th Floor
Barcelona, 08009, Spain
+34 (830) 830512

Home Healthcare Services provided by:
Symphony Clinical Research
700 Deerpath Drive
Vernon Hills, IL 60061

Pharmacokinetic (PK) Kits and Central Laboratory services provided by:
ICON Laboratories, Inc
123 Smith St.
Farmingdale, NY 11735
631-777-8833

Safety Management provided by:
Pharmalex Development Services, LLC
9302 Lee Highway, Suite 700
Fairfax, VA 22031
571-490-8020

PK Analysis and Bioanalytical Testing provided by:

ABS Laboratories, Ltd.
36 Hospital Fields Rd
York, YO10 4DZ, UK
+44 (0) 1707 358666

PK Report and Statistical Programming services provided by:

Everest Clinical Research Corporation
675 Cochrane Drive
East Tower, 4th Floor
Markham, Ontario, Canada L3R 0B8
1-905-752-5222

Printed Materials provided by:

Imperial Graphics
3100 Walkent Drive, NW
Grand Rapids, MI 49544
1-800-777-2591

7. INTRODUCTION

7.1. Background

Postsurgical pain is 1 of the most common forms of acute pain (Schug 1993; Carr 1999). 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 (Stephens 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. The consequences of poor pain control in the postoperative setting, 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 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. Morphine and paracetamol are commonly used in children (Lee 2014).

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). In a recent study, intraoperative intrathecal morphine dose predicted opioid consumption in the acute postoperative period in pediatric patients who underwent spine surgery (Li 2019).

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 (American Society of Anesthesiologists [ASA] Task Force 1995). A multimodal approach to postoperative analgesia, using a combination of agents (eg, opioids, local anesthetics, non-steroidal anti-inflammatory drugs [NSAIDs]), and delivery techniques (patient-controlled analgesia, epidural and regional blocks) is currently recognized as best practice for pain management (Breivik 1995a; Breivik 1995b; 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.

7.2. 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 <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).

7.3. Rationale for the Study

The purpose of this study was to evaluate the pharmacokinetics (PK) and safety of EXPAREL when administered via local infiltration in pediatric subjects aged 6 to <17 years who were undergoing surgery.

8. STUDY OBJECTIVES

8.1. Primary Objective

The primary objective was to evaluate the PK of EXPAREL in pediatric subjects aged 6 to <17 years undergoing various types of surgeries.

8.2. Secondary Objectives

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

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan: Description

This was a multicenter, randomized, open-label, 2-part study to evaluate the PK and safety of EXPAREL in pediatric subjects aged 6 to <17 years who were undergoing spine or cardiac surgeries. Both groups had 2 parts; Part 1 evaluated PK and safety, while Part 2 assessed safety. Subjects in each part were classified into groups by age: Group 1 enrolled subjects 12 to <17 years of age and Group 2 enrolled subjects 6 to <12 years of age (see Table 2).

Enrollment of both age groups was conducted in parallel. Subject enrollment for Part 2 commenced upon completion of enrollment of Part 1.

Table 2: Study Design for Study 402-C-319

	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 [n=15] bupivacaine HCl 2 mg/kg [n=15]	Spine Surgery EXPAREL 4 mg/kg [n=15] bupivacaine HCl 2 mg/kg [n=15]
Group 2 (subjects aged 6 to <12 years)	Spine or Cardiac Surgery EXPAREL 4 mg/kg [n=15]	Spine or Cardiac Surgery EXPAREL 4 mg/kg [n=15]

Abbreviations: HCl=hydrochloride; PK=pharmacokinetics

Dosing of EXPAREL was based on body weight, at a dose of 4 mg/kg (up to a maximum of 266 mg). Dosing of bupivacaine hydrochloride (HCl) was based on body weight, at a dose of 2 mg/kg (up to a maximum of 175 mg) in conformance with dose limits in published literature (Williams 2014).

Group 1 - Subjects aged 12 to <17 years

Group 1, Part 1 (PK and safety) was a randomized, multicenter, active-controlled, open-label, PK and safety evaluation in subjects aged 12 to <17 years undergoing spine surgery. Subjects were randomized 1:1 to receive a single dose of either EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) or bupivacaine HCl 2 mg/kg (not to exceed a maximum total dose of 175 mg) via local infiltration at the end of surgery. The planned sample size was 30 subjects (15 subjects per study arm).

Group 1, Part 2 (safety) was a randomized, multicenter, active-controlled, open-label, safety evaluation in subjects aged 12 to <17 years undergoing spine surgery. Subjects were randomized 1:1 to receive either a single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) or bupivacaine HCl 2 mg/kg (not to exceed a maximum total bupivacaine HCl dose of 175 mg) via local infiltration at the end of surgery. The planned sample size was 30 subjects (15 subjects per study arm).

Group 2 – Subjects aged 6 to <12 years

Group 2, Part 1 (PK and safety) was a multicenter, single-arm, open-label, PK and safety evaluation in subjects aged 6 to <12 years undergoing spine or cardiac surgery. Subjects received a single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration at the end of surgery. The planned sample size was 15 subjects.

Group 2, Part 2 (safety) was a single-arm, multicenter, open-label safety evaluation in subjects aged 6 to <12 years undergoing spine or cardiac surgery. Subjects received a single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration at the end of surgery. The planned sample size was 15 subjects.

The overall safety assessments included all subjects from Part 1 and Part 2, for a planned total of 90 subjects.

Procedures

Subjects were screened within 30 days prior to study drug administration. During the screening visit, subjects were assessed for past or present neurologic, cardiac, and general medical conditions that, in the opinion of the investigator, precluded them from study participation. After the ICF was signed by the subject's legal guardian and written assent was provided by the subject (if capable), medical and surgical histories were taken and the following assessments were performed: 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.

On Day 1, eligible subjects received the study drug before closure of the surgical site via local infiltration to produce local analgesia. Use of intraoperative opioids, acetaminophen, ketorolac, or other NSAIDs, was permitted in accordance with each respective study site's standard of care. Additional use of local anesthetics within 96 hours following the administration of EXPAREL (but not bupivacaine HCl) was to be avoided.

There was no required length of stay in the hospital; subjects were discharged based on the medical judgment of the treating physician. For subjects discharged from the hospital before all protocol-specified assessments until 96 hours were completed, a nurse performed follow-up visits at the subject's home to ascertain the required postsurgical assessments and collect PK samples until 96 hours.

A follow-up phone call was scheduled on Day 7 (± 1 day) and a follow-up visit was scheduled for Day 30. To accommodate the various workflows at the multiple clinical sites, the Day 30 visit window was changed to -16 days (Post-op Day 14) to +3 days (Post-op Day 33) (Protocol Clarification Letter 07 Feb 2019; Appendix 16.1.1).

Postsurgical Pain Management

Use of postsurgical pain medication in cases of insufficient analgesia was permitted according to each study site's standard of care. The investigator recorded all postsurgical pain management medications provided to the subjects until the hospital discharge.

Additional use of local anesthetics within 96 hours following the administration of EXPAREL was to be avoided.

Postsurgical Assessments

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

Adverse events (AEs) were recorded from the time the ICF was signed/assent was given until Day 30.

In case a cardiac or neurological AE of special interest (AESI) or serious AE (SAE) occurred during the study, if the investigator or medical monitor considered that the event may have been related to study treatment or suggested the possible occurrence of local anesthetic systemic toxicity (with or without the need for treatment [eg, intralipids]), or if a plausible etiology for the event could not be found, an unscheduled PK blood sample was collected and a 12-lead ECG, vital signs, and clinical laboratory tests (hematology and complete metabolic profile) may have been conducted according to each respective study site's standard of care.

Cardiac AESIs included chest pain, abnormal/irregular heart rate, and shortness of breath that required intervention. Neurologic AESIs included seizure, altered mental status/altered sensorium, rigidity, dysarthria, tremors, tinnitus, visual disturbance, and severe or worsening dizziness. Additionally, the following events were considered AESIs if they persisted or occurred beyond 72 hours post dose: dizziness, hyperesthesia, muscular twitching, and tingling/paresthesia.

Severity of dizziness was assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0. Severe dizziness was defined as severe unsteadiness or sensation of movement that limited self-care activities of daily living. Dizziness that was severe or worsened or persisted beyond 72 hours post dose was to be captured as an AESI.

Pharmacokinetic Assessment (Part 1 only)

A population PK sampling scheme was used to reduce the burden of the number of blood draws for each individual subject. On Day 1, eligible subjects were assigned to 1 of the 2 PK sampling groups shown below based on surgery type (Table 3). A total of 8 blood samples were collected from each subject at the specified time windows for the determination of bupivacaine plasma concentrations. Sparse PK sampling schemes were employed to allow for a comprehensive evaluation of the plasma concentration versus time profiles in each surgery while reducing the burden of blood sample collection on the individual pediatric participants.

Table 3: Pharmacokinetic Sample Collection Schedule

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

Abbreviations: h=hour(s); min= minutes; PK= pharmacokinetic

Subjects may have been fitted with a peripheral venous line at the discretion of the investigator to facilitate the collection of blood for PK assessment.

9.1.1. Duration of the Study and Subject Participation

Participation began when written informed consent/assent was obtained. No more than 30 days was to have passed between obtaining written consent/assent and the administration of study drug. The time from study drug administration until the end of participation was 30 ± 3 days. Therefore, subjects might have participated in the study up to 63 days.

To accommodate the various workflows at the multiple clinical sites, the Day 30 visit window was changed to -16 days (Post-op Day 14) to +3 Days (Post-op Day 33) (Protocol Clarification Letter 07 Feb 2019; Appendix 16.1.1).

9.1.2. Data Safety Monitoring Board

The study or a study site could have been terminated if conditions during the study indicated such action was warranted. A Data Safety Monitoring Board (DSMB) monitored the safety and dosing data on an ongoing basis, with additional expedited DSMB review conducted as necessary. The DSMB Charter is provided in Appendix 16.1.13.

9.1.3. Study Stopping Rules

If Pacira, the investigator, or officials from regulatory authorities discovered conditions during the study that indicated that the study or study site should be terminated, this action was taken after Pacira had consulted with appropriate regulatory authorities and notified the investigator(s).

The Pacira Medical Monitor and Pharmacovigilance team reviewed all SAEs reported from this study on an ongoing basis and in real time (ie, as the events are reported). The Medical Monitor was responsible for temporarily halting the study if the type, frequency, or seriousness/severity of such events suggested a potential threat to the safety of the study participants. If such action was taken, a thorough review of all available data was to be conducted. Based on the results of this review and discussions with investigators and/or regulatory authorities as warranted, the study may have been restarted or permanently terminated.

In addition, any death was to be thoroughly reviewed and appropriate action taken. There were no deaths reported during the study.

9.2. Discussion of the Study Design, Including the Choice of Control Groups

This study was designed to confirm the dosage for the safe administration of EXPAREL in the pediatric population aged 6 to <17 years. EXPAREL doses for pediatric subjects were based on body weight, consistent with general prescription standards used in pediatric practice.

A population PK sampling scheme (Appendix 16.1.14) was used to reduce the burden of the number of blood draws. Eight (8) blood samples were to be collected from each subject at the specific post-dose time windows shown in Table 3 for the determination of bupivacaine plasma concentrations.

9.3. Selection of Study Population

Subjects had to have met all eligibility criteria to be enrolled in this study.

9.3.1. Inclusion Criteria

For inclusion in the study, subjects were required to meet all of the following criteria:

1. Subjects whose parent(s) or guardian(s) had signed and dated the ICF for the subject to participate in the study, and subjects who had provided written assent to participate in the study (if capable).
2. ASA Class 1-3.
3. Male or female subjects 6 to <17 years of age on the day of surgery.
4. Body mass index (BMI) at screening within the 5^{th} to 95^{th} percentile for age and sex.
5. A negative pregnancy test for female subjects of childbearing potential must have been available prior to the start of surgery. The pregnancy test must have been conducted in the preoperative holding area according to the study site's standard of care.
6. Subjects and their parent(s)/guardian(s) were 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 to provide informed consent/assent.
7. Subjects must have been able to adhere to the study visit schedule and complete all study assessments.

9.3.2. Exclusion Criteria

A subject was not eligible for the study if any of the following criteria were 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, indicated 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 was 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 was ineligible to receive study drug if he or she met the following criterion during surgery:

9. Any clinically significant event or condition uncovered during the surgery (eg, excessive bleeding, acute sepsis) that might have rendered the subject medically unstable or complicated the subject's postoperative course.

9.3.3. Removal of Subjects from Therapy or Assessment

Every reasonable effort was made to maintain subject compliance and participation in the study. Subjects who withdrew from the study after receiving study drug were to undergo safety assessments until the end of the study (Day 30).

If a subject who withdrew from the study had an ongoing AE, every effort was made to monitor the event until satisfactory resolution was obtained, or further follow-up was otherwise no longer warranted.

9.3.3.1. Withdrawal Secondary to Adverse Events

If a subject experienced an AE that rendered him or her incapable of continuing with the remaining study assessments, then he or she was to be discontinued from further participation in the study. A final evaluation visit was performed so that the subject's study participation could have been terminated in a safe and orderly manner. Otherwise, the subject's parent or guardian was 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 was needed and the urgency of the situation permitted. Any subject exhibiting undesirable AEs received appropriate treatment at the discretion of the investigator.

This study involved a single administration of the study drug; therefore, subjects were not terminated from the ongoing study assessments as long as they were 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 were to be obtained by the investigator.

9.3.3.2. Voluntary or Study Investigator Withdrawal

Subjects (or their parent or guardian) were free to discontinue from the study at any time, without prejudice to future treatment. Nevertheless, subjects were encouraged to complete the study safety assessments. In addition, a subject could have been discontinued from the study if he or she refused to comply with study procedures. Reasons for discontinuation from the study were recorded.

If a subject was discontinued by the investigator or voluntarily withdrew from the study after receiving study drug, the subject was asked to complete a final evaluation so that he or she could 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 were recorded.

After termination from the study, the subject may have been monitored for safety, including monitoring of AEs, until Day 30.

9.4. Treatments

9.4.1. Identity of Investigational Products

EXPAREL was 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 in EXPAREL is present at a nominal concentration of 13.3 mg/mL. EXPAREL was provided in 20 mL, 1.3% (13.3 mg/mL) single-use, clear glass vials. EXPAREL vials were stored refrigerated between 2°C and 8°C (36°F to 46°F).

The reference product was bupivacaine HCl. All information on the drug administered, dose, frequency, and duration was captured in the electronic case report form.

The bupivacaine dose delivered by EXPAREL is expressed as bupivacaine free base equivalents (0.886 mg bupivacaine free base equivalents = 1.0 mg bupivacaine HCl equivalent), while the bupivacaine dose delivered from 0.5% bupivacaine HCl is expressed as bupivacaine HCl.

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

9.4.2. Administration of Study Drug

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

EXPAREL

Dosing of EXPAREL for this study was based on body weight, at a dose of 4 mg/kg, not to exceed a maximum total dose of 266 mg. This weight-based dosing applied to Part 1 and Part 2 of the study. EXPAREL was not to be administered to a subject if the vial had been open for more than 4 hours. In order to prevent the study drug from settling, it was recommended that the syringe be gently inverted and re-inverted several times prior to administration. No agents were to be admixed with EXPAREL.

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

All eligible subjects randomized to receive EXPAREL received a single dose of EXPAREL before closure of the surgical site via local infiltration into the surgical site. EXPAREL could have been administered as is or expanded with normal (0.9%) saline to increase the volume up to a final concentration of 0.89 mg/mL (ie, 1:14 dilution by volume). The total volume of expansion was dependent on the incision length.

Active Control: Bupivacaine HCl

Dosing of Bupivacaine HCl was based on body weight, at a dose of 2 mg/kg, not to exceed a maximum dose of 175 mg. Bupivacaine could have been administered as is or expanded to increase volume according to the study site's standard of care.

Total Volume of Expansion

The investigators were instructed to document the total volume of expansion used; and calculate the total volume for each surgery depending on the incision length by using the calculation method below:

- EXPAREL 4 mg/kg (with a maximum total dose of 266 mg) + normal saline (20–60 mL based on the incision size) = total volume.
- For example: If the infiltration sites were 1.5 cm apart, then a 10 cm incision was 10 × 2 sides × 3 layers = 60 cm. If 1 mL was infiltrated every 1.5 cm, the total volume was 40 mL.

In Part 1, all eligible subjects received a single dose of EXPAREL before closure of the surgical site via local infiltration. EXPAREL could have been administered as is or expanded to increase volume as described above.

In Part 2, all eligible subjects randomized to EXPAREL received a single dose of EXPAREL before closure of the surgical site via local infiltration. Dosing was informed by the results of Part 1 and any recommendations based on the complete safety review.

9.4.3. Method of Assigning Subjects to Study arms

Approximately 90 subjects were planned for this study: 60 in Group 1 (12 to <17 years) and 30 in Group 2 (6 to <12 years). Subjects in Group 1 were randomized 1:1 to receive either a single dose of EXPAREL or bupivacaine HCl. Subjects in Group 2 received a single dose of EXPAREL. The randomization code was generated by a centralized randomization system, which was also used to communicate subject randomizations to study sites. All randomized subjects had both a unique subject identifier and a unique random code identifier. No subject or random code identifiers were reused once assigned.

Once a subject was identified as being qualified to participate in the study and was at the study site for surgery, the authorized site staff or designee obtained a randomization assignment. The subject was considered randomized into the study once the study treatment assignment was received.

9.4.3.1. Replacement of Subjects

Subjects who were withdrawn from the study before receiving study drug could have been replaced. Once assigned, subject numbers were not reused; subjects enrolled to replace those who withdrew were assigned a unique subject number.

9.4.4. Selection of Doses in the Study

The dose of EXPAREL (4 mg/kg up to a maximum total dose of 266 mg) was selected to provide exposure in pediatric subjects similar to that 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 <17 years. According to the model, a dose of 4 mg/kg would produce bupivacaine concentrations in pediatric patients aged 6 to <17 years analogous to those observed in the adult infiltration studies. The dose of EXPAREL administered was not to exceed 266 mg, regardless of the weight of the subject.

The selection of the 4 mg/kg dose was also supported by real world evidence collected at the Cleveland Clinic (Protocol Section 11.5, Appendix 16.1.1), where 375 pediatric patients had received EXPAREL at a mean dose of 4.1 ± 1.8 mg/kg, with no significant AEs attributed to EXPAREL use.

9.4.5. Selection and Timing of Dose for Each Subject

The doses chosen for this study are presented in Table 2.

9.4.6. Blinding

This was an open-label study. Blinding was not performed.

9.4.7. Prior and Concomitant Therapy and Medications

All medications taken within 30 days prior to study drug administration until Day 30 after study drug administration or until the subject was withdrawn from the study, whichever was sooner, were recorded on the electronic case report form. Additionally, any medications administered in association with an AE were recorded until Day 30. All postsurgical analgesics administered were documented until 96 hours after surgery.

9.4.7.1. Medications and Therapy Before Study Drug Administration

Permitted Prior Medications and Therapy:

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

Restricted Prior Medications and Therapy:

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

9.4.7.2. Medications and Therapy During Surgery

Permitted Medications and Therapy During Surgery:

- Use of intraoperative opioids, acetaminophen, ketorolac, or other NSAIDs was permitted according to each respective site's standard of care.

Restricted Medications and Therapy During Surgery:

- No drugs were to be admixed with EXPAREL (eg, epinephrine, dexamethasone, clonidine).
- Additional use of local anesthetics within 96 hours following administration of EXPAREL (but not bupivacaine HCl) was to be avoided.

9.4.7.3. Medications and Therapy After Surgery

Permitted Medications and Therapy After Surgery:

- In case of insufficient analgesia, postsurgical rescue pain management was handled according to each study site's respective standard of care.
- Parenteral antiemetic medication was administered, as needed.

Restricted Medications After Surgery:

- Additional use of local anesthetics within 96 hours following administration of EXPAREL (but not bupivacaine HCl) was to be avoided.

9.4.8. Treatment Compliance

Study drug was administered intraoperatively by study staff; therefore, treatment compliance was ensured.

The investigator or designee maintained 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. Drug accountability data were confirmed by a study monitor. Inventory records were readily available for inspection by the study monitor and appropriate regulatory authorities at any time.

9.5. Pharmacokinetic, Safety, and Other Variables

9.5.1. Pharmacokinetic, Safety, and Other Measurements and Schedule of Assessments

The time and events schedule of study procedures is presented in Table 4.

Table 4: 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[1]
Time Window	**Within 30 d**			**±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	X	X																	
Urine drug screen and alcohol breath test at the investigator's discretion	X	X																	
Physical examination	X																		X
12-lead ECG[2]	X[3]																		
Clinical laboratory tests (hematology, chemistry, urinalysis)[4]	X	X														X			
Perform neurological assessment	X						X	X	X	X	X	X	X	X	X	X	X		X
Measure and record vital signs[5]	X	X					X	X	X	X	X	X	X	X	X	X	X		X
Record age-specific pain intensity score[6]	X							X	X	X	X	X	X	X	X	X	X		
Collect PK blood samples per time windows in Table 3				◄	-	-	-	-	-	-	-	-	-	-	-	►			
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[1]
Time Window	**Within 30 d**			**±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[7]	←	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	X
Record AEs beginning at the time the ICF or assent is signed[2,4,5,8]	←	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	X

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(s); 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

Note: Postsurgical assessments were conducted at the timepoints specified after the end of study drug administration.

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

1 The Day 30 Visit window was changed to -16 days (Post-op Day 14) to +3 days (Post-op Day 33) (Protocol Clarification Letter 07 Feb 2019; Appendix 16.1.1).

2 ECG abnormalities that were clinically significant were to be recorded as AEs. A 12-lead ECG could also be performed if a subject experienced an AESI (ie, cardiac AE or neurological AE), or an SAE; see footnote 8.

3 A baseline 12-lead ECG was to be recorded prior to surgery and could have been performed either at the screening visit or in the preoperative holding area on Day 1.

4 May also have conducted clinical laboratory tests if a subject experienced an AESI or an SAE; see footnote 7.

5 Vital signs (temperature, resting heart rate, respiratory rate, oxygen saturation and blood pressure) were measured after the subject had rested in a supine position for at least 5 minutes. May also have measured vital signs if a subject experienced an AESI (ie, cardiac AE or neurological AE), or an SAE; see footnote 7.

6 Pain intensity was measured using the 11-point NRS-R for subjects aged 12 to <17 years (Appendix 1 of the protocol; Appendix 16.1.1) and CAS for subjects aged 6 to <12 years (Appendix 2 of the protocol). The preoperative pain intensity assessment was to have been conducted immediately prior to each administration of postoperative opioid pain management medication until 96 hours. If a subject was too anesthetized at the time of a scheduled pain intensity assessment, the assessment was to be skipped.

7 Subject was instructed to discontinue prohibited medications. The date and time of all medications starting at least 30 days prior to study drug administration until 96 hours after study drug administration were recorded. Medications administered for treatment of an AE until Day 30 were recorded.

8 In case a cardiac or neurological AESI or SAE occurred during the study, if the investigator or medical monitor considered the event to be related to study treatment or suggested the possible occurrence of local anesthetic systemic toxicity (with or without the need for treatment [eg, intralipids]), or if a plausible etiology for the event could not be found, an unscheduled PK blood sample was to be collected and a 12-lead ECG, vital signs, and clinical laboratory tests (hematology and complete metabolic profile) according to the study site's standard of care could have been conducted. Additional information on handling of AESIs was provided in Section 13.1.7 and Appendix 6 of the protocol (Appendix 16.1.1). Cardiac or neurological events that did not meet 1 of these 3 criteria were to be reported as described in Section 14.1 of the protocol (Appendix 16.1.1).

Cardiac AESIs included chest pain, abnormal/irregular heart rate, and shortness of breath requiring intervention. Neurologic AESIs included seizure, altered mental status/altered sensorium, rigidity, dysarthria, tremors, tinnitus, visual disturbance, and severe or worsening dizziness. Additionally, the following events could have been of special interest if they persisted or occurred beyond 72 hours post dose: dizziness, hyperesthesia, muscular twitching, and tingling/paresthesia. Severity of dizziness was assessed based on NCI CTCAE (Version 5.0). Dizziness was captured as an AESI if it was severe or worsened or persisted beyond 72 hours post dose (see Section 13.1.7 of the protocol; Appendix 16.1.1).

9.5.2. Pharmacokinetics Assessments and Parameters

9.5.2.1. Pharmacokinetic Assessments

A total of 8 blood samples were to be collected per subject at specific time windows (Table 3) for the determination of plasma concentrations.

9.5.2.2. Pharmacokinetic Parameters

The following PK parameters were 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)

9.5.3. Safety Assessments and Endpoints

9.5.3.1. Safety Assessments

Safety assessments in this study consisted of vital signs, 12-lead ECGs, neurological assessments, laboratory tests, and AEs. The safety measurements were conducted at the timepoints specified:

- Vital signs (resting heart rate, systolic and diastolic blood pressure, temperature, oxygen saturation, and respiratory rate) at screening; upon arrival in the post-anesthesia care unit; 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.
- 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.
- ECGs were assessed at screening or on Day 1 prior to surgery and could also have been conducted if a subject experienced an AESI (ie, cardiac AE or neurological AE), or an SAE.
- AEs from the time the ICF was signed/assent was obtained until Day 30.

9.5.3.2. Safety Endpoints

The following safety endpoints were assessed based on the safety measurements conducted at the specified timepoints:

- Change from baseline in vital signs (temperature, resting heart rate, respiratory rate, oxygen saturation, and blood pressure).
- Summary of neurological assessments (subjects who were oriented, disoriented, not assessable), numbness (of lips, tongue, or around mouth), metallic taste, hearing

problems, vision problems, and muscle twitching. The number and percentage of subjects were tabulated for each neurologic assessment for each age group and overall.

- Change from baseline in clinical laboratory data.
- ECG tracings were classified as ‘normal, ‘abnormal not clinically significant’ or ‘abnormal clinically significant’.
- Incidence of treatment-emergent AEs (TEAEs) and SAEs until Day 30.

9.5.4. Other Measurements and Other Endpoints

9.5.4.1. Other Measurements

The following efficacy measurements were assessed 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 until 96 hours; and at hospital discharge. If a subject was too anesthetized at the time of a scheduled pain intensity assessment, the assessment was skipped. Pain intensity scores were collected using the following instruments:
  - 11-point NRS-R for subjects aged 12 to <17 years
  - CAS for subjects aged 6 to <12 years
- Time and dose of all postoperative opioid pain management medication administered up to hospital discharge.

9.5.4.2. Other Endpoints

Analyses of these other endpoints were conducted for exploratory purposes only. The efficacy endpoints listed below were assessed based on the efficacy measurements conducted at the timepoints specified.

- Pain intensity scores.
- The AUC of pain intensity scores for the specified time intervals.
- Total opioid consumption in oral morphine equivalents.
- Time to first postsurgical use of opioid medication.

9.5.5. Appropriateness of Measurements

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

9.6. Data Quality Assurance

Data for this study were recorded via an electronic data capture system using CRFs and were source-document verified. Each CRF was reviewed and approved by the investigator. A comprehensive validation check program was used to verify the data. Discrepancies were

generated accordingly and transferred electronically to the CRF at the study center for resolution by the investigator/study coordinator.

9.7. Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1. Statistical and Analytical Plans

A comprehensive statistical analysis plan was developed for this study and is provided in Appendix 16.1.9. The endpoints assessed in this study are listed in Section 9.5.2.2 (PK endpoints), Section 9.5.3.2 (safety endpoints), and Section 9.5.4.2 (other endpoints).

All analyses and tabulations were performed using SAS® Version 9.4 or later, with the exception that PK descriptive statistics were performed using Sigmastat and Microsoft Excel. Continuous variables were summarized using descriptive statistics (sample size [n], mean, standard deviation [SD], minimum, median, and maximum). Categorical variables were tabulated with number and percentage of subjects. Unless otherwise noted, percentages were based on the number of subjects in the study arm or group within the analysis population. Individual subject data were provided in listings. All listings were sorted by group, treatment (Group 1), surgery type (Group 2), site, subject and, if applicable, collection date and time.

For tables presenting summaries of pain intensity scores, if more than 1 score was presented for a specific timeframe/timepoint of interest, the highest score within that specific timeframe/timepoint was chosen for analysis. If there were multiple pain intensity score values for the same parameter prior to the end of study drug administration, the last value was chosen for Baseline. Unless otherwise stated, separate summaries and data listings were presented for each age group (Group 1, Group 2). Unless otherwise noted, summaries for Group 1 were presented by study arm and summaries for Group 2 were presented by type of surgery (spine or cardiac).

9.7.1.1. Analysis Sets

Analysis sets were defined as follows:

Safety: The Safety population consisted of all subjects who underwent the planned surgery and received study treatment. All analyses based on the Safety population were by actual treatment received.

Pharmacokinetic: The PK population consisted of subjects who received study drug and provided at least 1 quantifiable plasma concentration. All analyses were by actual treatment received.

9.7.1.2. Subject Disposition

Subject disposition summaries included the number of subjects who were screened, randomized (treated and not treated), included in the Safety population, included in the PK population, who completed the study as planned, and who discontinued from the study (and the reasons for discontinuation from the study).

9.7.1.3. Demographic, Other Baseline Characteristics, and Surgery Characteristics

Demographic and baseline characteristics data were summarized for the PK population and the Safety population.

Descriptive statistics were provided for pain scores, height, weight, and BMI at baseline. The number and percent of subjects were tabulated for the various categories of ASA classification.

Surgery characteristics included duration of surgery and total incision length. Duration of surgery was calculated as the difference between the end of surgery and start of surgery times and reported in hours. Surgical characteristics were summarized using descriptive statistics.

9.7.1.4. Prior, Intraoperative, and Concomitant Medications

Intraoperative, prior, and concomitant medications were coded using the World Health Organization Drug Dictionary and classified according to the default anatomical therapeutic chemical (ATC 4) classification term and preferred term (PT).

Intraoperative medications were defined as medications given as part of the surgical procedure. These may have included anesthesia, opioids or other medications with start and stop dates on the day of surgery and start times overlapping within the surgery start and stop times.

Prior medications were defined as medications with a stop date and time prior to the start of surgery.

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

Intraoperative, prior and concomitant medications were summarized separately using n (%) of subjects within each age group and, study arm of the study by ATC class and PT for the Safety population. Subjects may have had more than 1 medication per ATC category and PT. At each level of subject summarization, a subject was counted once if 1 or more medications were reported by the subject at that level.

Additional information regarding the definitions of prior, concomitant, and intraoperative medications is provided in the Statistical Analysis Plan (SAP), Section 6.5 (Appendix 16.1.9).

9.7.1.5. Pharmacokinetic Analyses

A sparse PK sampling scheme was used to limit the number of blood draws from individual subjects. On Day 1, eligible subjects were assigned to 1 of 2 PK sampling groups shown in Table 3 based on surgery type. A total of 8 blood samples were collected from each subject at the specific time windows shown for the determination of bupivacaine plasma concentrations.

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

9.7.1.5.1. Pharmacokinetic Parameters Calculation Methods

Methods for calculating PK parameters are presented in the SAP (Appendix 16.1.9, Section 6.7.2).

A noncompartmental analysis (NCA) was performed to calculate the PK parameters. All PK parameters were presented in listings and descriptive summary statistics, including the geometric mean, coefficient of variation, arithmetic mean, standard deviation, median, and range, were presented in tables.

Population PK modeling was also performed using all PK data collected during the study. The population PK model estimated EXPAREL and bupivacaine HCl individual and population PK parameters and exposure, inter-individual variability of PK parameters, and intra-individual variability of bupivacaine concentrations. Details and results of this mixed-effect modeling analysis were reported separately.

9.7.1.5.2. Pharmacokinetic Concentrations and Variables

A data listing was provided for all PK bupivacaine concentration data. Concentrations that were below the level of quantification (BLQ) were indicated in the listing.

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

Plasma bupivacaine concentrations for each formulation were summarized at each nominal time window (any out-of-window results were shown only in a listing). The following descriptive statistics were presented: n, geometric mean, arithmetic mean, SD, percent coefficient of variance (%CV), median, minimum, and maximum.

Plots of mean bupivacaine concentration over time were created with the original scale and semi-log scale overlain on the same page. If the number of subjects in a group was ≤3, then individual concentration over time curves were plotted instead of the mean concentration. For Group 1, there were 2 plots overlain for the 2 treatments. For Group 2, there were 2 separate plots for the 2 types of surgery.

Pharmacokinetics parameters were presented using descriptive summary statistics, including the arithmetic mean, median, minimum, maximum, SD, %CV of mean, geometric mean, and %CV of geometric mean. Differences were compared between the 2 formulations using single factor analysis of variance.

9.7.1.6. Safety Analyses

Safety assessments in this study consisted of vital signs, 12-lead ECGs, neurological assessments, and AEs. Vital signs, ECGs, and neurological assessments were serially collected at the timepoints specified in the protocol. Adverse events were collected from the time of informed consent through to the final Day 30 visit.

9.7.1.6.1. Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1.

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

If an AE had a partial onset date and time, the imputed start and stop dates and times were used to determine treatment-emergence (eg, stop date and time was before start time of study drug

administration). All AE summaries presented TEAEs only; AEs that were not treatment-emergent were included in listings but not summarized.

The incidence of subjects reporting TEAEs was tabulated by the number and percentage of subjects reporting the TEAE. Incidence was defined as a subject reporting at least 1 TEAE within the summary level. Summary levels were ‘at least 1 TEAE’, System Organ Class (SOC) and PT. Subjects were counted only once within each reporting level on the table. A summary of subjects reporting at least 1 TEAE during the study was also presented.

The following summaries were presented for the AEs reported by the subjects:

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

- Any TEAE
- Any TEAE by level of maximum severity (mild, moderate, severe)
- At least 1 related TEAE
- At least 1 serious TEAE
- At least 1 TEAE of special interest
- Subjects discontinued due to a TEAE
- Died on study (ie, within 30 days of study drug administration)

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

Adverse event tables presented the data within each age group of the study. Incidence tables were created for the following groups of TEAEs:

- All TEAEs by System Organ Class (SOC) and PT sorted by the decreasing order of subject incidence
- All TEAEs by relationship to study drug
- All TEAEs by severity
- All TEAEs of special interest
- All serious TEAEs

Adverse events were considered related if the investigator assessment of relationship to study treatment was either ‘possible’, ‘probable’ or ‘definite’. Adverse events were considered unrelated if the investigator assessment of relationship to study treatment was either ‘unrelated’, ‘unlikely related.

Adverse Events of Special Interest (AESIs)

The MedDRA terms for AESIs defined for this study are presented in Table 5. All AEs reported by investigators were based on these terms along with their clinical judgment.

Table 5: MedDRA Terms for Adverse Events of Special Interest

Group	Protocol term	MedDRA 21.1 Dictionary Preferred Term
Cardiac	Chest pain	Chest Pain
	Abnormal/irregular heart rate	Heart Rate Irregular
	Shortness of breath requiring intervention	Dyspnoea
Neurologic	Seizure	Seizure
	Altered mental status	Mental Status Changes
	Altered sensorium	Depressed Level of Consciousness
	Rigidity	Muscle Rigidity
	Dysarthria	Dysarthria
	Tremors	Tremor
	Tinnitus	Tinnitus
	Visual disturbance	Visual Impairment
	Dizziness[1]	Dizziness
Other	Dizziness[2]	Dizziness
	Hyperesthesia[2]	Hyperaesthesia
	Muscular twitching[2]	Muscle Twitching
	Tingling[2]	Paresthesia
	Paresthesia[2]	Paresthesia

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities
1 If severe or worsening
2 If event persisted or occurred 72 hours after start of study treatment dose

9.7.1.6.2. Vital Signs

Vitals signs were resting heart rate in beats per minute (bpm), systolic blood pressure in millimeters of mercury (mmHg), diastolic blood pressure (mmHg), temperature (ºC), oxygen saturation (%), and respiratory rate (breaths/min). Vital signs were summarized within each age group, study arm (Group 1), type of surgery (Group 2), and part of the study at each assessment timepoint.

Summaries of vital signs presented both observed results by timepoint and change-from-baseline results. Baseline was defined as the last measurement prior to the end of study drug administration. Baseline statistics were presented at each assessment timepoint for those subjects reporting data at that timepoint.

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

Additional information regarding vital sign analysis study windows is provided in the SAP, Table 3 (Appendix 16.1.9).

9.7.1.6.3. Electrocardiograms

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

9.7.1.6.4. Neurologic Assessments

Neurological assessments included orientation (orientated, disoriented, not assessable), numbness (of lips, tongue, or around mouth), metallic taste, hearing problems, vision problems, and muscle twitching. The number and percentage of subjects were tabulated for each neurological assessment up for each age group and overall, at any time after baseline and at each assessment timepoint.

9.7.1.6.5. Laboratory Parameters

Clinical laboratory assessments (hematology, chemistry, and urinalysis) were collected at screening, baseline (Day 1 prior to the end of study drug administration) and 96 hours after the end of study drug administration. Laboratory results were summarized within each age group at each assessment timepoint. Summaries presented both actual and change-from-baseline results. Baseline statistics were presented at each assessment timepoint for those subjects reporting data at that timepoint.

Tabulations of the number and percentage of subjects with value below normal, normal or above normal were provided within each age group and study arm (Group 1) or by type of surgery (Group 2), at each assessment timepoint.

Additional information regarding clinical laboratory analysis study windows is provided in the SAP, Table 6 (Appendix 16.1.9).

9.7.1.7. Efficacy Analyses

For exploratory efficacy analyses, descriptive statistics that were appropriate for the efficacy variable were shown within each age group and study arm (Group 1) or type of surgery (Group 2 only) for the Safety population.

9.7.1.7.1. Pain Intensity Score

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

9.7.1.7.2. Area Under the Curve

AUC was derived using the linear trapezoidal rule (see Section 6.9.1.1 of the SAP; Appendix 16.1.9) on the pain scores. AUC started with the first pain assessment obtained after surgery and used all subsequent pain assessments including those collected prior to administration of opioid medication and unscheduled assessments. Actual assessment times were used in deriving AUC. Summary statistics were presented for the following pain intensity AUCs: $AUC_{adjusted(4\text{-}24)}$, $AUC_{adjusted(4\text{-}48)}$, $AUC_{adjusted(4\text{-}72)}$, $AUC_{adjusted(4\text{-}96)}$ and $AUC_{adjusted(4\text{-Hospital Discharge})}$.

Additional information regarding pain intensity scores analysis study windows is provided in the SAP, Table 7 (Appendix 16.1.9).

9.7.1.7.3. Opioid Consumption

Opioid doses were converted to oral morphine equivalent dose (MED mg) using the appropriate conversion factor (see Appendix 16.1.9, Table 8) for all summaries. Total opioid dose was the oral morphine equivalent sum of all opioids taken after surgery up to the timepoint of interest. Subjects with no opioid use during the period in question were assigned a dose of 0 for summaries and changed to the lesser of 0.1 or half of the smallest total amount observed in the study, whichever was smaller, prior to being transformed with the natural logarithm for analysis. Total postsurgical opioid dose was calculated through 24, 48, and 72 hours. In addition to the descriptive statistics for continuous data, geometric mean and coefficient of variation (CV) were also included and mean and SD were excluded.

9.7.1.7.4. Time to First Postsurgical Use of Opioid Medication

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

Kaplan-Meier plots from both analyses of the time from end of surgery to first opioid rescue medication use were presented within age group and part of the study, and a log-rank test p-value of treatment difference shown for Group 1.

9.7.2. Determination of Sample Size

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

9.8. Changes in the Conduct of the Study and Planned Analyses

9.8.1. Changes in the Conduct of the Study

The original study protocol dated 01-Oct-2018, had no protocol amendments issued. There were 2 protocol clarification letters, 1 dated 21 Nov 2018 and 1 dated 07 Feb 2019. The protocol clarification letters are provided in Appendix 16.1.1.

Protocol Clarification Letter dated 21 Nov 2018 noted the following changes to the assessments:

1. Neurological assessments were to be collected for both Group 1 and Group 2 for all parts of the study.
2. Urine pregnancy tests were to be collected for both Group 1 and Group 2 for all parts of the study (for Group 2, urine pregnancy test was to be based on clinical judgment).

3. Urine drug screen and alcohol breath test were to be collected for both Group 1 and Group 2 for all parts of the study at the investigator's discretion.

Protocol Clarification Letter dated 07 Feb 2019 noted the following changes to the assessments:

1. Clinical laboratory tests (hematology, chemistry, urinalysis):
   - Clinical laboratory tests performed at Screening could have been analyzed by the central laboratory, ICON, or the site's local laboratory. Local laboratory results could have been used to help assess subjects' eligibility per the investigator's discretion (laboratory results were not part of the inclusion/exclusion criteria).
   - Day 1 pre-operative and 96-hour samples collected for clinical laboratory tests were required to be analyzed by the central ICON laboratory.
   - Day 1 pre-operative laboratory samples could have been drawn in the operating room (OR); either in the pre-op holding area or in the OR after the subject was asleep.
   - Due to ethical consideration for pediatric population and to avoid additional needle insertion and associated pain, pre-operative clinical laboratory tests could have been collected when the arterial or venous (central or peripheral) line was installed. Samples for the 96-hour clinical laboratory tests could have been collected at the time of the last PK sample collection (Part 1) or right before the venous line was pulled (Parts 1 and 2) or at 96 hours.
2. To accommodate the various workflows at the multiple clinical sites, the Day 30 visit window was changed to -16 days (post-op Day 14) to +3 days (post-op Day 33).
3. Based on the standard of care, the following hierarchical order was recommended for collecting the Part 1 PK samples: arterial line (to be considered first), followed by venous central line, and venous peripheral line (if central line was not available) if already in place per the standard of care. Once the arterial line was removed per the standard of care, remaining PK samples were to be collected from the venous line (central or peripheral following the same hierarchical order).

9.8.2. Changes to the Statistical Analysis Plan

No changes were made to the statistical analysis plan.

The SAP specified an additional analysis that was not specified in the protocol. In this analysis (NCA), PK parameters were calculated with a noncompartmental analysis method as specified in SAP Section 6.7.2 (Appendix 16.1.9).

A post-hoc listing (Listing 16.2-21.1.3 Study Drug Administration-Group 1 Bupivacaine) and post-hoc table (Table 14.5-1.1 Weight Normalized Dose in Bupivacaine Free Base [mg/kg] by Group, Surgery Type, and Treatment Group) were created for this study.

10. STUDY SUBJECTS

Subjects in this study were categorized into two age groups: 12 to <17 years (Group 1) and 6 to <12 years (Group 2), which were analyzed separately. Additionally, data for all subjects who underwent spine surgery, whether in Group 1 or Group 2, were pooled for analyses of PK and safety. This pooled analysis set comprised 36 EXPAREL subjects (31 in Group 1 and 5 in Group 2) and 30 bupivacaine subjects (all in Group 1). Subjects who underwent cardiac surgery were all in Group 2; the PK and safety results for these subjects were presented separately.

10.1. Disposition of Subjects

For Group 1, 61 subjects were screened and 61 subjects (31 EXPAREL, 30 bupivacaine) were randomized and received study drug. The majority of subjects completed the study.

For Group 2, 37 subjects were screened and 37 subjects were randomized (6 in the spine surgery group, 30 in the cardiac surgery group, and 1 subject (128-0074) was discontinued after enrollment because study drug was not available at the site; the surgery type was not specified (Listing 16.2-1.1.2). A total of 34 subjects received study treatment (5 in the spine surgery group and 29 in the cardiac surgery group) and the majority completed the study.

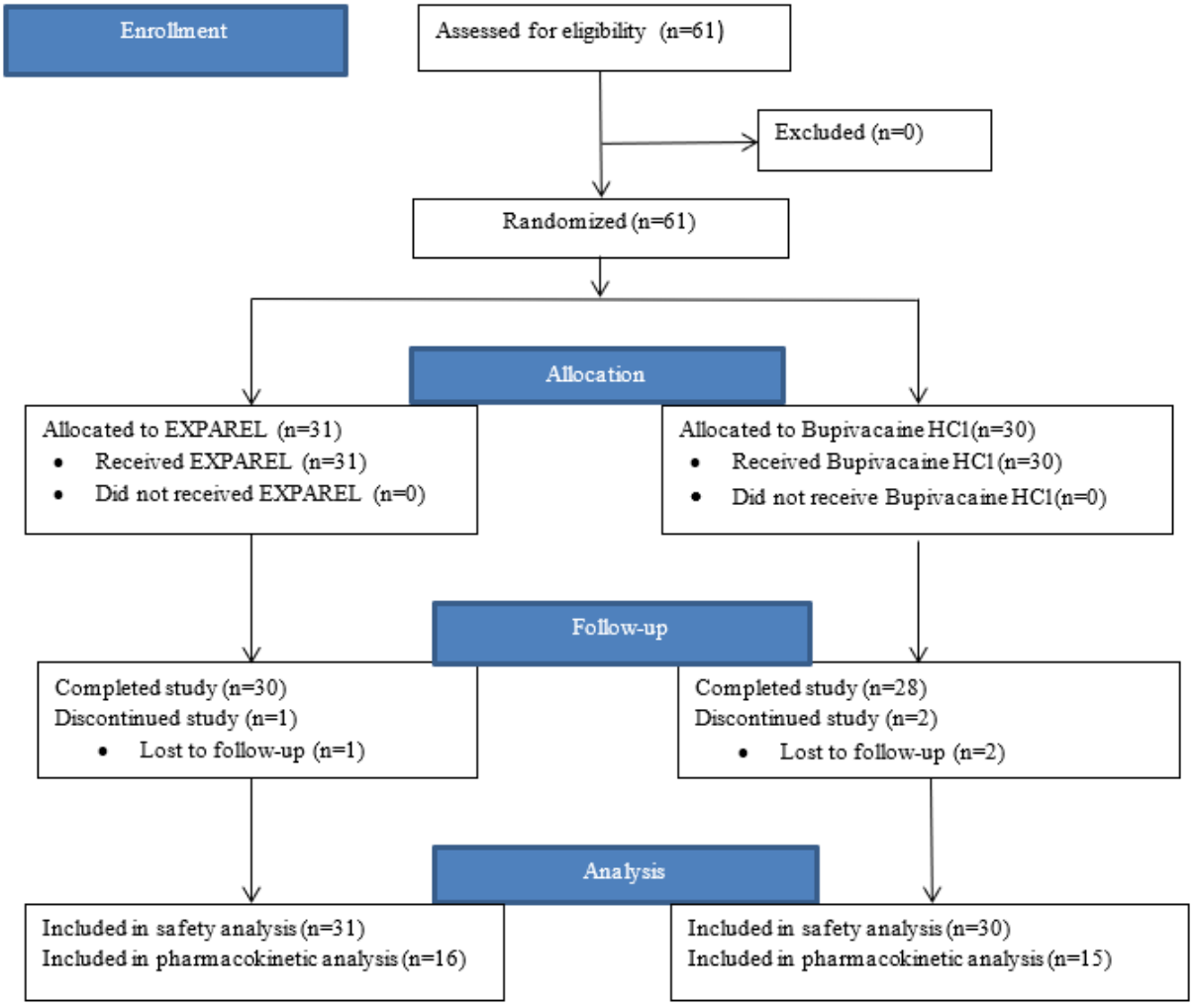
Subject disposition is summarized for both groups in Table 6, for Group 1 in Figure 1, and for Group 2 in Figure 2.

Table 6: Summary of Subject Disposition – All Screened Subjects

	Group 1 (12 to <17 years)			Group 2 (6 to <12 years)		
	EXPAREL 4 mg/kg	Bupivacaine HCl 2 mg/kg	Total	Spine surgery	Cardiac surgery	Total[1]
Screened[2], n	31	30	61	6	30	37[1]
Randomized, n	31	30	61	6	30	37[1]
Not Treated, n	0	0	0	1	1	3[1]
Treated, n	31	30	61	5	29	34
Completed Study[3], n (%)	30 (96.8)	28 (93.3)	58 (95.1)	5 (83.3)	28 (93.3)	33 (89.2)
Discontinued from Study[3], n (%)	1 (3.2)	2 (6.7)	3 (4.9)	1 (16.7)	2 (6.7)	4 (10.8)
Reasons for Discontinuation[3], n (%)						
Death, n (%)	0	0	0	0	0	0
Adverse Event, n (%)	0	0	0	1 (16.7)	0	1 (2.7)
Lack of Efficacy, n (%)	0	0	0	0	0	0
Lost to Follow-up, n (%)	1 (3.2)	2 (6.7)	3 (4.9)	0	1 (3.3)	1 (2.7)
Withdrawal by Subject, n (%)	0	0	0	0	0	0
Other, n (%)	0	0	0	0	1 (3.3)	2 (5.4)

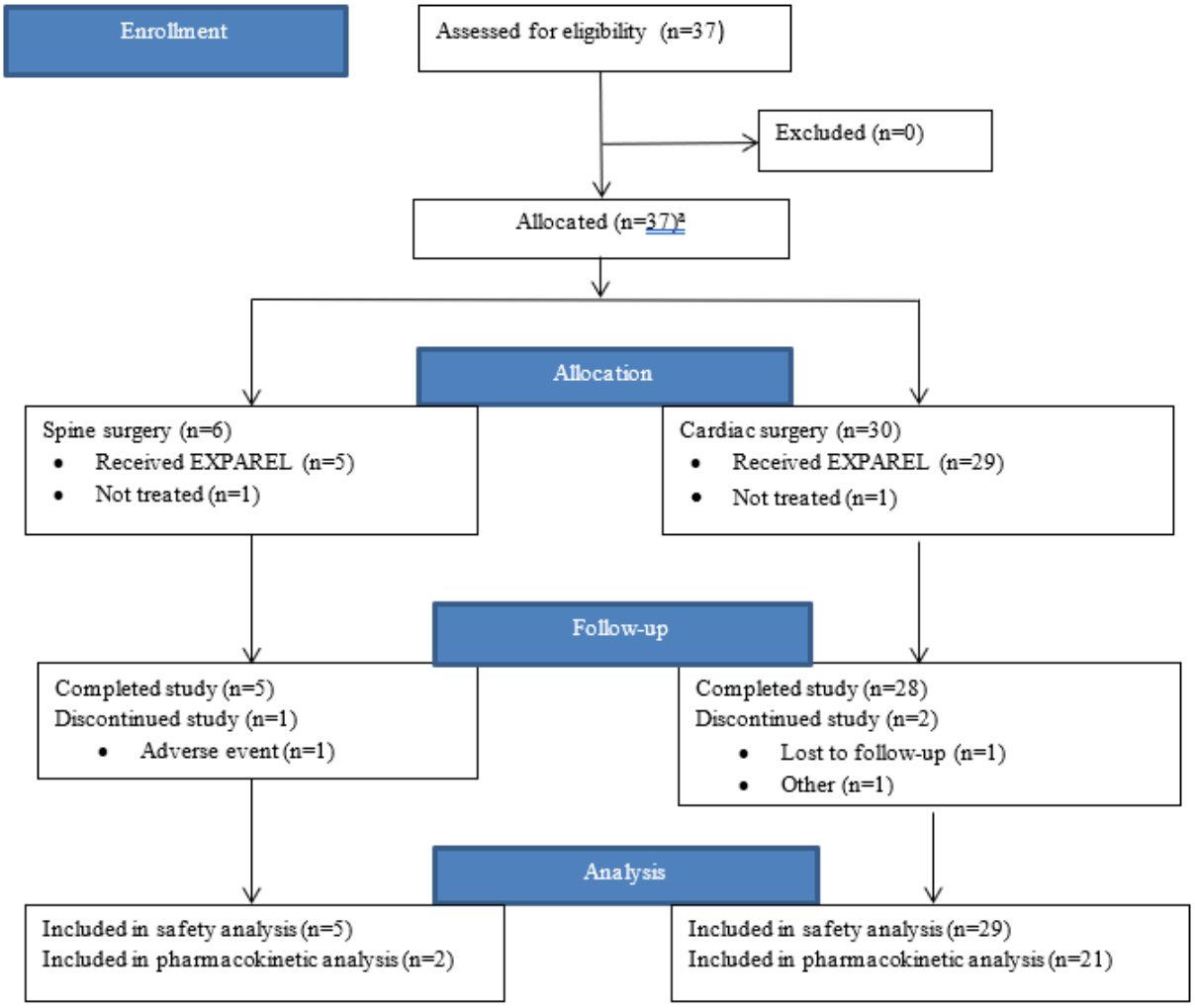
Abbreviations: HCl=hydrochloride
1 Subject 128-0074 was not treated and the surgery type was unavailable.
2 Signed the informed consent form.
3 As randomized.
Source: Table 14.1-1.1.1 and Table 14.1-1.1.2

Figure 1: Subject Disposition, Group 1 (12 to <17 years)



Abbreviations: HCl=hydrochloride
Source: Table 14.1-1.1.1

Figure 2: Subject Disposition, Group 2 (6 to <12 years)



a: Subject 128-0074 was not treated and the surgery type was unavailable.
Source: Table 14.1-1.1.2

Disposition data are listed in Listing 16.2-1.1.1 (Group 1) and Listing 16.2-1.1.2 (Group 2). Screen failures are listed in Listing 16.2-1.1.3.

Data on informed consent are listed in Listing 16.2-24.1.1 (Group 1) and Listing 16.2-24.1.2 (Group 2). Data on subject eligibility are listed in Listing 16.2-25.1.1 (Group 1) and Listing 16.2-25.1.2 (Group 2). Data on inclusion and exclusion criteria are listed in Listing 16.2-25a and Listing 16.2-25b, respectively.

10.2. Protocol Deviations

Protocol deviations are listed in Listing 16.2-28.1.1 (Group 1) and Listing 16.2-28.1.2 (Group 2).

10.3. Surgery

Characteristics of the surgeries are listed in Listing 16.2-5.1.1 (Group 1) and Listing 16.2-5.1.2 (Group 2). Admission and discharge data are listed in Listing 16.2-23.1.1 (Group 1) and Listing 16.2-23.1.2 (Group 2).

Group 1

In Group 1, the mean (± SD) duration of surgery was 4.9 (±1.19) hours in the EXPAREL group and 4.8 (± 1.20) hours in the bupivacaine HCl group (Table 14.1-4.1.1). The mean (±SD) total incision length was 30.9 (± 5.71) cm in the EXPAREL group and 30.3 (± 4.09) cm in the bupivacaine HCl group.

Group 2

In Group 2, the mean (±SD) duration of surgery was 3.3 (±0.81) hours in the spine surgery group and 3.7 (± 1.83) hours in the cardiac surgery group (Table 14.1-4.1.2). The mean (± SD) total incision length was 19.3 (± 13.58) cm in the spine surgery group and 13.0 (± 3.74) cm in the cardiac surgery group.

10.4. Prior, Intraoperative, and Concomitant Medications

Unique medication terms and associated coded terms are listed in Listing 16.2-27.

10.4.1. Prior Medications

Prior medications are provided by subject in Listing 16.2-18.1.1.1 (Group 1) and Listing 16.2-18.1.1.2 (Group 2).

Group 1

In Group 1, at least 1 prior medication was used by 30 EXPAREL subjects (96.8%) and 28 bupivacaine subjects (93.3%) (Table 14.3-7.1.1). The most commonly taken prior medications (≥50% of subjects overall) in Group 1 were dexamethasone (70.5%), midazolam (67.2%), propofol (65.6%), fentanyl (62.3%), gabapentin (52.5%), and cefazolin (50.8%).

Usage was generally similar between the study arms. The percentages of subjects who had used fentanyl and midazolam were higher in the EXPAREL group compared with the bupivacaine HCl group; for fentanyl, 77.4% and 46.7%, respectively, and for midazolam, 77.4% and 56.7%, respectively.

Group 2

In Group 2, at least 1 prior medication was used by 3 subjects (60.0%) who underwent spine surgery and 29 subjects (100%) who underwent cardiac surgery (Table 14.3-7.1.2). The most commonly taken prior medications (≥50% of subjects overall) in Group 2 were cefazolin (79.4%), fentanyl (79.4%), midazolam (76.5%), rocuronium (67.6%), and protamine (61.8%). The percentages of subjects using prior medications were generally higher in the cardiac surgery group.

Spine surgery (pooled)

In an analysis of all subjects who underwent spine surgery (age 6 to <17 years), at least 1 prior medication was used by 33 of 36 EXPAREL subjects (91.7%) and 28 of 30 bupivacaine

subjects (93.3%) (Table 14.3-7.1.3). The most commonly reported prior medications (≥50% of subjects overall) were dexamethasone (68.2%), midazolam (65.2%), propofol (63.6%), fentanyl (60.6%), and cefazolin (51.5%).

10.4.2. Intraoperative Medications

Intraoperative medication data are provided by subject in Listing 16.2-20.1.1 (Group 1) and Listing 16.2-20.1.2 (Group 2).

Group 1

All subjects who underwent surgery in Group 1 received at least 1 intraoperative medication (Table 14.1-5.1.1). The most commonly used intraoperative medications (≥50% of subjects overall) were propofol (95.1%), fentanyl (90.2%), ondansetron (90.2%), tranexamic acid (88.5%), dexamethasone (83.6%), paracetamol (72.1%), remifentanil (70.5%), cefazolin (70.5%), rocuronium (57.4%), lidocaine (55.7%), and midazolam (52.5%).

Group 2

All subjects who underwent surgery in Group 2 received at least 1 intraoperative medication (Table 14.1-5.1.2). The most commonly used intraoperative medications (≥50% of subjects overall) were cefazolin (97.1%), fentanyl (94.1%), rocuronium (76.5%), dexmedetomidine (76.5%), protamine (61.8%), tranexamic acid (55.9%), sugammadex (52.9%), propofol (50.0%), and dexamethasone (50.0%).

10.4.3. Concomitant Medications

All concomitant medications are provided by subject in Listing 16.2-18.2.1.1 (Group 1) and Listing 16.2-18.2.1.2 (Group 2).

Group 1

All subjects (100%) in Group 1 received at least 1 concomitant medication (Table 14.3-8.1.1). Overall, anilides (98.4% of subjects) and natural opium alkaloids (98.4%) were the most commonly used concomitant medications in both study arms. Other concomitant medication ATCs used by >50% of subjects overall included other analgesics and antipyretics, osmotically acting laxatives, acetic acid derivatives and related substances, softeners (emollients), serotonin (5HT3) antagonists, other centrally acting agents, and first-generation cephalosporins.

Group 2

All subjects (100%) in Group 2 received at least 1 concomitant medication (Table 14.3-8.1.2). Overall, anilides (94.1%) and natural opium alkaloids (94.1%) were the most commonly used concomitant medications in both study arms. Other concomitant medication ATCs used by >50% of subjects overall included acetic acid derivatives and related substances, first-generation cephalosporins, solutions affecting the electrolyte balance, and H2-receptor antagonists.

Spine surgery (pooled)

Results were similar for all subjects who underwent spine surgery (age 6 to <17 years) (Table 14.3-8.1.3). All subjects (100%) in both the EXPAREL and bupivacaine study arms received at least 1 concomitant medication. Overall, anilides (98.5% of subjects) and natural

opium alkaloids (97.0%) were the most commonly used concomitant medications. Other concomitant medication ATCs used by >50% of subjects overall included osmotically acting laxatives, other analgesics and antipyretics, acetic acid derivatives and related substances, softeners (emollients), serotonin (5HT3) antagonists, other centrally acting agents, and first-generation cephalosporins.

10.5. Medical /Surgical History

Medical/surgical history data are listed in Listing 16.2-19.1.1 (Group 1) and Listing 16.2-19.1.2 (Group 2).

11. PHARMACOKINETICS AND EFFICACY EVALUATION

11.1. Data Sets Analyzed

Group 1

A total of 61 subjects in Group 1 (31 EXPAREL; 30 bupivacaine) received study drug and were included in the safety analysis (Table 7). Of these, 31 subjects (16 EXPAREL; 15 bupivacaine) were included in the PK population.

A listing of the subjects included in each analysis set for Group 1 is presented in Listing 16.2-2.1.1.

Group 2

A total of 34 subjects (5 spine surgery; 29 cardiac surgery) in Group 2 received study drug and were included in the safety analysis (Table 7). Of these, 23 subjects (2 spine surgery; 21 cardiac surgery) were included in the PK population.

A listing of the subjects included in each analysis set for Group 2 is presented in Listing 16.2-2.1.2 (Group 2).

Spine surgery (pooled)

Safety and PK analyses were performed on an analysis set that included all subjects (age 6 to <17 years) who underwent spine surgery. This analysis set comprised 36 EXPAREL subjects and 30 bupivacaine subjects.

Table 7: Summary of Analysis Populations

	Group 1 (12 to <17 years)			Group 2 (6 to <12 years)		
	EXPAREL 4 mg/kg [n=31]	Bupivacaine HCl 2 mg/kg [n=30]	Total [N=61]	Spine surgery [n=6]	Cardiac surgery [n=30]	Total [N=37]
Screened, n	31	30	61	6	30	37[1]
Safety Population[2], n (%)	31 (100.0)	30 (100.0)	61 (100.0)	5 (83.3)	29 (96.7)	34 (91.9)
PK Population[3], n (%)	16 (51.6)	15 (50.0)	31 (50.8)	2 (33.3)	21 (70.0)	23 (62.2)

Abbreviations: HCl=hydrochloride
1 Subject 128-0074 was not treated and the surgery type was unavailable.
2 Received study drug and surgery.
3 Received study drug and provided at least 1 quantifiable plasma concentration.
Source: Table 14.1-1.1.1 and Table 14.1-1.1.2

11.2. Demographic and Other Baseline Characteristics

11.2.1. Demographic Characteristics

Group 1

Demographic characteristics for Group 1 (Safety population) are summarized in Table 8. Individual subject demographic data for Group 1 are provided in Listing 16.2-3.1.1.

Table 8: Summary of Subject Demographic Characteristics, Group 1 (12 to <17 years) – Safety Population

Characteristic	Group 1 (12 to <17 years)		
	EXPAREL 4 mg/kg n (%)	Bupivacaine HCl 2 mg/kg n (%)	Total
Age (years)			
n	31	30	61
Mean	13.8	13.9	13.8
SD	1.33	1.33	1.32
Median	14.0	14.0	14.0
Minimum, Maximum	12, 16	12, 16	12, 16
Sex, n (%)			
Female	28 (90.3)	22 (73.3)	50 (82.0)
Male	3 (9.7)	8 (26.7)	11 (18.0)
Ethnicity, n (%)			
Hispanic or Latino	10 (32.3)	7 (23.3)	17 (27.9)
Not Hispanic or Latino	19 (61.3)	23 (76.7)	42 (68.9)
Not reported	2 (6.5)	0	2 (3.3)
Race, n (%)			
Asian	2 (6.5)	0	2 (3.3)
Black/African American	5 (16.1)	3 (10.0)	8 (13.1)
White	21 (67.7)	26 (86.7)	47 (77.0)
Other	1 (3.2)	1 (3.3)	2 (3.3)
Native Hawaiian/ Pacific Islander	--	--	--
Not reported	2 (6.5)	0	2 (3.3)

Abbreviations: HCl=hydrochloride; SD=standard deviation
Source: Table 14.1-2.2.1 (Group 1)

There were no clinically significant differences between the EXPAREL and bupivacaine study arms in subject demographic characteristics for the Safety population of Group 1. The overall subject population was predominantly White (77.0%), non-Hispanic (68.9%), and female (82.0%). The mean age was 13.8 years (± 1.32 years).

Group 2

Demographic characteristics for Group 2 (Safety population) are summarized in Table 9. Individual subject demographic data for Group 2 are provided in Listing 16.2-3.1.2.

Table 9: Summary of Subject Demographic Characteristics, Group 2 (6 to <12 years) – Safety Population

Characteristic	Group 2 (6 to <12 years)		
	Spine Surgery	Cardiac Surgery	Total
Age (years), n			
n	5	29	34
Mean	10.0	8.7	8.9
SD	1.73	1.77	1.80
Median	11.0	8.0	9.0
Minimum, Maximum	7, 11	6, 12	6, 12
Sex, n (%)			
Female	2 (40.0)	14 (48.3)	16 (47.1)
Male	3 (60.0)	15 (51.7)	18 (52.9)
Ethnicity, n (%)			
Hispanic or Latino	0	9 (31.0)	9 (26.5)
Not Hispanic or Latino	5 (100.0)	20 (69.0)	25 (73.5)
Race, n (%)			
Asian	0	0	0
Black/African American	1 (20.0)	2 (6.9)	3 (8.8)
White	4 (80.0)	26 (89.7)	30 (88.2)
Other	0	0	0
Native Hawaiian/ Pacific Islander	0	1 (3.4)	1 (2.9)

Abbreviations: HCl=hydrochloride; SD=standard deviation
Source: Table 14.1-2.2.2 (Group 2)

For Group 2, the overall subject population was predominantly White (88.2%), non-Hispanic (73.5%), and almost evenly divided between males (52.9%) and females (47.1%). The overall mean age was 8.9 years (±1.80 years); the mean age was slightly higher in the spine surgery group (10.0 years) than in the cardiac surgery group (8.7 years), but the sample sizes were small.

Results for the PK population were similar to those for the Safety population. Demographic characteristics for the PK population are summarized in Table 14.1-2.1.1 (Group 1) and Table 14.1-2.1.2 (Group 2).

For Group 1 (PK population), there were no clinically significant differences between the EXPAREL and bupivacaine HCl groups in subject demographic characteristics for the PK population. The overall subject population was predominantly White (77.4%), non-Hispanic (64.5%), and female (87.1%). The mean age was 13.9 years (± 1.34 years).

For Group 2 (PK population), the overall subject population was predominantly White (91.3%), non-Hispanic (65.2%), and almost evenly divided between males (47.8%) and females (52.2%). The overall mean age was 8.9 years (±1.79 years); the mean age was slightly higher in the spine surgery group (10.5 years) than in the cardiac surgery group (8.7 years), but the sample sizes were small.

11.2.2. Baseline Characteristics

Group 1

Baseline characteristics for Group 1 (Safety population) are summarized in Table 10 and in Table 14.1-3.2.1. Individual subject data for height and weight for Group 1 are listed in Listing 16.2-4.1.1.

In Group 1 (Safety population), the study arms were generally similar with respect to baseline characteristics.

Table 10: Summary of Baseline Characteristics, Group 1 (12 to <17 years) – Safety Population

Characteristic	Group 1 (12 to <17 years)		
	EXPAREL 4 mg/kg [N=31]	**Bupivacaine HCl 2 mg/kg [N=30]**	**Total [N=61]**
ECG*, n (%)			
Normal	21 (67.7)	20 (66.7)	41 (67.2)
Abnormal, NCS	9 (29.0)	8 (26.7)	17 (27.9)
Abnormal, CS	0	0	0
Baseline NRS Pain Intensity			
n	30	28	58
Mean	0.4	0.5	0.5
SD	1.04	1.14	1.08
Median	0.0	0.0	0.0
Minimum, Maximum	0, 5	0, 4	0, 5
ASA Classification, n (%)			
1	14 (45.2)	13 (43.3)	27 (44.3)
2	16 (51.6)	13 (43.3)	29 (47.5)
3	1 (3.2)	4 (13.3)	5 (8.2)
Height (cm)			
n	31	30	61
Mean	158.75	160.91	159.81
SD	13.636	11.180	12.432
Median	160.00	162.05	160.90
Minimum, Maximum	113.8, 178.0	139.7, 189.6	113.8, 189.6

Characteristic	Group 1 (12 to <17 years)		
	EXPAREL 4 mg/kg [N=31]	**Bupivacaine HCl 2 mg/kg [N=30]**	**Total [N=61]**
Weight (kg)			
n	31	30	61
Mean	53.37	54.67	54.01
SD	11.463	13.352	12.341
Median	51.20	53.25	52.20
Minimum, Maximum	28.3, 87.6	30.4, 87.9	28.3, 87.9
Body mass index (kg/m^2)			
n	31	30	61
Mean	21.05	20.94	21.00
SD	2.792	3.940	3.377
Median	20.90	20.40	20.70
Minimum, Maximum	16.8, 28.9	15.4, 32.8	15.4, 32.8

Abbreviations: ASA=American Society of Anesthesiologists; CS=clinically significant; ECG=electrocardiogram; HCl=hydrochloride; NCS=not clinically significant; NRS= Numeric Rating Scale; SD=standard deviation
*Percentages do not add up to 100% due to missing data.
Source: Table 14.1-3.2.1

Baseline characteristics for Group 1 (PK population) are summarized in Table 14.1-3.1.1.

Group 2

Baseline characteristics for Group 2 (Safety population) are summarized in Table 11 and Table 14.1-3.2.2. Individual subject data for height and weight for Group 2 are listed in Listing 16.2-4.1.2.

In Group 2 (Safety population), the study arms were generally similar with respect to baseline characteristics. Mean height and weight were somewhat lower in the cardiac surgery group, which is not unexpected, as the mean age was lower in the cardiac surgery group.

Table 11: Summary of Baseline Characteristics, Group 2 (6 to <12 years) – Safety Population

Characteristic	Group 2 (6 to <12 years)		
	Spine surgery [N=5]	Cardiac surgery [N=29]	Total [N=34]
ECG, n (%)			
Normal	3 (60.0)	8 (27.6)	11 (32.4)
Abnormal, NCS	2 (40.0)	17 (58.6)	19 (55.9)
Abnormal, CS	0	0	0
Baseline NRS Pain Intensity			
n	5	27	32
Mean	0.8	0.0	0.1
SD	1.79	0.00	0.71
Median	0.0	0.0	0.0
Minimum, Maximum	0, 4	0, 0	0, 4
ASA Classification, n (%)			
1	1 (20.0)	0	1 (2.9)
2	2 (40.0)	2 (6.9)	4 (11.8)
3	2 (40.0)	27 (93.1)	29 (85.3)
Height (cm)			
n	5	29	34
Mean	141.46	134.15	135.23
SD	17.641	12.981	13.697
Median	137.50	134.60	135.80
Minimum, Maximum	118.0 – 162.6	109.6 – 159.2	109.6 – 162.6
Weight (kg)			
n	5	29	34
Mean	39.08	34.90	35.51
SD	14.662	12.560	12.734
Median	33.20	31.70	32.45
Minimum, Maximum	26.2 – 57.0	17.3 – 66.8	17.3 – 66.8
Body mass index (kg/m^2)			
n	5	29	34
Mean	18.92	18.87	18.87
SD	3.056	4.299	4.100
Median	19.00	18.10	18.40
Minimum, Maximum	14.5 – 21.9	11.6 – 29.3	11.6 – 29.3

Abbreviations: ASA=American Society of Anesthesiologists; CS=clinically significant; ECG=electrocardiogram; HCl=hydrochloride; NCS=not clinically significant; NRS= Numeric Rating Scale; SD=standard deviation
Source: Table 14.1-3.2.2

Baseline characteristics for the PK population are summarized in Table 14.1-3.1.2 (Group 2, PK population).

Urine drug screen, alcohol blood test, and pregnancy test data are listed in Listing 16.2-22.1.1 (Group 1) and Listing 16.2-22.1.2 (Group 2).

Subject 112-0078 (EXPAREL, Group 1 [12 to <17 years) had a positive urine drug test at Screening. No other subject tested positive for drugs, and no subject tested positive for alcohol or pregnancy.

11.2.3. Electrocardiograms

A 12-lead ECG was performed prior to surgery and may have been performed at the screening visit or in the preoperatively on Day 1.

Group 1

In Group 1, baseline ECG results were normal for 67.2% of subjects and were abnormal, not clinically significant for 27.9% of subjects overall in the Safety population (Table 14.1-3.2.1). No subject in Group 1 had an ECG that was abnormal, clinically significant. Results were similar for the PK population (Table 14.1-3.1.1).

Group 2

In Group 2, ECG results were normal for 32.4% of subjects and were abnormal, not clinically significant for 55.9% of subjects in the Safety population (Table 14.1-3.2.2). No subject in Group 2 had an ECG that was abnormal, clinically significant. Results were similar for the PK population (Table 14.1-3.1.2).

ECG findings are listed by subject in Listing 16.2-15.1.1 (Group 1) and Listing 16.2-15.1.2 (Group 2).

11.3. Measurements of Treatment Compliance

Study drug was administered by the study staff and, thus, treatment compliance was ensured.

Study drug administration data are listed in Listing 16.2-21.1.1 (Group 1) and Listing 16.2-21.1.2 (Group 2). Study drug administration data for Group 1 bupivacaine HCl are listed in Listing 16.2-21.1.3. Data for the weight normalized dose in bupivacaine free base are provided in Table 14.5-1.1.

11.4. Pharmacokinetic and Efficacy Results

11.4.1. Pharmacokinetic Results

11.4.1.1. Subjects in Pharmacokinetic Population

Plasma concentration data were obtained from 15 subjects given bupivacaine HCl (Group 1) and 39 subjects given EXPAREL (Group 1 and Group 2).

No blood samples were obtained after 1.25 hours for Subject 111-0003 (EXPAREL). This subject was excluded from all calculations. Subject 111-0004 was not treated with study drug, hence, no concentrations were available.

Subject 116-0030 received 192 mg of bupivacaine HCl and was over dosed. Based on her body weight of 48 kg, she received 4 mg/kg of bupivacaine HCl (equivalent to 3.544 mg/kg in bupivacaine free base). This subject is further described in Section 12.1.

There were only 3 subjects given EXPAREL where the t½ and other dependent parameters could not be determined due to lack of, or inconsistent, decline in the plasma concentrations during the terminal phase of the concentration vs time profiles.

The protocol called for all cardiac subjects to be <12 years of age. However, there was 1 subject in Group 2 whose age was 12 years. This subject was retained in analysis and compiled summaries of the cardiac group.

11.4.1.2. Pharmacokinetic Results

Group 1

Group 1 included subjects aged 12 to <17 years undergoing spine surgery who received either EXPAREL 4 mg/kg or bupivacaine HCl 2 mg/kg. Summary PK data are presented in Table 12. Mean concentration vs. time profiles for Group 1 are presented in Figure 3.

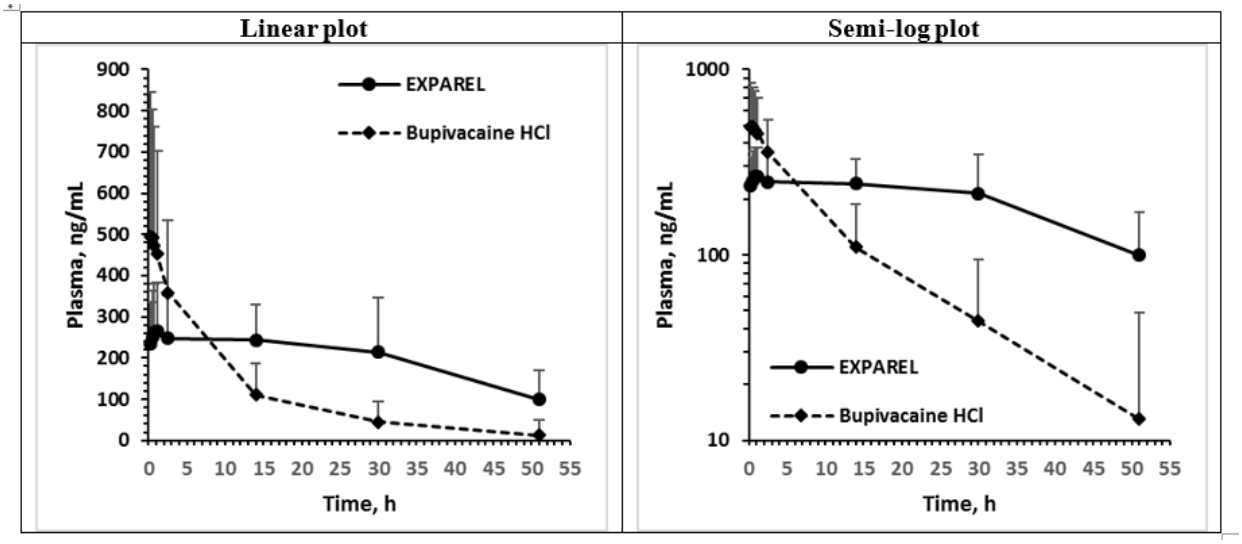
Table 12: Summary of Pharmacokinetics of Bupivacaine after Administration of a Single Dose of EXPAREL or Bupivacaine to Pediatric Subjects, Group 1 (12 to <17 years) (PK Population)

		Group 1	
	Formulation	**EXPAREL**	**Bupivacaine HCl**
Parameter	Dose mg/kg Age, y	3.97 ±0.14 13.6 ±1.36	1.89 ±0.46[†] 14.2 ±1.26
$AUC_{0\text{-}tlast}$, ng*h/mL	Mean ±SD Geomean (CV%) n	9042.5 ±3762.82 8296.9 (46.6) 15	5232.9 ±2538.37 4791.4 (43.7) 15
$AUC_{0\text{-}\infty}$, ng*h/mL	Mean ±SD Geomean (CV%) n	14246.1 ±9118.83 12256.8 (59.0) 15	5709.4 ±3281.74 5064.2 (51.0) 15
C_{max}, ng/mL	Mean ±SD Geomean (CV%) n	357.3 ±125.31 336.8 (37.2) 15	563.6 ±320.93 488.2 (60.0) 15
t_{max}, h	Median (range) n	1.1 (0.3-26.1) 15	0.9 (0.3-2.5) 15
C_{max1}, ng/mL	Mean ±SD Geomean (CV%) n	321.6 ±134.28 295.9 (45.3) 15	- - -
t_{max1}, h	Median (range) n	1.1 (0.3-2.7) 15	- -
C_{max2}, ng/mL	Mean ±SD Geomean (CV%) n	264.3 ±105.10 245.7 (41.5) 15	- - -
t_{max2}, h	Median (range) n	18.0 (11.1-26.1) 15	- -
t½, h	Mean ±SD Geomean (CV%) n	26.8 ±21.26 21.2 (77.3) 15	8.4±6.26 7.4 (47.8) 15

	Formulation	Group 1	
		EXPAREL	Bupivacaine HCl
CL/F, L/h	Mean ±SD	17.5±7.47	20.5±8.27
	Geomean (CV%)	16.0 (47.7)	18.9 (45.7)
	n	15	15
Vd/F, L	Mean ±SD	546.4 ±269.42	226.8 ±110.63
	Geomean (CV%)	488.4 (53.3)	200.9 (56.8)
	n	15	15

Abbreviations: $AUC_{0-\infty}$ = the area under the plasma concentration-versus-time curve from the time of administration extrapolated to infinity; $AUC_{0-tlast}$ = the area under the plasma concentration-versus-time curve from start of dosing to the time of the last quantifiable plasma concentration; CL/F = total body clearance divided by bioavailability (F); C_{max} = the maximum observed plasma concentration; C_{max1} = the maximum observed plasma concentration before 4 h after the dose of EXPAREL; C_{max2} = the maximum observed plasma concentration beyond 4 h after the dose of EXPAREL; geomean = geometric mean; HCl=hydrochloride; %CV = percent coefficient of variance; SD=standard deviation; t_{max} = the time at which C_{max} was observed; t_{max1} = the time at which C_{max1} was observed; t_{max2} = the time at which C_{max2} was observed; t½ = the apparent terminal elimination half-life determined by dividing 0.693 by the terminal elimination rate constant; Vd/F = the volume of distribution calculated as CL/F divided by the terminal phase rate constant; y=years.
† In bupivacaine free base. 0.886 mg bupivacaine free base equivalent = 1.0 mg bupivacaine HCl equivalent.
Source: Table 14.4-1.1, Table 14.5-1.1

Figure 3: Mean (± SD) Bupivacaine Concentrations (ng/mL) Over Time, Group 1 (12 to <17 years) (Linear and Semi-log Scales) – PK Population



Source: Figure 2.1.1, Figure 3.1.1

Subject 116-0030 received a higher dose of bupivacaine HCl (4 mg/kg of bupivacaine HCl) than the protocol specified (2 mg/kg bupivacaine HCl), but a complete set of samples for plasma concentration determinations was also taken. The subject was retained in the summary of descriptive statistics of PK because none of the values were outliers, and because the calculation of CL/F and Vd/F naturally accounts for dose (CL/F is the inverse of dose-normalized AUC). Systemic concentrations of bupivacaine in the EXPAREL treatment arm were more sustained than those in the bupivacaine HCl treatment arm (Figure 3), which lead to a higher C_{max} (Table 12) but exhibited rapidly and consistently declining bupivacaine levels

after C_{max} was achieved (Table 12 and Figure 3). The higher AUC values in EXPAREL-treated subjects were consistent with the higher doses of bupivacaine base given to EXPAREL-treated subjects. The C_{max} observed in the bupivacaine HCl treatment arm was higher (1.45-fold geometric mean) than in the EXPAREL treatment arm, even though the overall t_{max} values were very similar (~1 h). Two t_{max} values were visually apparent for EXPAREL; a rapid short-lived spike followed by a later peak several hours later. In the spine Group 1 subjects, the bupivacaine overall t_{max} after EXPAREL was similar to the t_{max1}, occurring less than 4 h after dosing. No such consistent late peak was seen after bupivacaine HCl. The bupivacaine t½ (2.9-fold geometric mean) was considerably higher for EXPAREL than for the bupivacaine HCl treatment arm. The CL/F values, however, were less than 15% apart between the EXPAREL (16.0 L/h geometric mean) and bupivacaine HCl (18.9 L/h geometric mean) treatment arms. The calculation used for Vd/F yielded values for EXPAREL that were noticeably higher than bupivacaine HCl (488.4 L vs. 200.9 L).

Individual subject data for subjects in Group 1 are provided in the following listings:

- Listing 16.2-9.1.1.1: bupivacaine concentrations (raw) from subjects who received EXPAREL
- Listing 16.2-9.3.1.1: bupivacaine concentrations (raw) from subjects who received bupivacaine HCl
- Listing 16.2-9.5.1.1: PK parameter data for subjects who received EXPAREL
- Listing 16.2-9.6.1.1: PK parameter data for subjects who received bupivacaine HCl

Plots of mean ± SD bupivacaine plasma concentrations over time on a linear scale are provided for subjects who received EXPAREL or bupivacaine in Figure 2.1.1 (Group 1) and Figure 2.1.4 (Both Groups, spine surgery).

Plots of mean ± SD plasma concentrations over time on a semi-logarithmic scale are provided for subjects who received EXPAREL or bupivacaine in Figure 3.1.1 (Group 1) and Figure 3.1.4 (Both Groups, spine surgery).

Plots of individual EXPAREL plasma concentrations over time on linear-linear and log-linear scales are provided for EXPAREL in Figure 4.1.1 (Group 1). Plots of individual bupivacaine plasma concentrations over time on linear-linear and log-linear scales are provided in Figure 4.1.4 (Group 1).

Group 2

Group 2 comprised 23 subjects 6 to <12 years of age who underwent spine or cardiac surgery; 2 subjects underwent spine surgery and the remaining 21 subjects underwent cardiac surgery. All subjects in Group 2 received a single dose of EXPAREL 4 mg/kg.

Pharmacokinetic parameters for subjects in Group 2 are provided in Table 13 and Figure 4.

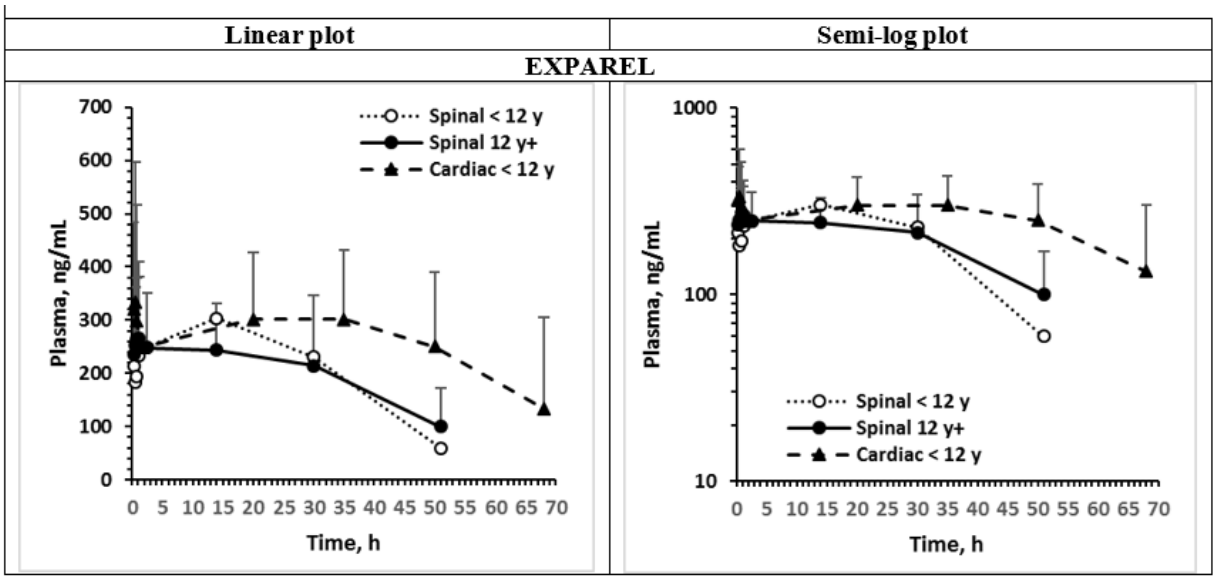
Table 13: Summary of Pharmacokinetics of Bupivacaine after Administration of a Single Dose of EXPAREL to Pediatric Subjects, Group 2 (6 to <12 years) - PK Population

		Group 2, EXPAREL	
	Formulation	**Spine Surgery***	**Cardiac Surgery**
Parameter	Dose mg/kg Age, y	4.00 10.5	4.00 ±0.00 8.7±1.79
$AUC_{0-tlast}$, ng*h/mL	Mean ±SD Geomean (CV%) n	10249.6 - 2	16776.4 ±7935.80 15316.0 (45.0) 21
$AUC_{0-\infty}$, ng*h/mL	Mean ±SD Geomean (CV%) n	11569.5 - 2	26164.0 ±28038.35 19707.4 (75.1) 18
C_{max}, ng/mL	Mean ±SD Geomean (CV%) n	319.5 - 2	447.1 ±243.41 403.4 (46.1) 21
t_{max}, h	Median (range) n	7.4 2	22.7 (0.2-54.5) 21
C_{max1}, ng/mL	Mean ±SD Geomean (CV%) n	249.0 2	372.6 ±271.42 306.9 (69.2) 21
t_{max1}, h	Median (range) n	2.4 2	0.4 (0.2-1.2) 21
C_{max2}, ng/mL	Mean ±SD Geomean (CV%) n	303.0 2	349.0 ±145.13 318.5 (48.2) 21
t_{max2}, h	Median (range) n	15.3 2	30.1 (15.0-69.3) 21
t½, h	Mean ±SD Geomean (CV%) n	13.4 - 2	24.9 ±20.58 20.5 (62.3) 18
CL/F, L/h	Mean ±SD Geomean (CV%) n	14.5 - 2	7.4 ±3.20 6.6 (57.6) 18
Vd/F, L	Mean ±SD Geomean (CV%) n	271.1 - 2	216.1 ±83.77 197.1 (50.7) 18

Abbreviations: $AUC_{0-\infty}$ = the area under the plasma concentration-versus-time curve from the time of administration extrapolated to infinity; $AUC_{0-tlast}$ = the area under the plasma concentration-versus-time curve from start of dosing to the time of the last quantifiable plasma concentration; CL/F = total body clearance divided by bioavailability (F); C_{max} = the maximum observed plasma concentration; C_{max1} = the maximum observed plasma concentration before 4 h after the dose of EXPAREL; C_{max2} = the maximum observed plasma concentration beyond 4 h after the dose of EXPAREL; geomean = geometric mean; %CV = percent coefficient of variance; SD=standard deviation; t_{max} = the time at which C_{max} was observed; t_{max1} = the time at which C_{max1} was observed; t_{max2} = the time at which C_{max2} was observed; t½ = the apparent terminal elimination half-life determined by dividing 0.693 by the terminal elimination rate constant; Vd/F = the volume of distribution calculated as CL/F divided by the terminal phase rate constant; y=years.

* Median shown because only 2 subjects were included in this group.
Source: Tables 14.4-1.2, 14.4-1.3, Table 14.5-1.1

Figure 4: Comparative Bupivacaine Mean Concentration vs. Arithmetic Mean Time Plots in Spine and Cardiac Subjects Given Bupivacaine as EXPAREL (Group 1 and Group 2 [spine] and Group 2 [cardiac]) – PK Population



Note: One subject in the cardiac group was 12 years of age but is included in the cardiac group.
Source: Figure 2.1.1, Figure 2.1.2, Figure 2.1.3, Figure 3.1.1, Figure 3.1.2, Figure 3.1.3

The mean-concentration vs. time data from the Group 2 subjects were plotted along with Group 1 subjects who received EXPAREL in Figure 4. The mean concentration vs. time curve of spine subjects in Group 2 and spine subjects in Group 1 who were treated with EXPAREL was similar (Figure 4). Pharmacokinetic parameters from Group 2 are also shown with the Group 1 data in Table 13. The $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max} were similar to those of the EXPAREL-treated Group 1 subjects. However, the pharmacokinetics of bupivacaine appeared to differ in cardiac subjects from spine subjects given EXPAREL. Because there were only 2 subjects receiving spine surgery in Group 2, only median values were tabulated in Table 13. The $AUC_{0\text{-}\infty}$ in the cardiac subjects was almost double that in spine subjects, and accordingly the cardiac subjects' CL/F values were approximately half as high (Table 13). This suggests that the concentrations were higher and more sustained for cardiac subjects than those of the spine subjects (Figure 4). In addition, the t_{max} in cardiac subjects tended to be in the later phase of t_{max2}, whereas spine subjects tended to have t_{max} occur in the first hour after dosing (Table 13).

Individual subject data for subjects in Group 2 are provided in the following listings:

- Listing 16.2-9.1.1.2: bupivacaine concentrations (raw) from subjects who received EXPAREL (Group 2)
- Listing 16.2-9.5.1.2: PK parameter data for subjects who received EXPAREL (Group 2), Spine surgery
- Listing 16.2-9.5.1.3: PK parameter data for subjects who received EXPAREL (Group 2), Cardiac surgery

Plots of mean ± SD bupivacaine plasma concentrations over time on a linear scale are provided for subjects who received EXPAREL in Figure 2.1.2 (Group 2, spine surgery) and Figure 2.1.3 (Group 2, cardiac surgery).

Plots of mean ± SD plasma concentrations over time on a semi-logarithmic scale are provided for subjects who received EXPAREL in Figure 3.1.2 (Group 2, spine surgery) and Figure 3.1.3 (Group 2, cardiac surgery).

Plots of individual EXPAREL plasma concentrations over time on a linear-linear and log-linear scale are provided for EXPAREL in Figure 4.1.2 (Group 2, spine surgery) and Figure 4.1.3 (Group 2, cardiac surgery).

11.4.1.3. Pharmacokinetics Discussion

The effective target dose of bupivacaine base administered as EXPAREL (4 mg/kg) was over twice the target dose given in the bupivacaine HCl comparator arm. In addition, not all subjects received the target dose of 1.772 mg/kg of bupivacaine base, which must be considered in comparing the bupivacaine exposure to EXPAREL based on the observed C_{max} and calculated AUC values.

In Group 1 subjects, the mean C_{max} for subjects receiving bupivacaine HCl (564 ng/mL, Table 12) was higher than that for subjects receiving EXPAREL (357 ng/mL, Table 12), owing to the lengthy absorption period of EXPAREL. However, EXPAREL had a considerably higher AUC values, which is to be expected given that the administered dosage was over twice that of bupivacaine HCl.

Group 2 subjects were aged 6 to <12 years old given EXPAREL 4 mg/kg only and included 21 cardiac subjects and 2 spine subjects. The exposure of the spine subjects closely matched that of the EXPAREL subjects in Group 1. However, it was apparent that the cardiac subjects had higher exposure than spine subjects, based on C_{max} and AUC. The higher AUC was in line with the reduced CL/F in cardiac vs. spine subjects (Table 13).

The presence of an initial t_{max1} after administration of EXPAREL has been reported previously in adult subjects (Hu 2013). This may perhaps reflect a rapid absorption of that portion of bupivacaine that was not fully or deeply encapsulated within the liposomes. It is clear from the results though that in these pediatric subjects, overall bupivacaine was absorbed much more rapidly when bupivacaine HCl was administered than EXPAREL (Figure 3). EXPAREL as a liposomal formulation was formulated to provide for a sustained exposure of the injected tissues to bupivacaine within the depot site, which has benefits for potentially affording more sustained post-surgical analgesia. This sustained exposure was evident in the concentration vs. time profiles, where a late t_{max2} with sizeable C_{max2} was apparent in each of the mean and individual plasma concentration vs. time profiles. This also resulted in a much longer mean t½ in subjects receiving EXPAREL compared to bupivacaine HCl.

In comparing arithmetic or geometric means of CL/F between the 2 formulations, the differences were relatively modest (within 15%, much less than differences in AUC, Table 12 and Table 13) and there was a considerable overlap in the SD and CV% values of each.

11.4.2. Efficacy Results

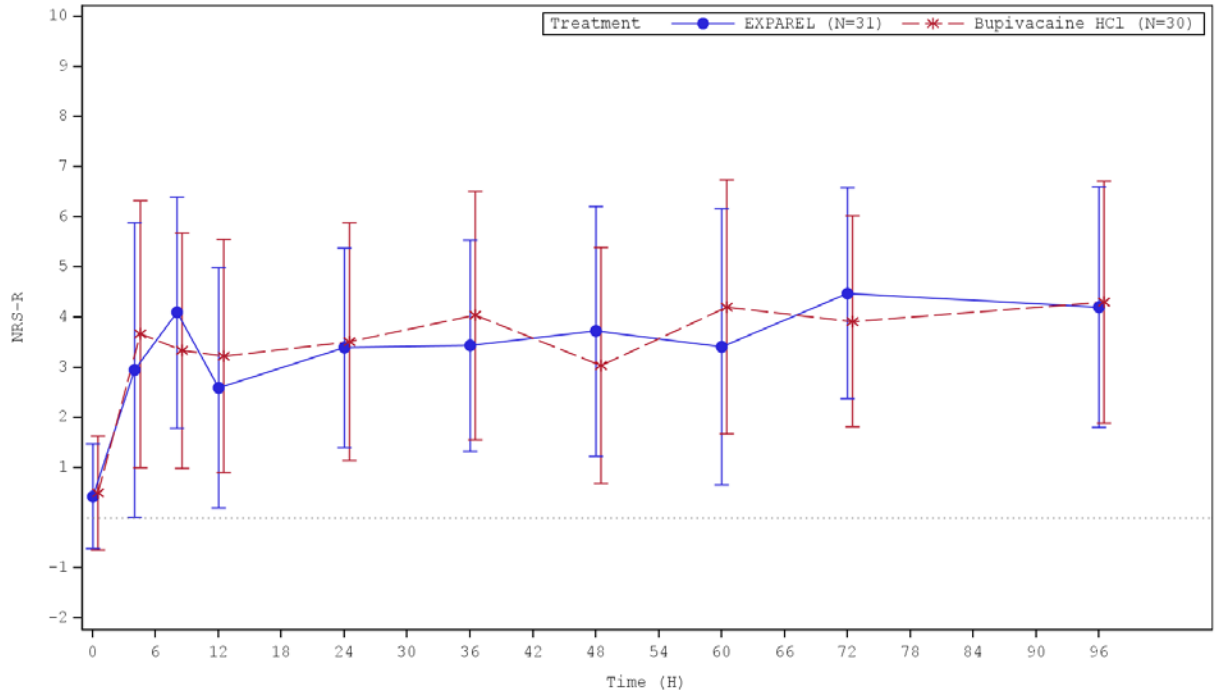
11.4.2.1. Pain Intensity Scores

Subjects assessed their postsurgical pain intensity 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 through 96 hours; and at hospital discharge. Subjects in Group 1 used the 0 to 10 NRS-R, where 0 = no pain and 10 = worst possible pain. Subjects in Group 2 assessed pain using the CAS where green/0 = no pain/no distress and red/10 = agonizing pain/unbearable distress.

Group 1

Pain intensity scores for Group 1 (12 to <17 years) using the NRS are displayed graphically in Figure 5 and are summarized in Table 14.2-1.1.1. Individual subject data for NRS pain scores for Group 1 are listed in Listing 16.2-6.1.1.

Figure 5: Plot of Mean (± SD) Numeric Rating Scale at Rest Pain Intensity Scores over Time, Group 1 (12 to <17 years) – Safety Population



Abbreviations: H=hours; HCl= hydrochloride; NRS-R=Numeric Rating Scale at Rest; SD=standard deviation
Source: Figure 5.1.1

The mean NRS pain scores were generally low in both study arms and were similar between the EXPAREL and bupivacaine HCl groups up through hospital discharge. Mean pain scores were highest (≥4) in the EXPAREL group at 8 hours (4.1), 72 hours (4.5), and 96 hours (4.2). In the bupivacaine subjects, mean pain scores were highest (≥4) at 36 hours (4.0), 60 hours (4.2), and 96 hours (4.3).

Area under the curve (AUC) data for NRS pain scores for Group 1 are summarized in Table 14.

Table 14: Summary of Area under the Curve Numeric Rating Scale Pain Intensity Scores, Group 1 (6 to <12 years) – Safety Population

	EXPAREL 4 mg/kg [N=31]	Bupivacaine HCl 2 mg/kg [N=30]
$AUC_{(4-24)}$		
n	31	30
Mean (SD)	51.0 (37.81)	64.7 (41.90)
Median	39.2	59.4
Minimum, Maximum	2, 140	0, 146
$AUC_{(4-48)}$		
n	31	30
Mean (SD)	139.0 (63.05)	154.6 (83.70)
Median	140.9	161.5
Minimum, Maximum	15, 260	23, 348
$AUC_{(4-72)}$		
n	31	30
Mean (SD)	232.6 (105.31)	241.4 (126.10)
Median	240.3	240.1
Minimum, Maximum	46, 415	36, 516
$AUC_{(4-96)}$		
n	31	30
Mean (SD)	306.7 (137.43)	304.2 (162.43)
Median	323.5	297.2
Minimum, Maximum	91, 568	36, 650
$AUC_{(4\text{-Hospital Discharge})}$		
n	29	27
Mean (SD)	264.9 (124.79)	262.4 (155.45)
Median	267.1	233.1
Minimum, Maximum	15, 426	36, 650

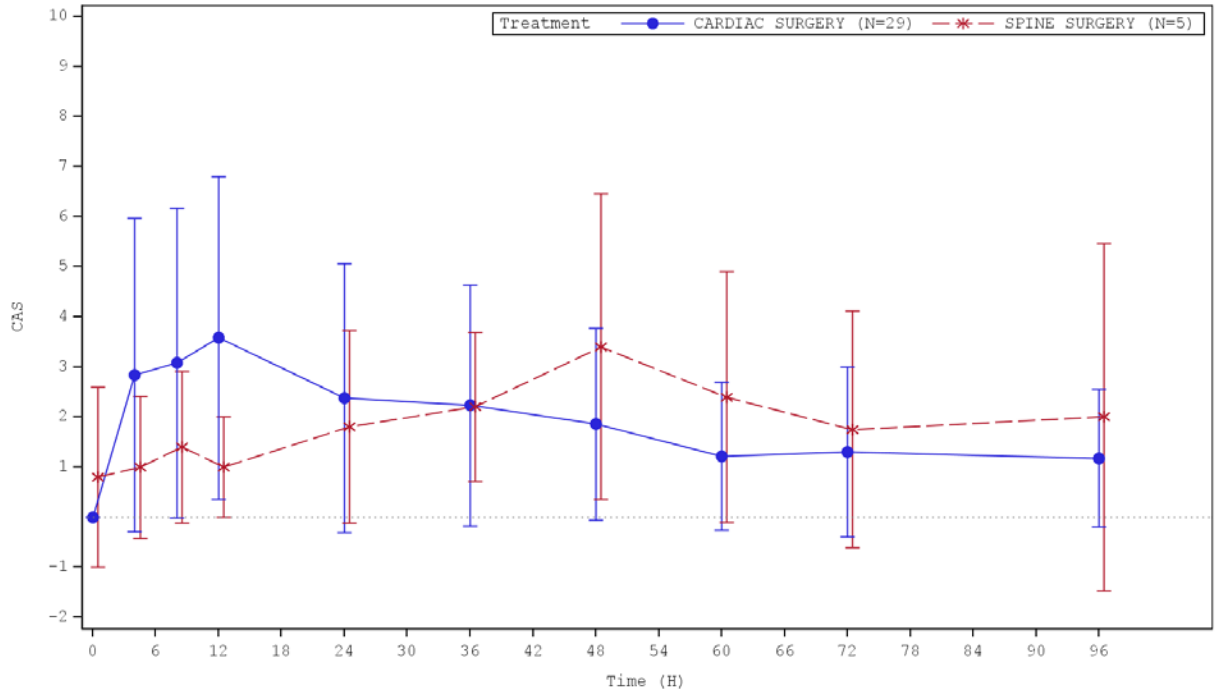
Abbreviations: AUC=area under the curve; HCl=hydrochloride; SD=standard deviation
Source: Table 14.2-2.1.1

The mean AUC for NRS pain intensity scores were somewhat lower in the EXPAREL group compared with the bupivacaine HCl group for the 4 to 24 hour, 4 to 48 hour, and 4 to 72 hour analysis intervals, although there was a lot of variability as shown by the minimums and maximums. The mean scores were generally similar for the 4 to 96 hour and 4 hours to hospital discharge intervals. Subjects received the study site's standard of care for pain control regardless of study drug throughout the study.

Group 2

Pain intensity scores for Group 2 (6 to <12 years) using the CAS are displayed graphically in Figure 6 and are summarized in Table 14.2-1.1.2. Individual subject data for the Group 2 CAS pain scores are listed in Listing 16.2-6.1.2.

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



Abbreviations: CAS=Color Analog Scale; SD=standard deviation
Source: Figure 5.1.2

The mean CAS pain scores were generally low in both surgery types. Of note, subjects received the study site's standard of care for pain control throughout the study.

For Group 2, AUC data for CAS pain scores are summarized in Table 15.

Table 15: Summary of Color Analog Scale Pain Intensity Scores and Area under the Curve, Group 2 (6 to <12 years) – Safety Population

Timepoint	Spine Surgery [N=5]	Cardiac Surgery [N=29]
$AUC_{(4-24)}$		
n	5	26
Mean (SD)	30.2 (21.99)	46.9 (45.04)
Median	33.7	43.6
Minimum, Maximum	0, 57	0, 140
$AUC_{(4-48)}$		
n	5	29
Mean (SD)	92.7 (64.53)	101.0 (76.35)
Median	97.0	83.7
Minimum, Maximum	0, 181	0, 279
$AUC_{(4-72)}$		
n	5	29
Mean (SD)	153.5 (113.87)	134.3 (89.09)
Median	159.5	127.3
Minimum, Maximum	0, 311	18, 338
$AUC_{(4-96)}$		
n	5	29
Mean (SD)	223.5 (184.73)	158.8 (104.26)
Median	203.8	127.3
Minimum, Maximum	0, 467	31, 376
$AUC_{(4\text{-Hospital Discharge})}$		
n	5	28
Mean (SD)	192.3 (141.43)	155.8 (99.07)
Median	203.8	131.6
Minimum, Maximum	0, 339	31, 376

Abbreviations: AUC=area under the curve; SD=standard deviation
Source: Table 14.2-2.1.2

The mean AUCs for CAS pain intensity scores were generally low in both surgery types. The mean AUC for 4 to 96 hours was notably lower in the cardiac surgery group compared with the spine surgery group. Of note, subjects received the study site's standard of care for pain control throughout the study.

11.4.2.2. Total Opioid Consumption

Total opioid consumption data for Group 1 are summarized in Table 16 and Table 14.2-3.1.1. Data for the opioid medication total dose (oral MED mg) and opioid-free status for Group 1 are

listed in Listing 16.2-7.1.1.1. Data for opioid medications for Group 1 are listed by subject in Listing 16.2-7.2.1.1.

Group 1

In Group 1, the geometric means for total opioid consumption were lower in the EXPAREL group compared with the Bupivacaine HCl group for all of the analysis time intervals.

Table 16: Summary of Total Opioid Consumption (MED mg), Group 1 (12 to <17 years) – Safety Population

Time Period [1]	EXPAREL 4 mg/kg [N=31]	Bupivacaine HCl 2 mg/kg [N=30]
0-24 hours		
N	31	29
Geometric Mean	46.06	52.66
%CV	91.665	70.126
Minimum	0.0	0.5
Median	62.50	90.80
Maximum	320.0	290.0
0-48 hours		
N	31	29
Geometric Mean	100.05	113.17
%CV	80.116	64.124
Minimum	15.0	15.5
Median	109.50	132.95
Maximum	546.5	455.5
0-72 hours		
N	31	29
Geometric Mean	136.61	155.17
%CV	66.942	57.927
Minimum	30.0	49.2
Median	125.00	158.30
Maximum	546.5	532.5

Abbreviations: CV=coefficient of variation; HCl=hydrochloride; MED=morphine equivalent dose
1 Time is defined as the time of the end of surgery.
Post-surgery pain medications (including opioids) for Subject 124-0072 are missing.
Source: Table 14.2-3.1.1.

Group 2

Total opioid consumption data for Group 2 are summarized in Table 17 and Table 14.2-3.1.2. Data for rescue medications by total dose (MED mg) and opioid-free status for Group 2 are listed by subject in Listing 16.2-7.1.1.2. Data for rescue medication in Group 2 are listed in Listing 16.2-7.2.1.2.

The total opioid consumption in Group 2 was low in both the spine surgery and cardiac surgery groups through 72 hours postsurgery.

Table 17: Summary of Total Opioid Consumption (MED mg), Group 2 (6 to <12 years) – Safety Population

Time Period [1]	Spine Surgery [N=5]	Cardiac Surgery [N=29]
0-24 hours		
N	5	29
Geometric Mean	1.84	16.63
%CV	120.869	74.389
Minimum	0.0	0.5
Median	3.75	18.00
Maximum	16.8	70.5
0-48 hours		
N	5	29
Geometric Mean	6.48	20.94
%CV	82.613	80.100
Minimum	0.0	0.0
Median	15.00	27.00
Maximum	34.2	91.0
0-72 hours		
N	5	29
Geometric Mean	10.65	23.53
%CV	80.991	88.519
Minimum	0.0	0.0
Median	30.45	27.00
Maximum	64.2	145.0

Abbreviations: CV= coefficient of variation; MED=morphine equivalent dose
1 Time is defined as the time of the end of surgery.
Source: Table 14.2-3.1.2

11.4.2.3. Time to First Postsurgical Opioid Medication

The time to first use of postsurgical opioid medication for Group 1 is summarized in Table 18 and Table 14.2-4.1.1 and is presented graphically in Figure 7.

Table 18: Time to First Postsurgical Opioid Medication Use, Group 1 (12 to <17 years) – Safety Population

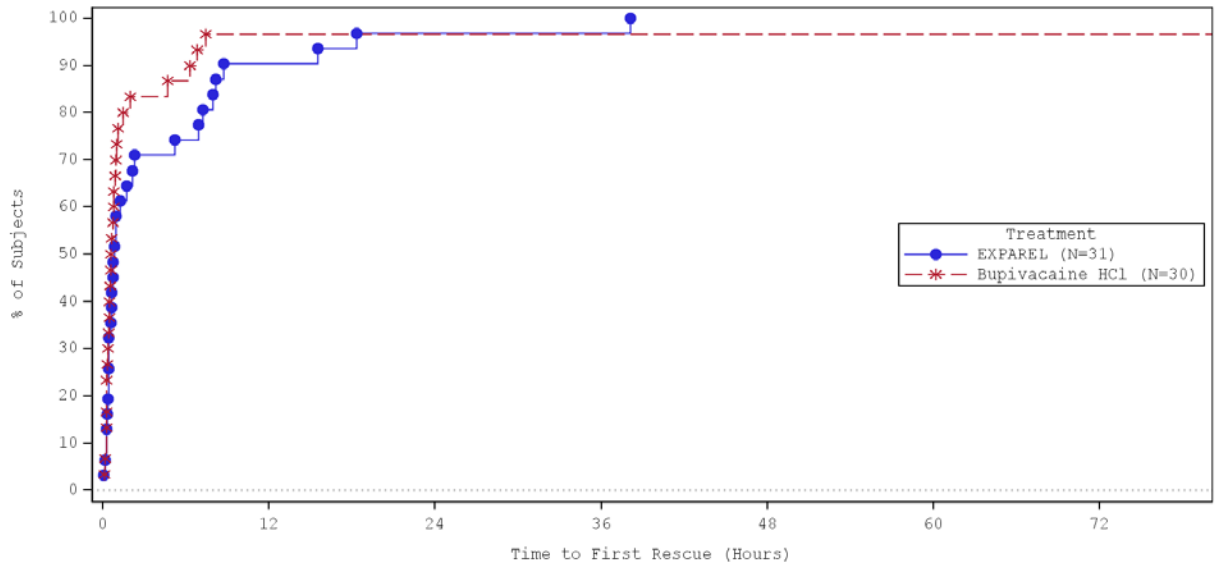
	Statistics	EXPAREL 4 mg/kg [N=31]	Bupivacaine HCl 2 mg/kg [N=30]
Number of subjects			
Rescue medication	n (%)	31 (100.0)	29 (96.7)
Time to first rescue, hours[1]			
Quartiles[2]			
First (25% rescued)	Estimate (95% CI)	0.40 (0.25, 0.63)	0.33 (0.25, 0.48)
Median (50% rescued)	Estimate (95% CI)	0.82 (0.43, 2.12)	0.60 (0.35, 0.88)
Third Quartile (75% rescued)	Estimate (95% CI)	6.90 (0.95, 8.70)	0.98 (0.75, 4.68)
Minimum, Maximum	Observed	0.05, 38.10	0.13, 7.43

Abbreviations: CI=confidence interval; HCl=hydrochloride
Subjects who were not administered an opioid rescue medication by 72 hours were censored at 72 hours after surgery or at the time of last follow-up, whichever was earliest.
1 Time 0 is defined as the time of the end of surgery
2 Estimates from Kaplan-Meier analysis.
Post-surgery pain medications (including opioids) for Subject 124-0072 are missing.
Source: Table 14.2-4.1.1

Most subjects in both the EXPAREL and bupivacaine study arms (100% and 96.7%, respectively) received rescue medication; however, subjects were treated according to the study site's standard of care for pain medication.

The time to first postsurgical rescue medication ranged from 0.05 hours to 38.10 hours for subjects in the EXPAREL group and from 0.13 hours to 7.43 hours in subjects in the bupivacaine HCl group.

Figure 7: Plot of Time to First Rescue Medication Use, Group 1 (12 to <17 years) – Safety Population



Rescue Time (h)	12	24	36	48	72
Treatment with EXPAREL					
Number (%) of Subjects	28 (90.3%)	30 (96.8%)	30 (96.8%)	31 (100%)	31 (100%)
Number of Censored Observations	0	0	0	0	0
Treatment with Bupivacaine HCl					
Number (%) of Subjects	29 (96.7%)	29 (96.7%)	29 (96.7%)	29 (96.7%)	29 (96.7%)
Number of Censored Observations	0	0	0	0	0

Abbreviations: HCl=hydrochloride; h=hours
Subjects who were not administered an opioid rescue medication by 72 hours were censored at 72 hours after surgery or at the time of last follow-up, whichever was earlier.
Post-surgery pain medications (including opioids) for Subject 124-072 are missing.
Source: Figure 1.1.1

Group 2: The time to first use of postsurgical opioid medication for Group 2 are summarized in Table 19 and Table 14.2-4.1.3 and presented graphically in Figure 8.

Most subjects in both surgery types (80.0% for spine surgery; 96.6% for cardiac surgery) received rescue medication.

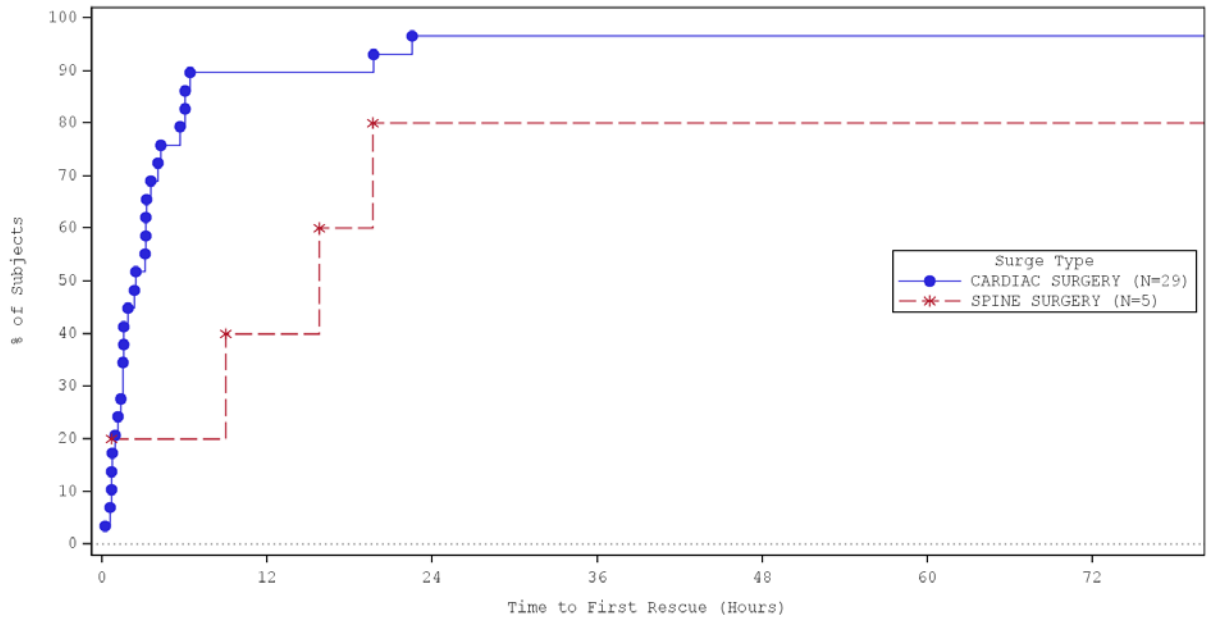
The time to first postsurgical rescue medication ranged from 0.68 hours to more than 72 hours for subjects who underwent spine surgery and ranged from 0.22 hours to more than 72 hours in subjects who underwent cardiac surgery.

Table 19: Time to First Postsurgical Opioid Medication Use, Group 2 (6 to <12 years) – Safety Population

	Statistics	Spine Surgery [N=5]	Cardiac Surgery [N=29]
Number of subjects			
Rescue medication	n (%)	4 (80.0)	28 (96.6)
No rescue medication	n (%)	1 (20.0)	1 (3.4)
Time to first rescue, hours[1]			
Quartiles[2]			
First (25% rescued)	Estimate (95% CI)	9.00 (0.68, 19.68)	1.37 (0.67, 1.58)
Median (50% rescued)	Estimate (95% CI)	15.77 (0.68,)	2.43 (1.53, 3.53)
Third Quartile (75% rescued)	Estimate (95% CI)	19.68 (0.68,)	4.25 (3.17, 6.37)
Minimum, Maximum	Observed	0.68, 72.00*	0.22, 72.00*

Abbreviations: CI=confidence interval
*Indicated censored observation
Subjects who were not administered an opioid rescue medication by 72 hours were censored at 72 hours after surgery or at the time of last follow-up, whichever was earliest.
1 Time 0 is defined as the time of the end of surgery
2 Estimates from Kaplan-Meier analysis.
Source: Table 14.2-4.1.3

Figure 8: Plot of Time to First Rescue Medication Use, Group 2 (6 to <12 years) – Safety Population



Rescue Time (hours)	12	24	36	48	72
Cardiac Surgery					
Number (%) of Subjects	26 (89.7%)	28 (96.6%)	28 (96.6%)	28 (96.6%)	28 (96.6%)
Number of Censored Observations	0	0	0	0	1
Spine Surgery					
Number (%) of Subjects	2 (40.0%)	4 (80.0%)	4 (80.0%)	4 (80.0%)	4 (80.0%)
Number of Censored Observations	0	0	0	0	1

Subjects who were not administered an opioid rescue medication by 72 hours were censored at 72 hours after surgery or at the time of last follow-up, whichever was earlier.
Source: Figure 1.1.2

11.4.2.4. Day 7 Phone Call

Information obtained at the Day 7 phone call (number of pain-related phone calls and office visits, number of Emergency Room visits, and AEs assessed) are listed in Listing 16.2-8.1.1 (Group 1) and Listing 16.2-8.1.2 (Group 2).

11.4.2.5. Day 30 Visit

Data obtained at the Day 30 visit are listed in Listing 16.2-8.1.3 (Group 1) and Listing 16.2-8.1.4 (Group 2).

11.4.3. Statistical/Analytical Issues

11.4.3.1. Adjustments for Covariates

Not applicable.

11.4.3.2. Handling of Dropouts or Missing Data

It was expected that all necessary information on study drug exposure, surgery, and postsurgical rescue medication (dates and times) would be complete. Any such information that was missing and could not be obtained through query resolution may have been imputed, on a case-by-case basis, in a conservative manner that minimized bias.

For postsurgical opioid medication, if a subject discontinued the study early before the end of the analysis time interval (eg, 72 hours after the end of surgery), the subject's total opioid rescue pain medication usage through the time interval would have been a projected amount (see Appendix 16.1.9, Section 6.1.1.2).

For AEs or concomitant medications with missing or partially missing start/stop date/time, imputation was applied following the rules specified in the SAP (See Appendix 16.1.9, Section 6.1.1.3).

For AE severity, if the severity was not reported, the event was classified as 'severe'. If relationship to study drug was not reported for an AE, the event was assigned the relationship 'definite'. If the AE began before study drug administration, the relationship 'unrelated" was presumed.

For time of events, when only the hour was reported, the minutes were set to zero.

11.4.3.3. Multicenter Studies

This study was conducted at 15 sites in the US. No treatment-by-center analyses were performed.

11.4.3.4. Multiple Comparisons/Multiplicity

No multiplicity adjustments were made.

11.4.3.5. Use of an "Efficacy Subset" of Subjects

Not applicable.

11.4.3.6. Active-Control Studies Intended to Show Equivalence

Not applicable.

11.4.3.7. Examination of Subgroups

Not applicable.

11.4.4. Tabulation of Individual Response Data

Tabulations of data by subject were not prepared for this study. Listings of individual subject data by assessment/variable are provided in Appendix 16.2.

11.4.5. Drug Dose, Drug Concentration, and Relationship to Response

Not applicable.

11.4.6. Drug-Drug and Drug-Disease Interactions

Not applicable.

11.4.7. By-Subject Displays

Tabulations of data by subject were not prepared for this study.

11.4.8. Pharmacokinetic and Efficacy Conclusions

11.4.8.1. Pharmacokinetic Conclusions

Bupivacaine pharmacokinetics of single 4 mg/kg dose of EXPAREL were studied in pediatric subjects of 6 to less than 17 years undergoing spine or cardiac surgeries. For comparison, the pharmacokinetics of single 2 mg/kg doses of bupivacaine HCl were administered to pediatric subjects of 12 to less than 17 years undergoing spine surgeries. The results (geometric mean comparisons for Group 1 spine and Group 2 cardiac, and median for Group 2 spine) indicated that:

- Spine subjects in Group 1 who received bupivacaine HCl had a higher C_{max} (488.2 ng/mL) than matching subjects given an average 1.45-fold higher bupivacaine dose as EXPAREL (336.8 ng/mL).
- In Group 1, bupivacaine overall median t_{max} after Bupivacaine HCl and EXPAREL were short (<1.5 h); however, EXPAREL was associated with a later t_{max2} (median 18.0 h, range 11.1-26.1 h after the dose) and hence more sustained bupivacaine concentrations than seen with the Bupivacaine HCl.
- In Group 1, the AUC of bupivacaine was higher after administration of EXPAREL than when bupivacaine HCl was administered to spine subjects (8296.9 vs. 4791.4 ng x h/mL for $AUC_{0\text{-}tlast}$; 12256.8 vs. 5064.2 ng x h/mL for $AUC_{0\text{-}\infty}$), consistent with a higher bupivacaine dose when given as EXPAREL.
- The AUC of bupivacaine after administration of EXPAREL was higher in cardiac subjects from Group 2 compared with spine subjects from Group 1 (15316.0 vs. 8296.9 ng x h/mL for $AUC_{0\text{-}tlast}$; 19707.4 vs. 12256.8 ng x h/mL for $AUC_{0\text{-}\infty}$).
- The bupivacaine C_{max} was higher in the cardiac subjects (403.4 ng/mL) than in the spine subjects (336.8 ng/mL in Group 1 and 319.5 ng/mL in Group 2 age-matched subjects).
- The time to C_{max} was delayed for the cardiac subjects comparing with spine subjects (median t_{max} over 22.7 vs. < 8 h).
- The CL/F of bupivacaine in Group 2 cardiac subjects given EXPAREL (6.6 L/h) was lower than that after EXPAREL or Bupivacaine HCl when given to spine subjects (14.5 to 18.9 L/h).
- The geometric mean estimation of Vd/F yielded a value of 488.4 L for older spine-surgery subjects who received EXPAREL, which was numerically higher than those for other groups (ranging from 197.1 to 271.1 L).

11.4.8.2. Efficacy Conclusions

This study was not powered to evaluate efficacy; efficacy was examined for descriptive purposes only. Efficacy results are presented below.

Pain Scores

- Mean NRS pain intensity scores for Group 1 (12 to <17 years) are displayed below:

Mean (SD) NRS Pain Intensity Scores, Group 1 (12 to <17 years)						
Timepoint	**EXPAREL**	**Bupivacaine HCl**		**Timepoint**	**EXPAREL**	**Bupivacaine HCl**
Baseline	0.4 (1.04)	0.5 (1.14)		48 hours	3.7 (2.49)	3.0 (2.35)
4 hours	2.9 (2.93)	3.7 (2.66)		60 hours	3.4 (2.75)	4.2 (2.54)
8 hours	4.1 (2.30)	3.3 (2.35)		72 hours	4.5 (2.10)	3.9 (2.10)
12 hours	2.6 (2.40)	3.2 (2.33)		96 hours	4.2 (2.40)	4.3 (2.41)
24 hours	3.4 (1.99)	3.5 (2.37)		Discharge	3.7 (2.32)	3.3 (2.18)
36 hours	3.4 (2.10)	4.0 (2.47)				

- Mean AUC for NRS pain scores for Group 1 (12 to <17 years) are displayed below:

Mean (SD) AUC for NRS Intensity Scores, Group 1 (12 to <17 years)		
Interval	**EXPAREL**	**Bupivacaine HCl**
$AUC_{(4\text{-}24)}$:	51.0 (37.81)	64.7 (41.90)
$AUC_{(4\text{-}48)}$:	139.0 (63.05)	154.6 (83.70)
$AUC_{(4\text{-}72)}$:	232.6 (105.31)	241.4 (126.10)
$AUC_{(4\text{-}96)}$:	306.7 (137.43)	304.2 (162.43)
$AUC_{(4\text{-hospital discharge})}$:	264.9 (124.79)	262.4 (155.45)

- Mean CAS pain scores for Group 2 (6 to <12 years) are displayed below:

Mean (SD) CAS Pain Intensity Scores, Group 2 (6 to <12 years)						
Timepoint	**Spine**	**Cardiac**		**Timepoint**	**Spine**	**Cardiac**
Baseline	0.8 (1.79)	0.0 (0.00)		48 hours	3.4 (3.05)	1.9 (1.92)
4 hours	1.0 (1.41)	2.8 (3.13)		60 hours	2.4 (2.51)	1.2 (1.48)
8 hours	1.4 (1.52)	3.1 (3.09)		72 hours	1.8 (2.36)	1.3 (1.69)
12 hours	1.0 (1.00)	3.6 (3.22)		96 hours	2.0 (3.46)	1.2 (1.37)
24 hours	1.8 (1.92)	2.4 (2.68)		Discharge	3.4 (3.58)	0.8 (1.37)
36 hours	2.2 (1.48)	2.2 (2.41)				

- Mean AUC for CAS pain scores for Group 2 (6 to <12 years) are displayed below:

Mean (SD) AUC for CAS Intensity Scores, Group 2 (6 to <12 years)		
Interval	**Spine Surgery**	**Cardiac Surgery**
$AUC_{(4\text{-}24)}$:	30.2 (21.99)	46.9 (45.04)
$AUC_{(4\text{-}48)}$:	92.7 (64.53)	101.0 (76.35)
$AUC_{(4\text{-}72)}$:	153.5 (113.87)	134.3 (89.09)
$AUC_{(4\text{-}96)}$:	223.5 (184.73)	158.8 (104.26)
$AUC_{(4\text{-hospital discharge})}$:	192.3 (141.43)	155.8 (99.07)

Total Opioid Consumption

- Total opioid consumption data for Group 1(12 to <17 years) are displayed below:

Geometric Mean (%CV) for Total Opioid Consumption (MED mg), Group 1 (12 to <17 years)		
Interval	**EXPAREL**	**Bupivacaine HCl**
0 – 24 hours	46.06 (91.665)	52.66 (70.126)
0 – 48 hours	100.05 (80.116)	113.17 (64.124)
0 – 72 hours	136.61 (66.942)	155.17 (57.9)

- Total opioid consumption data for Group 2 (6 to <12 years) are displayed below:

Geometric Mean (%CV) for Total Opioid Consumption (MED mg), Group 2 (6 to <12 years)		
Interval	**Spine Surgery**	**Cardiac Surgery**
0 – 24 hours	1.84 (120.869)	16.63 (74.389)
0 – 48 hours	6.48 (82.613)	20.94 (80.100)
0 – 72 hours	10.65 (80.991)	23.53 (88.519)

Time to Rescue Medication

- For Group 1 (12 to <17 years), median time to first rescue medication was 0.82 hours and 0.60 hours in the EXPAREL and bupivacaine HCl groups, respectively.
- For Group 2 (6 to <12 years), median time to first rescue medication was 15.77 hours and 2.43 hours in the spine surgery and cardiac surgery groups, respectively

12. SAFETY EVALUATION

12.1. Extent of Exposure

Subjects in Part 1, Group 1 and Part 2, Group 1 were to receive a single dose of either EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) or bupivacaine HCl 2 mg/kg (not to exceed a maximum total bupivacaine HCl dose of 175 mg) via local infiltration.

Subjects in Group 2 (Part 1 or Part 2) were to receive a single dose of EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration.

Study drug administration data are listed in Listing 16.2-21.1.1 (Group 1) and Listing 16.2-21.1.2 (Group 2).

The mean (± SD) weight-normalized dose in bupivacaine free base equivalents was 3.97 (0.14) mg/kg in the Group 1 EXPAREL subjects; 1.89 (0.46) mg/kg in the Group 1 bupivacaine HCl; 4.00 mg/kg in the Group 2 spine surgery subjects, and 4.00 (0.00) mg/kg in the Group 2 cardiac subjects (Table 14.5-1.1).

One subject received a dose of bupivacaine HCl that exceeded the dose specified in the protocol. Subject 116-0030, a 14-year-old female (Part 1) received 192 mg of bupivacaine HCl, which, based on her body weight (8 kg), was a dose of 4 mg/kg of bupivacaine HCl (equivalent to 3.544 mg/kg in bupivacaine free base). The subject had one TEAE (mild pleural effusion) on Days 3-5 that was considered unrelated to treatment. The subject appeared to have suffered no ill effects from the overdosage.

12.2. Adverse Events

The safety population (ie, all subjects who received study drug) was used for assessment of all AE data. All incidence tables of AE data are presented by the MedDRA (version 21.1) system organ class and PT.

12.2.1. Brief Summary of Adverse Events

An overview of AEs in the Safety population is presented in Table 20, Table 14.3-4.1.1 (Group 1), Table 14.3-4.1.2 (Group 2), Table 14.3-4.1.3 (both groups, spine surgery), and Table 14.3-4.1.4 (EXPAREL Group 1 and Group 2, spine subjects pooled).

Adverse events are listed by subject in Listing 16.2-17.1.1.1 (Group 1) and Listing 16.2-17.1.1.2 (Group 2). Unique AE terms and associated coded terms are listed in Listing 16.2-26.

Table 20: Overview of Treatment-Emergent Adverse Events – Safety Population

	Group 1 (12 to <17 years)		Group 2 (6 to <12 years)	
	EXPAREL 4 mg/kg [N=31] n (%)	Bupivacaine HCl 2 mg/kg [N=30] n (%)	Spine surgery [N=5] n (%)	Cardiac surgery [N=29] n (%)
Subjects with Any TEAE	19 (61.3)	22 (73.3)	5 (100.0)	9 (31.0)
Maximum Severity of Mild	12 (38.7)	14 (46.7)	3 (60.00)	6 (20.7)
Maximum Severity of Moderate	7 (22.6)	7 (23.3)	2 (40.0)	3 (10.3)
Maximum Severity of Severe	0	1 (3.3)	0	0
At least 1 Related	2 (6.5)	5 (16.7)	3 (60.0)	0
At least 1 Serious	0	0	0	2 (6.9)
At least 1 TEAE of Special Interest	2 (6.5)	3 (10.0)	0	0
Subjects Discontinued due to TEAE	0	0	0	0
Died on Study	0	0	0	0

Abbreviations: AE=adverse event; CRF=case report form; HCl=hydrochloride; TEAE= treatment-emergent adverse event.
Related TEAEs are those AEs indicated as 'possible', 'probable', or 'definite' related by the investigator on the AE CRF.
Source: Table 14.3-4.1.1 (Group 1), Table 14.3-14.1.2 (Group 2), and Table 14.3-4.1.3 (both groups)

Group 1

In Group 1, 19 subjects (61.3%) in the EXPAREL group and 22 subjects (73.3%) in the bupivacaine HCl group experienced a TEAE during the study. Most TEAEs in both groups were mild or moderate in severity. Two (2) subjects (6.5%) in the EXPAREL group and 3 subjects (10.0%) in the bupivacaine HCl group experienced a TEAE considered related to study treatment. There were no SAEs and no subject discontinued the study due to a TEAE.

Group 2

In Group 2, all 5 of the subjects (100%) in the spine surgery group and 9 subjects (31%) in the cardiac surgery group experienced a TEAE and all were considered mild or moderate in severity. Three subjects (60.0%) in the spine surgery group and none in the cardiac surgery had TEAEs considered related to study treatment. Two subjects (6.9%) in the cardiac surgery group had SAEs. There were no AESIs and no discontinuations due to TEAE in Group 2.

Spine surgery (pooled)

Table 14.3-4.1.4 presents an overview of TEAEs for EXPAREL subjects (pooled Group 1 and Group 2, spine surgery) and bupivacaine subjects. In this analysis, 24 of 36 subjects (66.7%) and 22 of 30 subjects (73.3%) in the EXPAREL and bupivacaine HCl groups, respectively, experienced a TEAE. Five of 36 subjects (13.9%) who received EXPAREL and 5 of 30 subjects (16.7%) who received bupivacaine HCl had a treatment-related TEAE. One subject (3.3%) in the bupivacaine HCl group had a severe TEAE; all others were mild or moderate in severity. Adverse events of special interest occurred in 2 subjects (5.6%) and 3 subjects (10.0%) in the EXPAREL and bupivacaine HCl groups, respectively.

12.2.2. Display of Adverse Events

12.2.2.1. All TEAEs

Group 1

A summary of TEAEs experienced by subjects in Group 1 is presented in Table 21.

For Group 1, 19 subjects (61.3%) in the EXPAREL group and 22 subjects (73.3%) in the bupivacaine HCl group experienced a TEAE, as shown in Table 21. The SOC with the highest overall incidence of TEAEs was Gastrointestinal Disorders.

The most common TEAEs (≥10% of subjects) in the EXPAREL group were nausea (32.3%), vomiting (29.0%), constipation (25.8%), vision blurred (12.9%), and anemia postoperative (12.9%). In the bupivacaine HCl group, the most common TEAEs were constipation (30.0%), muscle twitching (26.7%), hypotension (23.3%), nausea (20.0%), vomiting (16.7%), tachycardia (13.3%), hypoesthesia oral (10.0%), muscular weakness (10.0%), and vision blurred (10.0%).

Table 21: Summary of Treatment-Emergent Adverse Events Reported by Subjects in Group 1 (12 to <17 years) – Safety Population

System Organ Class Preferred Term	EXPAREL 4 mg/kg [N=31] n (%)	Bupivacaine HCl 2 mg/kg [N=30] n (%)
Subjects with at least one TEAE	**19 (61.3)**	**22 (73.3)**
Gastrointestinal disorders	**14 (45.2)**	**15 (50.0)**
Constipation	8 (25.8)	9 (30.0)
Nausea	10 (32.3)	6 (20.0)
Vomiting	9 (29.0)	5 (16.7)
Hypoesthesia oral	1 (3.2)	3 (10.0)
Diarrhea	2 (6.5)	0
Dyspepsia	1 (3.2)	0
Musculoskeletal and connective tissue disorders	**6 (19.4)**	**11 (36.7)**
Muscle twitching	2 (6.5)	8 (26.7)
Muscle spasms	3 (9.7)	0
Muscular weakness	0	3 (10.0)
Musculoskeletal pain	1 (3.2)	0
Pain in extremity	0	1 (3.3)
Eye disorders	**7 (22.6)**	**6 (20.0)**
Vision blurred	4 (12.9)	3 (10.0)
Visual impairment	2 (6.5)	2 (6.7)
Diplopia	1 (3.2)	0
Lacrimation increased	0	1 (3.3)
Nervous system disorders	3 (9.7)	8 (26.7)
Dizziness	2 (6.5)	2 (6.7)
Dysgeusia	1 (3.2)	1 (3.3)
Headache	0	2 (6.7)
Hypoesthesia	0	2 (6.7)
Paranesthesia	0	2 (6.7)
Syncope	1 (3.2)	0

System Organ Class Preferred Term	EXPAREL 4 mg/kg [N=31] n (%)	Bupivacaine HCl 2 mg/kg [N=30] n (%)
Vascular disorders	2 (6.5)	8 (26.7)
Hypotension	2 (6.5)	7 (23.3)
Hot flush	0	1 (3.3)
Systolic hypertension	0	1 (3.3)
Injury, poisoning and procedural complications	6 (19.4)	1 (3.3)
Anemia postoperative	4 (12.9)	0
Incision site hemorrhage	1 (3.2)	0
Joint dislocation	1 (3.2)	0
Procedural hemorrhage	0	1 (3.3)
Cardiac disorders	2 (6.5)	4 (13.3)
Tachycardia	1 (3.2)	4 (13.3)
Bradycardia	1 (3.2)	0
Respiratory, thoracic and mediastinal disorders	2 (6.5)	2 (6.7)
Bradypnea	0	1 (3.3)
Hypopnea	1 (3.2)	0
Hypoxia	1 (3.2)	0
Pleural effusion	0	1 (3.3)
Tachypnoea	0	1 (3.3)
Skin and subcutaneous tissue disorders	2 (6.5)	2 (6.7)
Pruritus	1 (3.2)	2 (6.7)
Pruritus generalized	1 (3.2)	0
Ear and labyrinth disorders	2 (6.5)	1 (3.3)
Hypoacusis	2 (6.5)	1 (3.3)
General disorders and administration site conditions	2 (6.5)	1 (3.3)
Chest pain	1 (3.2)	0
Generalized edema	0	1 (3.3)
Pyrexia	1 (3.2)	0
Investigations	2 (6.5)	0
Heart rate increased	1 (3.2)	0
Urine output decreased	1 (3.2)	0
Renal and urinary disorders	2 (6.5)	0
Incontinence	2 (6.5)	0
Immune system disorders	0	1 (3.3)
Hypersensitivity	0	1 (3.3)
Infections and infestations	1 (3.2)	0
Ear infection	1 (3.2)	0
Psychiatric disorders	0	1 (3.3)
Anxiety	0	1 (3.3)

Abbreviations: TEAE=treatment-emergent adverse event
Adverse events coded using the Medical Dictionary for Regulatory Activities (MedDRA 21.1).
Sorted by descending total incidence by system organ class and preferred term within system organ class.
Subjects experiencing the same TEAE more than once are counted only once at each summary level.
Source: Table 14.3-4.2.1

Group 2

A summary of TEAEs experienced by subjects in Group 2 is presented in Table 22.

For Group 2, 5 subjects (100%) in the spine surgery group and 9 subjects (31.0%) in the cardiac surgery group experienced a TEAE. The SOC with the highest overall incidence of TEAEs was Gastrointestinal Disorders.

The most common TEAEs (≥40%, or at least 2 subjects) in the spine surgery group were hypoesthesia oral (3 subjects; 60.0%), vision blurred (60.0%), hypotension (2 subjects; 40.0%), and pruritus (40.0%). The most common TEAEs (≥10%, or at least 3 subjects) in the cardiac surgery group were constipation (4 subjects; 13.8%) and vomiting (13.8%).

Table 22: Summary of Treatment-Emergent Adverse Events Reported by Subjects in Group 2 (6 to <12 years) –Safety Population

System Organ Class Preferred Term	Spine Surgery [N=5] n (%)	Cardiac Surgery [N=29] n (%)
Subjects with at least one TEAE	5 (100.0)	9 (31.0)
Gastrointestinal disorders	4 (80.0)	7 (24.1)
Constipation	1 (20.0)	4 (13.8)
Vomiting	1 (20.0)	4 (13.8)
Hypoesthesia oral	3 (60.0)	0
Nausea	1 (20.0)	2 (6.9)
Diarrhea	1 (20.0)	0
Eye disorders	3 (60.0)	1 (3.4)
Vision blurred	3 (60.0)	1 (3.4)
Metabolism and nutrition disorders	0	3 (10.3)
Acidosis	0	1 (3.4)
Hyperglycemia	0	1 (3.4)
Hypomagnesaemia	0	1 (3.4)
Metabolic acidosis	0	1 (3.4)
Musculoskeletal and connective tissue disorders	2 (40.0)	1 (3.4)
Muscle twitching	1 (20.0)	1 (3.4)
Muscle spasms	1 (20.0)	0
Vascular disorders	2 (40.0)	1 (3.4)
Hypotension	2 (40.0)	0
Hypertension	0	1 (3.4)
Cardiac disorders	1 (20.0)	1 (3.4)
Bradycardia	1 (20.0)	0
Sinus tachycardia	0	1 (3.4)
Injury, poisoning and procedural complications	2 (40.0)	0
Anemia postoperative	1 (20.0)	0
Delayed recovery from anesthesia	1 (20.0)	0
Seroma	1 (20.0)	0

System Organ Class Preferred Term	Spine Surgery [N=5] n (%)	Cardiac Surgery [N=29] n (%)
Respiratory, thoracic and mediastinal disorders	1 (20.0)	1 (3.4)
Dyspnea	0	1 (3.4)
Tachypnoea	1 (20.0)	0
Skin and subcutaneous tissue disorders	2 (40.0)	0
Pruritus	2 (40.0)	0
General disorders and administration site conditions	0	1 (3.4)
Face edema	0	1 (3.4)
Infections and infestations	0	1 (3.4)
Wound infection fungal	0	1 (3.4)

Abbreviations: TEAE=treatment-emergent adverse event
Adverse events coded using the Medical Dictionary for Regulatory Activities (MedDRA 21.1).
Sorted by descending total incidence by system organ class and preferred term within system organ class.
Subjects experiencing the same TEAE more than once are counted only once at each summary level.
Source: Table 14.3-4.2.2

Spine surgery (pooled)

A summary of TEAEs experienced by EXPAREL subjects (pooled Group 1 and Group 2, spine surgery) and bupivacaine subjects is presented in Table 14.3-4.2.3.

In this analysis, 24 of 36 subjects (66.7%) in the EXPAREL group and 22 of 30 subjects (73.3%) in the bupivacaine HCl group experienced a TEAE. The Gastrointestinal Disorders SOC had the highest overall incidence of TEAEs (50.0% of subjects in each analysis group).

The most common TEAEs (≥10% of subjects) in the EXPAREL group were nausea (30.6%), vomiting (27.8%), constipation (25.0%), vision blurred (19.4%), and anemia postoperative (13.9%), hypoesthesia oral (11.1%), muscle spasms (11.1%), hypotension (11.1%).

In the bupivacaine HCl group, the most common TEAEs (≥10% of subjects) were constipation (30.0%), muscle twitching (26.7%), hypotension (23.3%), nausea (20.0%), vomiting (16.7%), tachycardia (13.3%), hypoesthesia oral (10.0%), muscular weakness (10.0%), and vision blurred (10.0%).

12.2.2.2. Treatment-related TEAEs

Treatment-emergent AEs are summarized by relationship to study treatment in Table 23 and Table 14.3-4.4.1 (Group 1), Table 24 and Table 14.3-4.4.2 (Group 2), and Table 14.3-4.4.3 (Both groups, spine surgery).

Treatment-related TEAEs are listed in Listing 16.2-17.2.2.1.1 (Group 1) and Listing 16.2-17.2.2.1.2 (Group 2).

Group 1

In Group 1, 2 subjects (6.5%) in the EXPAREL group and 5 subjects (16.7%) in the bupivacaine HCl group experienced TEAEs that were considered possibly related to study drug (Table 23). Nausea and constipation were the most common treatment-related TEAEs.

Table 23: Summary of Treatment-Related Treatment-Emergent Adverse Events, Group 1 (12 to <17 years) – Safety Population

System Organ Class Preferred Term	EXPAREL 4 mg/kg [N=31] n (%)	Bupivacaine HCl 2 mg/kg [N=30] n (%)
Subjects with any treatment-related TEAE	**2 (6.5)**	**5 (16.7)**
Gastrointestinal disorders	**2 (6.5)**	**5 (16.7)**
Constipation	1 (3.2)	3 (10.0)
Nausea	2 (6.5)	3 (10.0)
Vomiting	1 (3.2)	0
Hypoesthesia oral	0	1 (3.3)
Eye disorders	1 (3.2)	0
Vision blurred	1 (3.2)	0
Nervous system disorders	0	1 (3.3)
Paresthesia	0	1 (3.3)

Abbreviations: AE=adverse event; CRF=case report form; HCl=hydrochloride; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event
Adverse events coded using the MedDRA 21.1.
Sorted by descending total incidence by system organ class and preferred term within system organ class.
Subjects experiencing the same TEAE more than once are counted only once at each summary level.
Related TEAEs are those AEs indicated as 'possible', 'probable' or 'definite' related by the investigator on the AE CRF.
Source: Table 14.3-4.4.1

Group 2

In Group 2, 3 subjects (60.0%) in the spine surgery group and no subjects in the cardiac surgery group experienced TEAEs that were considered possibly related to study drug (Table 24). Hypoesthesia oral and vision blurred were the most common treatment-related TEAEs.

Table 24: Summary of Treatment-Related Treatment-Emergent Adverse Events, Group 2 (6 to <12 years) – Safety Population

System Organ Class Preferred Term	Spine Surgery [N=5] n (%)	Cardiac Surgery [N=29] n (%)
Subjects with any treatment-related TEAE	**3 (60.0)**	**0**
Gastrointestinal disorders	**2 (40.0)**	**0**
Vomiting	1 (20.0)	0
Hypoesthesia oral	2 (40.0)	0
Nausea	1 (20.0)	0
Eye disorders	**2 (40.0)**	**0**
Vision blurred	2 (40.0)	0
Injury, poisoning, and procedural complications	**1 (20.0)**	**0**
Delayed recovery from anesthesia	1 (20.0)	0

Abbreviations: AE=adverse event; CRF=case report form; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event
Adverse events coded using the MedDRA 21.1.
Sorted by descending total incidence by system organ class and preferred term within system organ class.
Subjects experiencing the same TEAE more than once are counted only once at each summary level.
Related TEAEs are those AEs indicated as 'possible', 'probable' or 'definite' related by the investigator on the AE CRF.
Source: Table 14.3-4.4.2

Spine surgery (pooled)

Table 25 presents an overview of TEAEs by relationship to study treatment for EXPAREL subjects (pooled Group 1 and Group 2, spine surgery) and bupivacaine subjects. In this analysis, 5 subjects (13.9%) in the EXPAREL group and 5 subjects (16.7%) in the bupivacaine HCl group experienced a TEAE considered by the investigator to be possibly related to study treatment. Nausea and constipation were the most common treatment-related TEAEs.

Table 25: Summary of Treatment-Related Treatment-Emergent Adverse Events, Spine Surgery (Pooled) (6 to <17 years) – Safety Population

System Organ Class Preferred Term	EXPAREL 4 mg/kg [N=36] n (%)	Bupivacaine HCl 2 mg/kg [N=30] n (%)
Subjects with any treatment-related TEAE	**5 (13.9)**	**5 (16.7)**
Gastrointestinal disorders	**4 (11.1)**	**5 (16.7)**
Constipation	1 (2.8)	3 (10.0)
Nausea	3 (8.3)	3 (10.0)
Vomiting	2 (5.6)	0
Hypoesthesia oral	2 (5.6)	1 (3.3)
Eye disorders	3 (8.3)	0
Vision blurred	3 (8.3)	0
Nervous system disorders	0	1 (3.3)
Paresthesia	0	1 (3.3)
Injury, poisoning, and procedural disorders	1 (2.8)	0
Delayed recovery from anesthesia	1 (2.8)	0

Abbreviations: AE=adverse event; CRF=case report form; HCl=hydrochloride; MedDRA= Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event
Adverse events coded using the MedDRA 21.1.
Sorted by descending total incidence by system organ class and preferred term within system organ class.
Subjects experiencing the same TEAE more than once are counted only once at each summary level.
Related TEAEs are those AEs indicated as 'possible', 'probable' or 'definite' related by the investigator on the AE CRF.
Source: Table 14.3-4.4.3

12.2.2.3. Severity of TEAEs

Group 1

Most TEAEs in Group 1 were either mild or moderate in severity (Table 14.3-4.3.1). Only 1 severe TEAE was experienced; severe constipation in 1 subject (3.3%) in the bupivacaine HCl group (Table 26).

Table 26: Summary of Severe Treatment-Emergent Adverse Events, Group 1 (12 to <17 years) – Safety Population

System Organ Class Preferred Term	EXPAREL 4 mg/kg [N=31] n (%)	Bupivacaine HCl 2 mg/kg [N=30] n (%)
Subjects with any Severe TEAE	**0**	**1 (3.3)**
Gastrointestinal disorders	**0**	**1 (3.3)**
Constipation	0	1 (3.3)

Abbreviations: HCl=hydrochloride; TEAE=treatment-emergent adverse event
Source: Table 14.3-4.3.1

Group 2

For Group 2, all of the TEAEs were mild or moderate in severity. No subjects in Group 2 had a severe TEAE (Table 14.3-4.3.2).

Spine surgery (pooled)

Table 14.3-4.3.3 presents an overview of TEAEs for EXPAREL subjects (pooled Group 1 and Group 2, spine surgery) and bupivacaine subjects. In this analysis, most TEAEs were either mild or moderate in severity. One subject (3.3%) in the bupivacaine HCl group had a severe TEAE (constipation).

12.2.3. Analysis of Adverse Events

Most of the TEAEs that occurred during the study were mild or moderate in severity and considered not related to study drug. The percentage of subjects with a TEAE was slightly lower in the EXPAREL group compared with the bupivacaine HCl group, but both treatments were generally well tolerated.

12.2.4. Listing of Adverse Events by Subject

Listings of all AEs are provided in Listing 16.2-17.1.1.1 (Group 1) and Listing 16.2-17.1.1.2 (Group 2). Listings of all TEAEs are provided in Listing 16.2-17.2.1.1.1 (Group 1) and Listing 16.2-17.2.1.1.2 (Group 2). Listings of treatment-related TEAEs are provided in Listing 16.2-17.2.2.1.1 (Group 1) and Listing 16.2-17.2.2.1.2 (Group 2). A listing of unique AE terms and associated coded terms is provided in Listing 16.2-26.

12.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1. Listings of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.1. Deaths

There were no deaths in the study (Table 14.1-1.1.1 and Table 14.1-1.1.2).

12.3.1.2. Serious Adverse Events

Group 1

No SAEs occurred in Group 1 (Table 14.3-5.1.1); nor did any treatment-emergent SAEs or treatment-emergent study drug-related SAEs. Thus, Listing 16.2-17.3.1.1 (SAEs), Listing 16.2-17.4.1.1.1 (treatment-emergent SAEs), and Listing 16.2-17.4.2.1.1 (treatment-emergent drug-related SAEs) are unpopulated.

Group 2

Three serious TEAEs were experienced in 2 subjects in Group 2 (both in the cardiac surgery group) (Table 27 and Table 14.3-5.1.2; Listing 16.2-17.3.1.2, and Listing 16.2-17.4.1.1.2). None of the SAEs were considered related to study treatment (Listing 16.2-17.4.2.1.2), led to discontinuation from the study, or resulted in death. All were mild or moderate in severity.

No SAEs occurred in the spine surgery group (Table 14.3-5.1.2) or when the spine surgery groups were combined (Table 14.3-5.1.3).

Table 27: Summary of Treatment-Emergent Serious Adverse Events – Safety Population

Subject	Preferred Term	Start Day	Stop Day	Serious Criterion	Severity	Relation-ship	Action Taken	Outcome
EXPAREL (Group 2; Cardiac Surgery)								
111-0010	Wound infection fungal	1	--	Required or Prolonged hospitalization	Mild	Unrelated	Medication	Recovering/ Resolving
	Vomiting	8	33	Required or Prolonged hospitalization	Moderate	Unrelated	Medication, Other (changed tube feedings)	Recovered/ Resolved
116-0035	Dyspnea	11	32	Required or Prolonged hospitalization	Moderate	Unrelated	Medication	Recovered/ Resolved

Source: Listing 16.2-17.4.1.1.2 (Group 2)

12.3.1.3. TEAEs Leading to Discontinuation

No subject in any study arm had a TEAE that led to study discontinuation (Table 14.3-4.1.3).

12.3.2. Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

Individual narratives for the 2 subjects who experienced treatment-emergent SAEs and the 5 subjects who experienced AESIs are provided in Section 14.3.3.

12.3.3. Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There were no deaths in the study.

Two subjects who underwent cardiac surgery in Group 2 experienced a total of 3 treatment-emergent SAEs. All of these events were considered unrelated to study drug and were mild or moderate in intensity. Two of the events resolved and the third was resolving.

Adverse Events of Special Interest

Summaries of AESIs are provided in Table 28 and Table 14.3-6.1.1 (Group 1), Table 14.3-6.1.2 (Group 2), and Table 14.3-6.1.3 (Both groups, spine surgery).

Group 1

Five subjects in Group 1 (2 subjects in the EXPAREL group and 3 subjects in the bupivacaine HCl group), had a TEAE of special interest. All were mild or moderate in severity and were considered unlikely or unrelated to study treatment. All but 1 event (muscle twitching in a bupivacaine subject) resolved.

Table 28: Summary of Treatment-Emergent Adverse Events of Special Interest, Group 1 (12 to <17 years) – Safety Population

	Group 1	
System Organ Class Preferred Term	**EXPAREL 4 mg/kg [N=31] n (%)**	**Bupivacaine HCl 2 mg/kg [N=30] n (%)**
Subjects with any AESI	**2 (6.5)**	**3 (10.0)**
Musculoskeletal and connective tissue disorders	**1 (3.2)**	**2 (6.7)**
Muscle twitching	1 (3.2)	2 (6.7)
Cardiac disorders	**0**	**1 (3.3)**
Tachycardia	0	1 (3.3)
Nervous system disorders	**1 (3.2)**	**0**
Dizziness	1 (3.2)	0

Abbreviations: AESI=adverse event of special interest; HCl=hydrochloride
Source: Table 14.3-6.1.1

Group 2

No AESIs were experienced in Group 2 (Table 14.3-6.1.2).

Spine surgery pooled

When both groups were combined (Group 1 and Group 2, spine surgery) (Table 29), results were similar to those of Group 1 (Table 28). A total of 2 subjects (5.6%) in the EXPAREL group and 3 subjects (10.0%) in the bupivacaine HCl group had an AESI.

Table 29: Summary of Treatment-Emergent Adverse Events of Special Interest, Spine Surgery Pooled (6 to <17 years) – Safety Population

System Organ Class Preferred Term	EXPAREL 4 mg/kg [N=36] n (%)	Bupivacaine HCl 2 mg/kg [N=30] n (%)
Subjects with any AESI	**2 (5.6)**	**3 (10.0)**
Musculoskeletal and connective tissue disorders	**1 (2.8)**	**2 (6.7)**
Muscle twitching	1 (2.8)	2 (6.7)
Cardiac disorders	**0**	**1 (3.3)**
Tachycardia	0	1 (3.3)
Nervous system disorders	**1 (2.8)**	**0**
Dizziness	1 (2.8)	0

Abbreviations: AESI=adverse event of special interest; HCl=hydrochloride
Source: Table 14.3-6.1.3

Details of the treatment-emergent AESIs are presented in Table 30.

Table 30: Treatment-Emergent Adverse Events of Special Interest – Safety Population

Subject	Preferred Term	Start Day	Stop Day	Severity	Relationship	Action Taken	Outcome
EXPAREL							
107-0013	Dizziness	2	21	Mild	Unlikely	Medication	Recovered/Resolved
116-0024	Muscle twitching	2	5	Moderate	Unlikely	None	Recovered/Resolved
Bupivacaine HCl							
101-0023	Tachycardia	1	17	Mild	Unrelated	None	Recovered/Resolved
101-0061	Muscle twitching	44	--	Mild	Unlikely	None	Not Recovered/ Not Resolved
101-0073	Muscle twitching	2	14	Moderate	Unlikely	Medication	Recovered/Resolved

Abbreviation: HCl=hydrochloride
Source: Listing 16.2-17.5.1.1.1 (Group 1)

Treatment emergent AESIs as reported by investigators are listed in Listing 16.2-17.5.1.1.1 (Group 1) and Listing 16.2-17.5.1.1.2 (Group 2). Adverse events of special interest as defined in the protocol are listed in Listing 16.2-17.5.3.1.1 (Group 1) and Listing 16.2-17.5.3.1.2 (Group 2).

Treatment emergent AESIs considered related to study treatment are listed in Listing 16.2-17.5.2.1.1 (Group 1) and Listing 16.2-17.5.2.1.2 (Group 2).

12.4. Clinical Laboratory Evaluation

Clinical laboratory parameters were conducted in accordance with the investigator's standard of care at screening. Urine drug screen, alcohol blood test, and pregnancy data are listed in Listing 16.2-22.1.1 (Group 1) and Listing 16.2-22.1.2 (Group 2).

12.4.1. Hematology

Hematology data are summarized by timepoint in Table 14.3-3.1.1.1 (Group 1), Table 14.3-3.1.1.2 (Group 2), and Table 14.3-3.1.1.3 (Both groups, spine surgery). Hematology data by subject are listed in Listing 16.2-10.1.1 (Group 1) and Listing 16.2-10.1.2 (Group 2). Tabulations of clinical laboratory range by timepoint for hematology are provided in Table 14.3-3.5.1.1 (Group 1), Table 14.3-3.5.1.2 (Group 2), and Table 14.3-3.5.1.3 (Both groups, spine surgery).

No clinically significant differences in mean data were noted between the study arms for hematology results.

12.4.2. Chemistry

Chemistry data are summarized in Table 14.3-3.2.1.1 (Group 1), Table 14.3-3.2.1.2 (Group 2), and Table 14.3-3.2.1.3 (Both groups, spine surgery). Chemistry data by subject are listed in Listing 16.2-11.1.1 (Group 1) and Listing 16.2-11.1.2 (Group 2). Tabulations of clinical laboratory range by timepoint for chemistry are provided in Table 14.3-3.6.1.1 (Group 1), Table 14.3-3.6.1.2 (Group 2), and Table 14.3-3.6.1.3 (Both Groups, spine surgery).

No clinically significant differences in mean data were noted between the study arms for chemistry results. All study arms had mean creatine kinase levels at 96 hours postsurgery that were elevated relative to the baseline levels; this finding has been described in the literature [Iglesias 2014].

12.4.3. Urinalysis

Urinalysis data are summarized in Table 14.3-3.3.1.1 (Group 1), Table 14.3-3.3.1.2 (Group 2), and Table 14.3-3.3.1.3 (Both groups) and are tabulated in Table 14.3-3.4.1.1 (Group 1), Table 14.3-3.4.1.2 (Group 2), and Table 14.3.-3.4.1.3 (Both groups, spine surgery). Urinalysis data (numeric results) are listed in Listing 16.2-12.1.1 (Group 1) and Listing 16.2-12.1.2 (Group 2). Urinalysis data (character results) are listed in Listing 16.2-13.1.1 (Group 1) and Listing 16.2-13.1.2 (Group 2).

Clinical laboratory range data are tabulated by timepoint in Table 14.3-3.7.1.1 (Group 1), and Table 14.3-3.7.1.2 (Group 2), and Table 14.3-3.7.1.3 (Both Groups, spine surgery).

No clinically significant differences in mean data were noted between the study arms for urinalysis results.

12.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

12.5.1. Vital Signs

No clinically significant differences in mean data for vital signs were noted between the study arms.

Vital signs data are summarized in Table 14.3-1.1.1 (Group 1), Table 14.3-1.1.2 (Group 2), and Table 14.3-1.1.3 (Both groups, spine surgery). Vital signs data are listed in Listing 16.2-14.1.1 (Group 1) and Listing 16.2-14.1.2 (Group 2).

12.5.2. Neurologic Assessments

Group 1

Neurologic data for Group 1 are summarized in Table 31 and Table 14.3-2.1.1 and are listed by subject in Listing 16.2-16.1.1.

In Group 1, the incidence of neurologic events was generally low. The most common post-baseline neurologic assessment findings were muscle twitching and vision problems.

Table 31: Summary of Neurologic Assessments, Group 1 (12 to <17 years) – Safety Population

Analysis timepoint:	Screen	2h	4h	8h	12h	24h	36h	48h	60h	72h	96h	Discharge	D30
Group 1: EXPAREL													
Not oriented	0	1 (3.2)	0	0	0	0	0	0	0	0	0	0	0
Numbness	0	0	0	0	0	0	1 (3.2)	0	0	0	0	0	0
Metallic taste	0	0	0	0	0	1 (3.2)	0	0	0	0	0	0	0
Hearing problems	1 (3.2)	0	0	0	0	0	0	1 (3.2)	1 (3.2)	1 (3.2)	0	0	0
Vision problems	0	1 (3.2)	1 (3.2)	1 (3.2)	1 (3.2)	1 (3.2)	1 (3.2)	2 (6.5)	2 (6.5)	1 (3.2)	0	0	0
Muscle twitching	0	0	0	0	0	1 (3.2)	0	0	0	0	1 (3.2)	0	0
Group 1: Bupivacaine HCl													
Not oriented	0	0	0	0	0	0	0	0	0	0	0	0	0
Numbness	0	1 (3.3)	2 (6.7)	1 (3.3)	1 (3.3)	1 (3.3)	0	0	0	0	0	0	0
Metallic taste	0	0	0	0	0	0	1 (3.3)	0	1 (3.3)	0	0	0	0
Hearing problems	0	0	2 (6.7)	0	0	0	0	0	0	0	1 (3.3)	0	0
Vision problems	0	2 (6.7)	3 (10.0)	2 (6.7)	0	0	0	0	0	0	1 (3.3)	0	0
Muscle twitching	0	0	0	0	0	6 (20.0)	1 (3.3)	1 (3.3)	3 (10.0)	3 (10.0)	1 (3.3)	2 (6.7)	0

Abbreviations: D=day; h=hour
Source: Table 14.3-2.1.1

Group 2

Neurologic data are summarized in Table 32 and Table 14.3-2.1.2 for Group 2 and Table 14.3-2.1.2 for both groups, spine surgery. Neurologic data are listed by subject in Listing 16.2-16.1.2 (Group 2).

In Group 2, the incidence of neurologic events was low. Muscle twitching was the most common post-baseline neurological finding.

Table 32: Summary of Neurologic Assessments, Group 2 (6 to <12 years) – Safety Population

Analysis timepoint:	Baseline	2h	4h	8h	12h	24h	36h	48h	60h	72h	96h	Discharge	D30
Group 2: Spine													
Not oriented	0	0	0	0	0	0	0	0	0	0	0	0	0
Numbness	0	3 (60.0)	0	0	0	0	0	0	0	0	0	0	0
Metallic taste	1 (20.0)	0	0	0	0	0	0	0	0	0	0	0	0
Hearing problems	0	0	0	0	0	0	0	0	0	0	0	0	0
Vision problems	0	2 (40.0)	1 (20.0)	0	0	0	0	0	0	0	0	0	0
Muscle twitching	1 (20.0)	1 (20.0)	1 (20.0)	0	0	0	0	0	0	0	0	1 (20.0)	0
Group 1: Cardiac													
Not oriented	0	0	0	0	0	0	0	0	0	0	0	0	0
Numbness	0	0	0	0	0	0	0	0	0	0	0	0	0
Metallic taste	0	0	0	0	0	0	0	0	0	0	0	0	0
Hearing problems	0	0	0	0	0	0	0	0	0	0	0	0	0
Vision problems	0	0	0	0	0	0	0	0	0	0	0	0	0
Muscle twitching	0	0	0	0	1 (3.4)	0	0	1 (3.4)	0	0	0	0	0

Abbreviations: D=day; h=hour
Source: Table 14.3-2.1.2

12.5.3. Physical Findings

A physical examination was conducted at screening and at the Day 30 follow-up visit. Physical examination data are listed in Listing 16.2-29.1.1 (Group 1) and Listing 16.2-29.1.2 (Group 2).

12.6. Safety Conclusions

In Group 1, 19 subjects (61.3%) who received EXPAREL and 22 subjects (73.3%) who received bupivacaine HCl experienced a TEAE. In Group 2, 5 subjects (100%) who underwent spine surgery and 9 subjects (31.0%) who underwent cardiac surgery experienced a TEAE.

The SOC with the highest incidence of TEAEs in both groups was Gastrointestinal Disorders. Only 1 severe TEAE was experienced (constipation in a subject who received bupivacaine in Group 1). Possibly treatment-related TEAEs were experienced in 7 subjects in Group 1 (2 EXPAREL, 6.5%; and 5 bupivacaine, 16.7%) and 3 subjects in Group 2 (3 spine surgery subjects, 60.0%).

No subject discontinued the study due to a TEAE. Two subjects, both in Group 2 (cardiac surgery) experienced at least 1 SAE; no SAE was considered related to study treatment, led to death, or led to discontinuation from the study. Five subjects in Group 1 (2 EXPAREL, 3 bupivacaine subjects) had a TEAE of special interest as reported by investigators; all were mild or moderate and were considered unrelated or unlikely related to study treatment. The incidence of post-baseline neurologic events was low and these events occurred in both the EXPAREL and bupivacaine arms.

No clinically significant changes in laboratory test results or vital signs were observed.

13. OVERALL CONCLUSIONS

Bupivacaine pharmacokinetics and safety of a single 4 mg/kg dose of EXPAREL were studied in pediatric subjects of 6 to <17 years undergoing spine or cardiac surgeries. For comparison, the pharmacokinetics and safety of single 2 mg/kg doses of bupivacaine HCl were administered to pediatric subjects of 12 to <17 years undergoing spine surgeries. The results (geometric mean comparisons for Group 1 spine and Group 2 cardiac, and median for Group 2 spine) indicated that:

- Spine subjects in Group 1 who received bupivacaine HCl had a higher C_{max} (488.2 ng/mL) than matching subjects given an average 1.45-fold higher bupivacaine dose as EXPAREL (336.8 ng/mL).
- In Group 1, bupivacaine overall median t_{max} after bupivacaine HCl and EXPAREL were short (<1.5 h); however, EXPAREL was associated with a later t_{max2} (median 18.0 h, range 11.1-26.1 h after the dose) and hence more sustained bupivacaine concentrations than seen with bupivacaine HCl.
- In Group 1, the AUC of bupivacaine was higher after administration of EXPAREL than when bupivacaine HCl was administered to spine subjects (8296.9 vs. 4791.4 ng×h/mL for $AUC_{0\text{-}tlast}$; 12256.8 vs. 5064.2 ng×h/mL for $AUC_{0\text{-}\infty}$), consistent with a higher bupivacaine dose when given as EXPAREL.
- The AUC of bupivacaine after administration of EXPAREL was higher in cardiac subjects from Group 2 compared with spine subjects from Group 1 (15316.0 vs. 8296.9 ng×h/mL for $AUC_{0\text{-}tlast}$; 19707.4 vs. 12256.8 ng×h/mL for $AUC_{0\text{-}\infty}$).
- The bupivacaine C_{max} was higher in the cardiac subjects (403.4 ng/mL) than in the spine subjects (336.8 ng/mL in Group 1 and 319.5 ng/mL in Group 2 age-matched subjects).
- The time to C_{max} was delayed for the cardiac subjects comparing with spine subjects (median t_{max} over 22.7 vs. <8 h).
- The CL/F of bupivacaine in Group 2 cardiac subjects given EXPAREL (6.6 L/h) was lower than that after EXPAREL or bupivacaine HCl when given to spine subjects (14.5 to 18.9 L/h).
- The geometric mean estimation of Vd/F yielded a value of 488.4 L for older spine-surgery subjects who received EXPAREL, which was numerically higher than those for other groups (ranging from 197.1 to 271.1 L).

Safety: Mean (± SD) exposure to study medication in bupivacaine free base equivalents was 3.97 (0.14) mg/kg in Group 1 EXPAREL subjects, 1.89 (0.46) mg/kg in Group 1 bupivacaine HCl subjects; 4.00 mg/kg in Group 2 spine surgery subjects, and 4.00 (0.00) mg/kg in Group 2 cardiac surgery subjects.

- At least 1 TEAE was reported in 19 of 31 subjects (61.3%) in EXPAREL Group 1 subjects; 22 of 30 subjects (73.3%) in bupivacaine HCl Group 1 subjects; 5 of 5 subjects (100%) in Group 2 spine surgery subjects, and 9 of 29 subjects (31.0%) in Group 2 cardiac surgery subjects.

The incidence of SAEs was low and none were considered related to study treatment. EXPAREL was generally well tolerated by the pediatric and adolescent subjects in this study.

Efficacy: This study was not powered to evaluate efficacy; efficacy was examined for descriptive purposes only.

In Group 1, mean pain intensity NRS scores tended to be lower through 36 hours in the EXPAREL group; AUC for mean pain intensity NRS scores and total opioid consumption were lower through 72 hours in the EXPAREL group compared with the Bupivacaine HCl group. Median time to first rescue medication was 0.82 hours and 0.60 hours in the EXPAREL and bupivacaine HCl groups, respectively.

In Group 2, the mean CAS pain intensity scores, AUC for mean pain intensity CAS scores, and total opioid consumption were generally low for both surgery types. Median time to first rescue medication was 15.77 hours and 2.43 hours in the spine surgery and cardiac surgery groups, respectively.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1. Disposition, Demographic, and Baseline Characteristics Summary Tables

14.2. Pharmacokinetic and Efficacy Data Summary Tables and Figures

14.2.1. Pharmacokinetic Data Summary Tables

14.2.2. Efficacy and Pharmacokinetic Figures

14.2.3. Efficacy Data Summary Tables

14.3. Safety Data Summary Tables

14.3.1. Displays of Adverse Events and Tabulations of Deaths, Other Serious and Significant Adverse Events

14.3.2. Listings of Deaths, Other Serious, and Significant Adverse Events

Not applicable

14.3.3. Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Narratives are provided below for the subjects who experienced treatment-emergent SAEs or AESIs during the study.

Subject ID	Study Part	Study Group	Study Drug	Reason for Narrative		
				SAE	DC for AE	AESI
319-101-0023	Part 1	Group 1	Bupivacaine			X
319-101-0061	Part 2	Group 1	Bupivacaine			X
319-101-0073	Part 2	Group 1	Bupivacaine			X
319-107-0013	Part 1	Group 1	EXPAREL			X
319-116-0024	Part 1	Group 1	EXPAREL			X
319-111-0010	Part 1	Group 2	EXPAREL, Cardiac surgery	X		
319-116-0035	Part 1	Group 2	EXPAREL, Cardiac surgery	X		

Abbreviations: AE=adverse event; AESI=adverse event of special interest; CRF=case report form; DC=discontinued; SAE=serious adverse event

Subject 101-0023

Subject 101-0023, a 13-year-old White female with adolescent idiopathic scoliosis of the thoracic region, participated in a clinical trial of EXPAREL for postsurgical analgesia in pediatric subjects undergoing spine or cardiac surgery. Additional ongoing medical history included Tetralogy of Fallot, DiGeorge's Syndrome, juvenile idiopathic arthritis, Hallux abducto valgus, foot pain, seasonal allergies, hammertoe, and long-term use of immunosuppressant medication. Results of an electrocardiogram (ECG) performed on 10 Jul 2019 were normal.

The subject underwent spine surgery on 10 Jul 2019 (Day 1) from 10:18 to 15:31 and received bupivacaine HCl (73 mg) that was administered from 14:30 to 14:37.

Following surgery, the subject received her first postsurgical opioid pain medication (hydromorphone 10 µg, epidural) at 16:00, per the institution's standard of care. The total oral morphine-equivalent postoperative opioid consumption was 76.20 MED mg.

On the day of surgery (10 Jul 2019, Day 1), the subject experienced the nonserious AEs of mild tachycardia (an AESI), mild tachypnea, and mild bradypnea, all of which were considered unrelated to study treatment as well as mild hypotension, which was considered unlikely related to study treatment. All these events resolved without treatment; the bradypnea on the day of onset (10 Jul 2019), the tachypnea on 13 Jul 2019 (Day 4), and both the tachycardia and hypotension on 26 Jul 2019 (Day 17).

The day after surgery (11 Jul 2019, Day 2), the subject experienced the nonserious AEs of mild headache and mild generalized edema, both of which were considered unrelated to study

treatment. Both events resolved without treatment; the headache resolved on 12 Jul 2019 (Day 3) and the edema resolved on 26 Jul 2019 (Day 17).

The subject was discharged from the hospital on 13 Jul 2019 (Day 4). She completed the Day 30 visit and completed the study on 26 Jul 2019 (Day 17).

Subject 101-0061

Subject 101-0061, a 13-year-old White female with scoliosis, participated in a clinical trial of EXPAREL for postsurgical analgesia in pediatric subjects undergoing spine or cardiac surgery. Additional medical history included a tonsillectomy (date unknown). Results of an ECG performed on 22 Jul 2019 were normal.

The subject underwent spine surgery on 22 Jul 2019 (Day 1) from 8:35 to 12:03 and received bupivacaine HCl (167.4 mg) that was administered from 11:05 to 11:11.

Following surgery, the subject received her first postsurgical opioid pain medication (hydromorphone 10 µg, epidural) at 12:20 on Day 1 per the institution's standard of care. The total oral morphine-equivalent postoperative opioid consumption was 82.95 MED mg.

On the day of surgery (22 Jul 2019, Day 1), the subject experienced the nonserious AEs of mild hypoaesthesia oral (numbness of the lips) and mild hypotension. The hypoaesthesia was considered possibly related to study treatment and resolved on the same day (22 Jul 2019) without treatment. The hypotension was considered unlikely related to study treatment and resolved on Day 2 (23 Jul 2019) without treatment.

On 23 Jul 2019 (Day 2), the subject experienced moderate nausea that was considered possibly related to study treatment. It was treated with scopolamine 1 mg transdermally from 23 to 25 Jul 2019 and the nausea resolved on 25 Jul 2019 (Day 4). The subject was discharged from the hospital on 25 Jul 2019 (Day 4).

On 03 Sep 2019 (Day 44), the subject experienced the nonserious AE of mild back muscle twitching (an AESI). This event was considered unlikely related to treatment and was ongoing (not recovered/not resolved). The subject completed the Day 30 visit and completed the study on 03 Sep 2019 (Day 44).

Subject 101-0073

Subject 101-0073, a 12-year-old White female with scoliosis of the thoracic spine, participated in a clinical trial of EXPAREL for postsurgical analgesia in pediatric subjects undergoing spine or cardiac surgery. Additional medical history included ongoing attention deficit hyperactivity disorder. Results of an ECG performed on 07 Aug 2019 were normal.

The subject underwent spine surgery on 07 Aug 2019 (Day 1) from 10:31 to 15:14 and received bupivacaine HCl (101 mg) that was administered from 14:15 to 14:20.

Following surgery, the subject received her first postsurgical opioid pain medication (hydro-morphone 10 µg, epidural) at 15:29 on 07 Aug 2019 (Day 1) per the institution's standard of care. The total oral morphine-equivalent postoperative opioid consumption was 90.45 MED mg.

On the day of surgery (07 Aug 2019; Day 1), the subject experienced the nonserious AE of moderate nausea, which was considered possibly related to study treatment. The nausea was treated with ondansetron 4 mg intravenously 4 times daily (QID) from 07 to 10 Aug 2019 (Days 1 to 4) and with scopolamine 1 mg transdermally as needed from 07 Aug to 11 Aug 2019 (Days 1 to 5); the nausea resolved on 11 Aug 2019 (Day 5).

The day following surgery (08 Aug 2019; Day 2), the subject experienced moderate muscle twitching (an AESI) which was considered unlikely related to study treatment. The muscle twitching was treated with diazepam 2 mg orally as needed on 10 Aug 2019 (Day 4) and resolved on 20 Aug 2019 (Day 14).

On 09 Aug 2019 (Day 3), the subject experienced moderate pruritus that was considered unrelated to study treatment. This event was treated with diphendyramine 25 mg intravenously as needed on 09 Aug 2019 (Day 3) and hydroxyzine 12.5 mg orally as needed on 10 Aug 2019 (Day 4); the AE resolved on 22 Aug 2019 (Day16).

On 10 Aug 2019 (Day 4), the subject experienced the nonserious AEs of mild tachycardia and mild hypotension that were considered unrelated and unlikely related to study treatment, respectively, and which resolved on the day of onset (Day 4) without treatment. The subject also experienced moderate constipation on Day 4 that was considered possibly related to study treatment. The constipation was treated once with magnesium citrate 106 mL orally on 10 Aug 2019 (Day 4) and once with magnesium hydroxide 400 mg orally on 11 Aug 2019 (Day 5) and resolved on 22 Aug 2019 (Day 16).

The subject was discharged from the hospital on 11 Aug 2019 (Day 5). She completed the Day 30 visit and completed the study on 22 Aug 2019 (Day 16).

Subject 107-0013

Subject 107-0013, a 14-year-old Asian female with adolescent idiopathic scoliosis, participated in a clinical trial of EXPAREL for postsurgical analgesia in pediatric subjects undergoing spine or cardiac surgery. Additional medical history included ongoing use of an orthodontic brace and a forearm biopsy in Aug 2014. Results of an ECG performed on 12 Jun 2019 were normal.

The subject underwent spine surgery on 12 Jun 2019 (Day 1) from 12:22 to 18:34 and received EXPAREL (182 mg) that was administered from 17:46 to 18:04.

Following surgery, the subject received her first postsurgical opioid pain medication (hydromorphone [Dilaudid], 100 µg intravenously via patient-controlled analgesia pump X 4 doses) at 10:05 on 13 Jun 2019 (Day 2). The total oral morphine-equivalent postoperative opioid consumption was 92.75 MED mg.

On 13 Jun 2019 (Day 2), the subject experienced the nonserious AE of mild dizziness (an AESI) that was considered unlikely related to study treatment. The event was treated with scopolamine (Transdermscop) transdermally every 3 days (Q3D) from 13 to 16 Jun 2019 (Day 2 to Day 5); the event resolved on 02 Jul 2019 (Day 21). Additionally, on 13 Jun 2019 (Day 2), the subject experienced the nonserious AEs of mild muscle spasm, mild nausea, mild vomiting, and moderate postoperative anemia. All were considered unlikely related to study treatment. The nausea and vomiting were treated with ondansetron (Zofran; 4 mg intravenously as needed) on 13 Jun 2019 (Day 2); the events resolved on 13 Jun 2019 (Day 2). The muscle

spasm was treated with lorazepam (Ativan; 0.25 mg intravenously 4 times daily [QID]) on 13 Jun 2019 (Day 2) and methocarbamol (Robaxin; 750 mg orally 3 times a day (TID) from 14 Jun (Day 3) to 15 Jun 2019 (Day 4); the event resolved on 15 Jun 2019 (Day 4). The anemia was ongoing (recovering/resolving).

The subject was discharged from the hospital on 17 Jun 2019 (Day 6). She completed the Day 30 visit and completed the study on 02 Jul 2019 (Day 21).

Subject 111-0010

Subject 111-0010, a 6-year-old White male with congenital heart disease, pulmonary artery stenosis, pulmonary valve stenosis, and hypoxic-ischemic encephalopathy participated in a clinical trial of EXPAREL for postsurgical analgesia in pediatric subjects undergoing spine or cardiac surgery. Additional ongoing medical history included cerebral palsy, history of seizures, seasonal allergies, as well as a pulomonic [sic] valve replacement in July 2013. Results of an ECG performed on 16 May 2019 were "abnormal, not clinically significant."

The subject underwent cardiac surgery on 17 May 2019 (Day 1) from 9:12 to 13:47 and received EXPAREL (100 mg) that was administered from 13:20 to 13:25.

Following surgery, the subject received his first postsurgical opioid pain medication (morphine 1.2 mg intravenously) at 16:57 on 17 May 2019 (Day 1). The total oral morphine-equivalent postoperative opioid consumption was 144.96 MED mg.

On the day of surgery (17 May 2019; Day 1), the subject had the SAE of sternal wound positive for fungal infection (*Candida albicans*). The positive culture was obtained prior to administration of EXPAREL from an area of concern from a previous surgery. The event, which prolonged the subject's hospitalization, was considered mild in severity and unrelated to study treatment. The subject was treated with fluconazole 300 mg intravenously once daily (QD) starting on 30 May 2019 (Day 15) and ongoing. This event was ongoing but resolving.

The subject experienced a second SAE, persistent vomiting, with onset on 24 May 2019 (Day 8). The event, which prolonged the hospitalization, was considered moderate in intensity and unrelated to study treatment. The event was treated with multiple actions including treatment with ondansetron 4 mg every 4 hours from 25 to 29 May 2019 (Days 9 to 13) and was resolved on 18 Jun 2019 (Day 33).

The subject was discharged from the hospital on 07 Jun 2019 (Day 22). The subject completed the Day 30 visit and completed the study on 18 Jun 2019 (Day 33).

Subject 116-0024

Subject 116-0024, a 15-year-old White female with idiopathic scoliosis, participated in a clinical trial of EXPAREL for postsurgical analgesia in pediatric subjects undergoing spine or cardiac surgery. No additional medical history was reported. Results of an ECG performed on 04 Jun 2019 were normal.

The subject underwent spine surgery on 12 Jun 2019 (Day 1) from 10:58 to 14:45 and received EXPAREL (228.8 mg) that was administered from 14:28 to 14:34.

Following surgery, the subject received her first postsurgical opioid pain medication (morphine 5 mg intravenously) at 15:00, followed by pethidine (meperidine) 10 mg intravenously at 15:10. The total oral morphine-equivalent postoperative opioid consumption was 186.30 MED mg.

On 13 Jun 2019 (Day 2), the subject experienced moderate muscle twitching along the incision line (an AESI). This event was considered unlikely related to study treatment. No action was taken, and the event was resolved on 16 Jun 2019 (Day 5).

The subject was discharged on 15 Jun 2019 (Day 4). She completed the Day 30 visit and completed the study on 11 Jul 2019 (Day 30).

Subject 116-0035

Subject 116-0035, a 6-year-old White male with patent foramen ovale and ventricular septal defect large inlet participated in a clinical trial of EXPAREL for postsurgical analgesia in pediatric subjects undergoing spine or cardiac surgery. Ongoing medical history included combined systolic and diastolic cardiac dysfunction, double inlet left ventricle, pulmonary valve regurgitation, pulmonary artery banding, and tricuspid regurgitation. Additional medical history included transportation of great arteries (I-TGA) (19 May 2013 to 24 Jun 2019), patent ductus arteriosus with left to right flow (19 May 2013 to 29 May 2018), pulmonary hypertension (19 May 2013 to 29 May 2018), and dual chamber epicardial pacemaker placement (29 May 2018). Results of an ECG performed on 10 Jun 2019 were “abnormal, not clinically significant.”

The subject underwent cardiac surgery on 24 Jun 2019 (Day 1) from 10:26 to 12:41 and received EXPAREL (91.2 mg) that was administered from 12:14 to 12:17.

The subject received no postsurgical opioid pain medications.

On 04 Jul 2019 (Day 11), the subject had the SAE of moderate shortness of breath (dyspnea). On 25 July 2019, the subject was brought to the Emergency Department and was admitted to the hospital. The event, which required hospitalization, was considered unrelated to study treatment. The subject was treated with milrinone 16.204 mg intravenously from 25 to 26 Jul 2019 (Days 32 to 33) and the event was resolved on 25 Jul 2019 (Day 32). The subject had the additional nonserious AE of mild facial edema with onset and resolution on 25 Jul 2019 (Day 32). The event was considered unrelated to study treatment

The subject was discharged from the hospital on 03 Jul 2019 (Day 10). He completed the Day 30 visit and completed the study on 07 Aug 2019 (Day 45).

14.3.4. Laboratory Findings and Other Data Related to Safety

Table 14.3-1.1.1	Summary of Vital Signs (Group 1: 12 to <17 years) – Safety Population
Table 14.3-1.1.2	Summary of Vital Signs (Group 2: 6 to <12 years) – Safety Population
Table 14.3-1.1.3	Summary of Vital Signs (Both Groups: 6 to <17 years) – Spine Surgery – Safety Population
Table 14.3-2.1.1	Summary of Neurological Assessments by Timepoint (Group 1: 12 to <17 years) – Safety Population
Table 14.3-2.1.2	Tabulation of Neurological Assessments by Timepoint (Group 2: 6 to <12 years) – Safety Population

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16. APPENDICES

16.1. Study Information

16.1.1. Protocol, Protocol Amendments, and Protocol Clarification Letters

16.1.2. Sample Case Report Form

16.1.3. List of IECs or IRBs and Representative Written Information for Subject and Sample Consent Forms

16.1.4. List and Description of Investigators and Other Important Participants in the Study

16.1.5. Signatures of Principal or Coordinating Investigator(s) or Sponsor's Responsible Medical Officer

16.1.6. Listing of Subjects Receiving Test Drug(s)/Investigational Product(s) from Specific Batches

16.1.7. Randomization Scheme and Codes

16.1.8. Audit Certificates

16.1.9. Documentation of Statistical Methods

16.1.10. Documentation of Inter-Laboratory Standardization Methods and Quality Assurance Procedures if Used

Not applicable

16.1.11. Publications Based on the Study

Not applicable

16.1.12. Important Publications Referenced in the Report

Not applicable

16.1.13. Data Safety Monitoring Board Charter

16.1.14. Pharmacokinetic Report and Population Pharmacokinetic Report

16.1.15. ABS Analytical Protocol

16.2. Subject Data Listings

16.2.1. Subject Disposition and Discontinued Subjects

16.2.2. Protocol Deviations

16.2.3. Subjects Excluded from the Efficacy Analysis

16.2.4. Demographic and Baseline Characteristics Data

16.2.5. Compliance and/or Drug Concentration Data

16.2.6. Individual Efficacy Response Data

16.2.7. Adverse Event Listings

16.2.8. Listings of Individual Laboratory Measurements by Subjects

16.2.9. Listings of Vital Signs, Electrocardiogram, and Neurologic Assessments

16.2.10. Listings of Medications, Medical History, Study Drug Administration, Screening Tests, Unique Terms, and Physical Examinations

16.3. Case Report Forms (CRFs)

16.3.1. CRFs for Deaths, Other Serious Adverse Events, and Withdrawals for Adverse Events

Subject ID	Study Part	Study Group	Study Drug	Reason for Providing CRF		
				SAE	DC for AE	AESI
319-101-0023	Part 1	Group 1	Bupivacaine			X
319-101-0061	Part 2	Group 1	Bupivacaine			X
319-101-0073	Part 2	Group 1	Bupivacaine			X
319-107-0013	Part 1	Group 1	EXPAREL			X
319-116-0024	Part 1	Group 1	EXPAREL			X
319-116-0035	Part 1	Group 2	EXPAREL, Cardiac surgery	X		
319-111-0010	Part 1	Group 2	EXPAREL, Cardiac surgery	X		

Abbreviations: AE=adverse event; AESI=adverse event of special interest; CRF=case report form; DC=discontinued; SAE=serious adverse event

16.3.2. Other CRFs Submitted

Not applicable