Office of Clinical Pharmacology Review

NDA:	22496- (S-035) Sequence No. 0223
Associated IND:	069198
Link to EDR:	\\cdsesub1\evsprod\nda022496\0223
Submission Date:	05/22/2020
Submission Type/Code:	Efficacy Supplement-035 / Required Pediatric Assessment to fulfill PMR 1834-5
Reference Drug:	Not applicable
Brand Name:	EXPAREL
Generic Name:	Bupivacaine
Formulation/Strength(s):	Bupivacaine liposome injection/13.3 mg/mL
Clinical Pharmacology Reviewer:	Suresh B Naraharisetti, DVM, PhD
Clinical Pharmacology Team Leader:	Yun, Xu, PhD
OCP Division:	Division of Neuropsychiatric Pharmacology (DNP)
OND Division:	Division of Anesthesiology, Addiction Medicine, Pain Medicine
Sponsor:	Pacira Pharmaceuticals, Inc.
Approved Indications:	Single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia

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1.0 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Neuropsychiatric pharmacology (OCP/DNP) has reviewed the information submitted on 05/22/2020 in the current supplemental application, NDA 022496 (S-035), for EXPAREL use in pediatric subjects of ages 6 to <17 y. From a clinical pharmacology perspective, the information submitted in this supplemental NDA is acceptable. When this review was uploaded to DARRTS, as per memo of Office of Study Integrity and Surveillance (OSIS) inspection, the bioanalysis portion of Study 319 was acceptable, while the clinical portion of the study is pending for inspection. As per email discussion, the OSIS inspection summary for clinical portion is expected to complete by 02/26/2021. No further communication is necessary with the Applicant at this point. Labeling changes are ongoing as of 02/12/2021.

1.2 Phase 4 Commitments

Not applicable

1.3 Summary of Clinical Pharmacology Findings

Background:
NDA 22496 for EXPAREL was originally approved on 10/28/2011. EXPAREL is a suspension of multivesicular liposomes containing bupivacaine (b) (4) . Bupivacaine is present at a concentration of 13.3 mg/mL in EXPAREL. The current approved adult indications of EXPAREL were for single-dose infiltration to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. The approved dosage was up to a maximum dose of 266 mg (20 mL) for single-dose infiltration and 133 mg (10 mL) for interscalene brachial plexus nerve block.

EXPAREL (bupivacaine) exerts its action at the level of local tissues, independently of systemic levels. The systemic bupivacaine levels from the product are not related to local efficacy but have implications for its systemic safety profile (clinical review, DARRTS, dated 9/24/2011).

From the clinical studies, it is known that the PK profile of EXPAREL varies with different surgical procedures. The rate of systemic absorption of bupivacaine from EXPAREL is dependent upon the total dose, the route, and the vascularity of administered site, hence, the PK of EXPAREL vary with surgical procedures.

With this submission, Pacira submitted supplement S-035, to fulfill PMR 1834-5, for use of EXPAREL via infiltration for postoperative local analgesia in pediatric subjects aged 6 to < 17 y. In support of this supplement, Pacira conducted two studies in pediatrics, a pilot study, Study 402-C-120 (Study 120) and a pivotal study, Study 402-C-319 (Study 319) and two studies in adults (Studies 117 and 118). The adult studies were performed to conduct PK and safety comparison between pediatrics and adults.

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On the basis of pediatric and adult studies conducted in this supplement, Pacira also proposed a change to the existing indication language to include pediatric population, in addition to the existing adult population. The proposed change to indication language is "EXPAREL is indicated for single-dose infiltration in patients aged 6 years and older to produce postsurgical local analgesia and in adults as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia".

With regards to this supplement, as per prior discussion between Pacira and the Agency at March 24, 2016 and April 23, 2018 meetings, Pacira noted that:

- As agreed, the extrapolation of efficacy data on EXPAREL from adults to pediatric patients aged 6 years and older in the setting of local analgesia is appropriate.
- The extrapolation of efficacy of EXPAREL from adults to pediatric patients is based on similar pathophysiology of postsurgical pain in pediatric and adult patients, similar mechanism of action, response to treatment, the prior demonstration of efficacy in adults, and the similar PK profiles of EXPAREL in pediatric and adult subjects.
- Study 319 evaluated EXPAREL in two surgical procedures in highly vascular anatomical compartments represented by spine and cardiac surgeries. These procedures were selected in order to evaluate the PK and safety of EXPAREL under conditions where the highest systemic levels of bupivacaine and corresponding risk for toxicity could be expected. This approach enables extension of the systemic safety from spine and cardiac surgeries to procedures with lower vasculature and lower systemic exposure. In addition, these surgeries also require a longer hospitalization than other common pediatric procedures, allowing for more intensive PK and safety evaluations and for complete characterization of the PK profile in these subjects.

In study 319, the efficacy assessments were included in the pediatric studies to inform clinical decision making, although these endpoints were not powered to make efficacy claims. Applicant concludes that, "the descriptive efficacy data from Study 319 (6 to <17 y) showed that EXPAREL was associated with similar postoperative pain intensity scores and use of postoperative opioid medication relative to bupivacaine HCl among pediatric subjects aged 12 to less than 17 years undergoing spine surgery when administered in the context of institutions' standard of care for postsurgical pain management." The clinical team with regards to the efficacy assessments notes that, since the Study 319 was not powered for efficacy, no conclusions about the efficacy data can be made; however, there was nothing in the results that made to question the extrapolation of efficacy from adults to children. Additionally, the clinical team's memo to PeRC assessment meeting (scheduled on 02/16/2021) concludes that, "the efficacy of EXPAREL for local infiltration for pediatric subjects aged 6 to less than 17 years of age was extrapolated from the efficacy of EXPAREL for local infiltration for adult subjects". Refer to the clinical review for further discussion on the efficacy assessments in pediatrics in Study 319.

It is to note that for local anesthetics, the report from the FDA's scientific workshop [*title: Pediatric Analgesic Clinical Trial Designs, Measures, and Extrapolation: Report of an FDA Scientific Workshop* (Berde et al[1])] concludes that the efficacy can be extrapolated from studies

[1] Pediatrics. 2012;129:354-364

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in adults to children 2 years and older. The parts of the conclusions quoted from the article are as below:

- "There are biological, empirical, and experiential bases to justify extrapolation of efficacy from studies in adults to children aged 2 years for m-opioids, local anesthetics, NSAIDs, and acetaminophen".
- "In this population, efficacy of mu-opioids, local anesthetics, NSAIDs, and acetaminophen may also be extrapolated, but PK, dose-ranging, and safety studies must be performed to define prescribing parameters for practitioners"

From the clinical pharmacology perspective, this submission is acceptable. We have the following PK comparison conclusions based on the applicant studies in pediatrics and adults in this supplement.

PK Comparison Conclusions:
In general, for peri-operative products like EXPAREL, the PK varies due to several factors, e.g., type of surgery, vasculature, and type of drug administration (number of infiltration spots), anatomical site etc. The following comparisons are made between adults and pediatrics in spine and cardiac surgical procedures.

- Comparison of EXPAREL PK between adults and pediatrics for the same surgical procedure (Table 1.3):
    - The pediatric subjects underwent matching surgical procedures in spine and cardiac as that of adults. In spine procedure, compared to the adults dosed at EXPAREL 266 mg, the pediatric subjects' (6 to <17 y) dosed at 4 mg/kg showed ~ 30% lower Cmax and 30% lower partial AUCs[2] up to $AUC_{0\text{-}40h.}$ In cardiac procedures, compared to the adults, the pediatric subjects (6 to <12 y) showed similar Cmax and ~18% increase in $AUC_{0\text{-}last}$ ($AUC_{0\text{-}72h}$). Owing to a cross-study comparison and multiple factors that may affect absorption of peri-operative product like EXPAREL, the observed PK differences between pediatrics dosed at 4 mg/kg and adults dosed at 266 mg cannot be considered drastically different. Hence, it is reasonable to say that the exposure in pediatrics in matching surgical procedures of cardiac and spine surgeries can be considered reasonably similar to the adults.

[2]Partial AUC as a PK parameter has no special clinical meaning, except that this happens to be the most common last measurable sampling time point across pediatrics and adults and therefore was reasonable measure for comparison.

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Table 1.3: Mean PK parameters of EXPAREL pediatrics and adults in spine and cardiac procedures.

PK Parameter *	Pediatrics, EXPAREL 4 mg/kg (Study 319)				Adults, EXPAREL 266 mg (3.8 mg/ kg for 70 kg adult)	
	Spine 6 to <12 y (N=2) $	**Spine** 12 to <17 y (N=15)	**Spine** 6 to <17 y (N=17)	**Cardiac** 6 to <12 y (N=21)	**Spine** (Study 117) N=11	**Cardiac** (Study 118) N=5
Cmax (ng/mL)	320 (203, 436)	357 (125)	353 (125)	447 (243)	513 (268)	445 (120)
$AUC_{0\text{-}24h}$ (ng.h/mL)	6469 (4207, 8732)	5800 (1482) (n,14)	5883 (1625) (n,16)	6617 (3107)	8229 (5572)	5515 (1000)
$AUC_{0\text{-}36h}$ (ng.h/mL)	8810 (5468, 12151)	8117 (2385) (n,14)	8203 (2545) (n,16)	10222 (4304)	12023 (8111)	8823 (1227)
$AUC_{0\text{-}40h}$ (ng.h/mL)	9365 (5739, 12990)	8699 (2681) (n,14)	8782 (2834) (n,16)	11286 (4791)	13035 (8782)	9867 (1332)
$AUC_{0\text{-}48h}$ (ng.h/mL)	NR[1]	NR[1]	NR[1]	13324 (5523)	14619 (9860)	11585 (1840)
$AUC_{0\text{-}60h}$ (ng.h/mL)	NR[1]	NR[1]	NR[1]	15856 (6974)		13297 (2840)
$AUC_{0\text{-}last}$ (ng.h/mL)	NR[1]	NR[1]	NR[1]	16776 (7936)[1]	17214 (11621) [2]	14277 (3449) [1]
AUC_{inf} (ng.h/mL)	NR[2]	NR[2]	NR[2]	NR[2]	17917 (12187)	15768 (4530)
Tmax (h)	7.4 (12.3, 2.4)	1.1 (0.30, 26.1)	1.1 (0.30, 26.1)	22.7 (0.21, 54.5)	0.6 (0.2, 37.0)	0.58 (0.55, 36.0)

*Arithmetic mean (standard deviation) except T_{max} where it is median (minimum, maximum)

$ N=2, hence, mean (individual values) are shown.

[1] $AUC_{0\text{-}last}$, 0-72 h. The median last sampling time point is 69 h in pediatric cardiac surgery.

[2] $AUC_{0\text{-}last}$, 0-96h.

NR[1], Not reported, since the last sampling time point varies among different patients.

NR[2], Not reported, since the terminal elimination phase was not adequately characterized in sufficient number of patients.

1.3.1 Proposed Supplement: S-035 to fulfill post marketing requirement (PMR)[3] 1834-5 of pediatric studies in ages 6 to <17 y:

Conducted Studies in S-035, Details:

In this submission Pacira conducted four studies, two studies in pediatrics, [Study 120 (a pilot study to support 4 mg/kg dosage) and Study 319 (pivotal study)], and two studies in adults in matching surgical procedures (Studies 117 and 118). The adult subjects were dosed with EXPAREL 266 mg. The 266 mg dose in adults corresponds to 3.8 mg/kg for 70 kg body weight

[3] Pacira is in the planning stage for two remaining PMRs that are for use of EXPAREL via infiltration for postoperative analgesia in lower age group pediatrics, PMR 1834-6 in subjects 2 to < 6 years, and PMR 1834-7 in subjects from birth to <2 years.

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which is approximately matching to the EXPAREL pediatric mg/kg dose. The pediatric subjects were dosed EXPAREL 4 mg/kg dose, not to exceed a maximum total dose of 266 mg.

Studies in Pediatrics (6 to < 17 y):

- Study 120: A phase 1, open label study to evaluate the PK and safety of local administration of EXPAREL for postsurgical analgesia in pediatric subjects 12 to <17 y of age who underwent a spinal surgery. It was a pilot study to support the dosing of 4 mg/kg in Study 319.
- Study 319: A multicenter 2-part study to evaluate the PK and safety of EXPAREL for postsurgical analgesia in pediatric subjects aged 6 to <17 y who underwent either a spinal or cardiac surgery. It is considered the pivotal PK and safety study supporting the use of EXPAREL for local infiltration in pediatrics with some efficacy assessments.
    - 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. Group 1 (12 to <17 y) underwent only spine surgery, while Group 2 (6 to <12 y) underwent spine or cardiac surgery.
    - Summary of study design (Table 1.3.1A) and summary of analysis populations (Table 1.3.1B) for Study 402-C-319 is shown below in the tables (copied from the study report).

Table 1.3.1A: Summary of Study Design for Study 402-C-319 (copied from the study report, page 3):

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

Table 1.3.1B: Summary of Analysis Populations (copied from the study report, page 59):

	Group 1 Spine (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 (b) (6) 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.

Studies conducted in adults (for PK comparison to pediatrics in the same surgical procedure):

Two supportive studies in matching surgical procedures, one in spine procedures and one in thoracic procedures among adult subjects who received EXPAREL 266 mg via local infiltration were performed to provide a scientific bridge between the pediatric and adult age groups. The details are as follows.

- Study 117: A phase 1, open-label study to evaluate the safety and PK of EXPAREL in subjects undergoing open posterior spinal fusion or reconstructive surgery.

- Study 118: A phase 1, open-label study to evaluate the safety and PK of EXPAREL in subjects undergoing posterolateral thoracotomy.

More details regarding dosage, number of subjects and age groups for PK population are shown in Table 1.3.1C.

Table 1.3.1C: Summary of PK population in pediatrics and adults

Age group	Study No.	Surgery Type	Age (y)	Formulation and Dose	No. Subjects in PK Population EXPAREL : Control
Pediatrics	120	Spine	12 to < 17	EXPAREL 4 mg/kg *	15 : NA
	319	Spine	12 to < 17 (Group 1)	EXPAREL 4 mg/kg * Bupivacaine HCl 2 mg/kg $	16 : 15
		Spine and cardiac	6 to < 12 (Group 2)	EXPAREL 4 mg/kg *	23 (2 spine, 21 cardiac): NA
Adults	117	Spine	≥18	EXPAREL 266 mg	11 : NA
	118	Thoracotomy	≥18	EXPAREL 266 mg	5 : NA

*EXPAREL 4 mg/kg, not to exceed a maximum total dose of 266 mg

$ Bupivacaine HCl 2 mg/kg, not to exceed a maximum total dose of 175 mg

1.3.2 Comparison of PK parameters:

The systemic exposure of EXPAREL in pediatrics were compared to adults for evaluation of systemic safety and efficacy.

As discussed above in detail in Section 1.3 above, the extrapolation of efficacy of EXPAREL from adults to pediatric patients is based on similar pathophysiology of postsurgical pain in pediatric and adult patients, similar mechanism of action, response to treatment, the prior demonstration of efficacy in adults, and the similar PK profiles of EXPAREL in pediatric and adult subjects. Also, it is to be noted that the report of an FDA scientific workshop on pediatric analgesic clinical trial designs, measures, and extrapolation by Berde et al[4] concludes that, for local anesthetics, the efficacy can be extrapolated from studies in adults to children 2 years and older.

The PK parameters of EXPAREL in spine and cardiac procedures in pediatrics were compared cross-study to adults in matching spine and cardiac procedures. In addition, other PK comparisons, listed below were also conducted. The following PK comparison were conducted:

- Pediatrics versus adults for the same procedure
    - EXPAREL: Pediatrics, 6 to <17 y (4 mg/kg) versus adults (266 mg) in similar spine procedure
    - EXPAREL: Pediatrics, 6 to <12 y (4 mg/kg) versus adults (266 mg) in similar cardiac procedure

Other PK comparisons:

- Cardiac versus spine in pediatrics or adults
    - EXPAREL 4 mg/kg: Pediatrics, 6 to <17 y in cardiac versus 12 to <17 y in spine
    - EXPAREL266 mg: Adults, cardiac versus spine
- EXPAREL versus Bupivacaine HCl in pediatrics for the same procedure

[4] Pediatrics. 2012;129:354-364

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- EXPAREL (4 mg/kg) versus bupivacaine HCl (2 mg/kg) in pediatrics 12 to <17 y in spine
- Effect of surgical incision length on PK parameters in spine and cardiac procedures

PK sampling, $AUC_{0\text{-last}}$ and AUC_{inf} Comparison

The proposed PK sampling, per protocol for each study is shown below. More details about PK sampling and evaluation of type of AUC is discussed below.

- Study 319 (pediatrics, spine and cardiac): Staggered PK sampling as follows.

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

- Study 117 (spine, adults): 0, 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, and 168[5] h
- Study 118 (cardiac, adults): 0, 0.5, 1, 4, 12, 24, 36, 48, 60, and 72 h

The PK parameters were calculated by non-compartmental analysis.

As can be noted from the PK sampling above, the last time points were different between pediatrics and adults. These differences in PK sampling times will affect the $AUC_{0\text{-last}}$ comparison between the treatments, i.e., between pediatrics and adults. The difference in PK sampling is more pronounced in spine procedure.

$AUC_{0\text{-last}}$ Comparison:

- Spine procedures: The range of last-sampling points in pediatric spine was 18 h to 60 h (n=15 subjects), while in adults it was for much longer duration of 96 h.

  Reviewer analysis: Since the last time points was varied, the most common PK sampling for longest duration in all subjects was examined. It was observed that the common PK sampling for most pediatric spine subjects (n=13 out of 15), was ≥40 hours. So, the partial AUC, $AUC_{0\text{-40h}}$ was utilized for comparison between pediatrics and adults. The $AUC_{0\text{-40h}}$ in adults' spine represents ~76% of $AUC_{0\text{-last}}$ and ~73% of AUC_{inf} (total AUC). Hence the $AUC_{0\text{-40h}}$ can be considered a reasonably appropriate AUC measure to compare between adults and pediatrics in spine procedures. In addition, other partial AUCs ($AUC_{0\text{-24h}}$ and $AUC_{0\text{-36h}}$) were also compared.
- Cardiac procedure: The range of last-sampling points in pediatric cardiac (6 to <12 y) was 40 h to 73 h, with majority of the subjects with common PK sampling of ≥ 60 h (17 out of 21 subjects). The median last PK sampling time was 69 h. In adult cardiac subjects (n=5), the last time point of sampling was 72 h.

  Reviewer analysis: In most pediatric cardiac subjects, the common PK sampling for ≥60 hours were obtained and there was only 5% difference in values of $AUC_{0\text{-60h}}$ and $AUC_{0\text{-last}}$ ($AUC_{0\text{-72h}}$). Hence both $AUC_{0\text{-60h}}$ and $AUC_{0\text{-last}}$ were compared

[5] Only three subjects had bupivacaine concentrations at this time point. In others either the sample was not obtained or below limit of quantitation.

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between pediatrics and adults in cardiac procedures. In addition, other partial AUCs ($AUC_{0\text{-}24h}$, $AUC_{0\text{-}36h}$ and $AUC_{0\text{-}48h}$) were also compared. The mean plasma bupivacaine PK profiles of EXPAREL in 6 to <12 y and adults in cardiac procedure are shown below in Figure 1.3.3.

AUC_{inf} Comparison:

- In general, the allowed extrapolation of AUC_{inf} to $AUC_{0\text{-}last}$ is ≤ 20%. In pediatric subjects of Study 319, when AUC_{inf} was evaluated by auto 'best-fit' method of Phoenix (most appropriate method) non-compartmental PK analysis, the AUC_{inf} in comparison to $AUC_{0\text{-}last}$ was extrapolated by >100 % in spine and >600% in cardiac procedure. The larger extrapolation was due to inadequate characterization of terminal elimination phase in sufficient number of patients. Hence, the AUC_{inf} cannot be used for comparison between pediatrics and adults.

Tmax Comparison

- It is known from the original NDA studies, that EXPAREL in its PK profile exhibits two peaks, an early and a late peak. (b) (4) [redacted]. In the Applicant's results, applicant reported three Tmaxs, 1) Tmax1 for the peak concentrations obtained before 4 h after dose, 2) Tmax2 for peak concentrations obtained after 4 h after the dose and 3) global Tmax to show observed peak concentration at any time after the dose.
- In this review, the median global Tmax that represents peak concentration any time after the dose is only shown. Any observed difference in median global Tmax between two procedures were impacted by the relative proportions of subjects whose peak concentrations observed either early or late. Therefore, the difference in median global Tmax between any two procedures is not clinically meaningful, and may simply reflect the numeric observations.

<u>Overall, for PK comparison between pediatric and adults:</u>

- in spine procedure, the Cmax, $AUC_{0\text{-}40h}$ along with partial areas, $AUC_{0\text{-}24\,h}$ and $AUC_{0\text{-}36h}$ were compared.
- in cardiac procedure, the Cmax, $AUC_{0\text{-}60h}$, $AUC_{0\text{-}last}$ ($AUC_{0\text{-}72h}$) along with partial areas, $AUC_{0\text{-}24h}$ and $AUC_{0\text{-}36h}$ were compared.

1.3.3 Comparison of PK parameters between pediatrics and adults

1.3.3.1 EXPAREL, Pediatrics versus adults in spine surgery:

As shown earlier in the review, as per 319 study design, the 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 y of age and Group 2 enrolled subjects 6 to <12 y of age. Group 1 (12 to <17 y) underwent only spine surgery, while Group 2 (6 to <12 y) underwent spine or cardiac surgery. As a result, for spine procedures, 15 subjects were evaluated in 12 to <17 y age group, while two subjects were evaluated in 6 to <12 y age group.

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It was noted that the mean PK values of 12 to <17 y age group in 15 subjects were numerically similar to two subjects of 6 to <12 y age group. Hence, both age groups were combined to represent PK for 6 to <17 y (n=17). In spine procedure, compared to the adults dosed at EXPAREL 266 mg (3.8 mg/kg for 70 kg body weight), the pediatric subjects, 6 to <17 y dosed at 4 mg/kg showed ~ 30% lower Cmax and 30% lower partial AUCs up to $AUC_{0\text{-}40h}$ (Table 1.3.3.1).

The $AUC_{0\text{-}last}$ or AUC_{inf} parameters cannot be compared in spine procedure for the reasons mentioned above in section 1.3.2. The Tmax is not compared for the reasons mentioned above in section 1.3.2.

The PK parameter values of pediatrics 6 to <12, 12 to <17 and combined age groups (6 to <17 y), and the adults in spine procedure were shown in Table 1.3.3.1. The comparative mean plasma bupivacaine PK profiles of EXPAREL in pediatric subjects, 6 to <17 y and adults is shown below in Figure 1.3.3.

Table 1.3.3.1: Mean PK parameters of EXPAREL in 12 to <17 y (n=15), 6 to <12 y age (n=2), combined age groups, 6 to <17 (n=17) and adults in spine procedure.

PK Parameter *	**Pediatrics EXPAREL 4 mg/kg (Study 319, Spine)**			**Adults EXPAREL 266 mg (Study 117, Spine)**	**Ratio Pediatrics 6 to <17 y / Adults**
	6 to <12 y (N=2) [$]	12 to <17 y (N=15)	6 to <17 y (N=17)	(N=11)	
Cmax (ng/mL)	320 (203, 436)	357 (125)	353 (125)	513 (268)	0.69 (~31 % lower)
$AUC_{0\text{-}24h}$ (ng.h/mL)	6469 (4207, 8732)	5800 (1482) (n,14)	5883 (1625) (n,16)	8229 (5572)	0.71 (~29 % lower)
$AUC_{0\text{-}36h}$ (ng.h/mL)	8810 (5468, 12151)	8117 (2385) (n,14)	8203 (2545) (n,16)	12023 (8111)	0.68 (~32 % lower)
$AUC_{0\text{-}40h}$ (ng.h/mL)	9365 (5739, 12990)	8699 (2681) (n,14)	8782 (2834) (n,16)	13035 (8782)	0.67 (~33 % lower)
$AUC_{0\text{-}last}$ (ng.h/mL)	NR[1]	NR[1]	NR[1]	17214 (11621)[1]	
AUC_{inf} (ng.h/mL)	NR[2]	NR[2]	NR[2]	17917 (12187)	
Tmax (h)	7.4 (12.3, 2.4)	1.1 (0.30, 26.1)	1.1 (0.30, 26.1)	0.6 (0.2, 37.0)	

*Arithmetic mean (standard deviation) except T_{max} where it is median (minimum, maximum)

[$] N=2, hence, mean (individual values) are shown

[1] $AUC_{0\text{-}last}$, 0-96h.

NR[1], Not reported, since the last sampling time point varies among different patients.

NR[2], Not reported, since the terminal elimination phase was not adequately characterized in sufficient number of patients.

1.3.3.2 EXPAREL, Pediatrics 6 to <12 y versus adults in cardiac surgery:

As shown earlier in the review, as per 319 study design, the Part 1 evaluated PK and safety, while Part 2 assessed safety. Subjects in each part were classified into groups by age:

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Group 1 enrolled subjects 12 to <17 y of age and Group 2 enrolled subjects 6 to <12 y of age. Group 1 (12 to <17 y) underwent only spine surgery, while Group 2 (6 to <12 y) underwent spine or cardiac surgery. As a result, all the cardiac surgery patients were in the age group of 6 to <12 y age group (n=21) while none are in 12 to <17 y age group.

In adult cardiac surgery, as per applicant, the study was initiated with a target enrollment of 24 subjects; however, the study was terminated due to slow enrollment. As a result, only 5 evaluable subjects completed the study.

In cardiac procedures, compared to the adults dosed at 266 mg, the pediatric subjects, 6 to <12 y dosed at 4 mg/kg showed no change in EXPAREL Cmax and ~18% increase in $AUC_{0\text{-last}}$. The partial areas calculated between 0 h to 60 h ($AUC_{0\text{-24h}}$ to $AUC_{0\text{-60h}}$) showed an increase between 15 to 20% in pediatrics compared to the adults. Also, based on applicant's responses to Day 74 letter comments, one of the pediatric subjects in cardiac procedure (subject # (b) (6)) had only one functioning kidney. It is known that bupivacaine is renally eliminated drug. When $AUC_{0\text{-last}}$ value of bupivacaine in this patient is compared to the mean value from all patients, it is numerically higher (2.47-fold). When this subject was excluded from comparative PK analysis, the Cmax was approximately similar (3% lower) and $AUC_{0\text{-last}}$ is only 9% higher in pediatrics compared to adults.

The mean PK parameters of EXPAREL in 6 to <12 y was compared to the adults in cardiac procedures in Table 1.3.3.2. The comparative mean plasma bupivacaine PK profiles of EXPAREL in 6 to <12 y and adults in cardiac procedure is shown below in Figure 1.3.3.

Table 1.3.3.2: Mean PK parameters of EXPAREL in 6 to <12 y (n=21) and adults in cardiac procedure.

PK Parameter *	**Pediatrics, 6 to 12 y EXPAREL 4 mg/kg (Study 319, cardiac) (N=21)**	**Adults EXPAREL 266 mg (Study 118, cardiac) (N=5)**	**Ratio Pediatrics 6 to <12 y / Adults**
Cmax	447 (243)	445 (120)	1.00 (no change)
$AUC_{0\text{-24h}}$ (ng.h/mL)	6617 (3107)	5515 (1000)	1.20 (20% higher)
$AUC_{0\text{-36h}}$ (ng.h/mL)	10222 (4304)	8823 (1227)	1.16 (16% higher)
$AUC_{0\text{-48h}}$ (ng.h/mL)	13324 (5523)	11585 (1840)	1.15 (15% higher)
$AUC_{0\text{-60h}}$ (ng.h/mL)	15856 (6974)	13297 (2840)	1.19 (19% higher)
$AUC_{0\text{-last}}$ (ng.h/mL)	16776 (7936)[1]	14277 (3449)[2]	1.18 (18% higher)
AUC_{inf} (ng.h/mL)	NR[1]	15768 (4530)	
Tmax (h)	22.7 (0.21, 54.5)	0.58 (0.55, 36.0)	

*Arithmetic mean (standard deviation) except T_{max} where it is median (minimum, maximum).
[1] $AUC_{0\text{-last}}$, 0-72 h. The median last sampling time point is 69 h in pediatric cardiac surgery.
[2] $AUC_{0\text{-last}}$, 0-72 h
NR[1] = Not reported, since the terminal elimination phase was not adequately characterized in sufficient number of patients.

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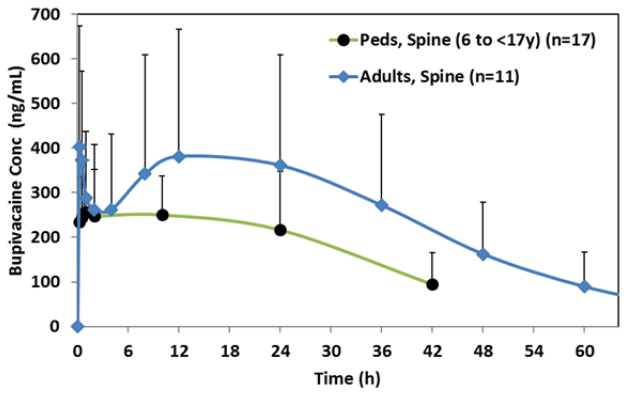
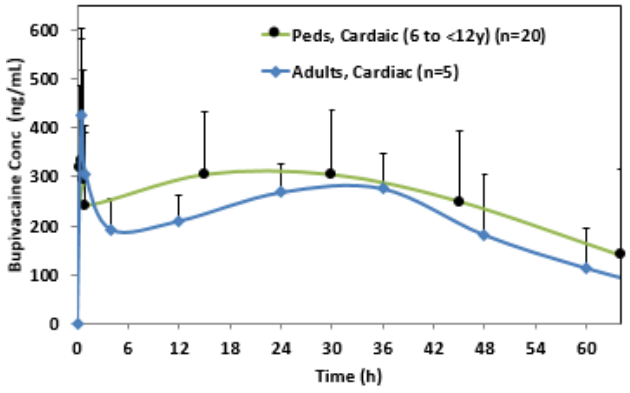
Figure 1.3.3: Comparative mean plasma bupivacaine PK profiles of EXPAREL in pediatric subjects versus adults in spine and cardiac procedures.

Spine: Pediatrics, 6 to <17 y versus adults	Cardiac: Pediatrics, 6 to <12 y versus adults
	

1.3.4 Other PK comparisons

During the internal team meetings, there were discussions about how the bupivacaine exposures from EXPAREL were compared between highly vascular procedures in adults. Hence, the PK of EXPAREL is compared between highly vascular procedures in adults (cardiac, spine in this efficacy supplement and hemorrhoidectomy procedures in the original NDA submission) and between cardiac versus spine in pediatrics. More details about this comparison are discussed below.

Additionally, the PK parameters of EXPAREL versus Bupivacaine HCl in pediatric spine surgery, and the effect of surgical incision-length on PK parameters in spine and cardiac procedures were also reviewed in this section.

1.3.4.1 Comparison of PK in highly vascular procedures in adults (cardiac, spine and hemorrhoidectomy procedures):

For conducting the pediatric PMR studies of EXPAREL via local infiltration, as per discussions between the Applicant and Agency, two highly vascular procedures (e.g., cardiac and spine procedures) where the highest systemic levels of bupivacaine and corresponding risk for systemic toxicity would be expected, and require a longer hospitalization were selected in order to evaluate the PK and systemic safety of EXPAREL. This selection approach enables evaluation of EXPAREL systemic safety in the worst possible scenarios of spine and cardiac surgeries in pediatrics.

The PK obtained in these two highly vascular procedures in pediatrics were compared to the adult subjects who received EXPAREL 266 mg via local infiltration in matching highly vascular, higher-risk spine and thoracotomy procedures for systemic safety and efficacy evaluation. As

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shown earlier in the review, the observed PK differences between pediatrics and adults cannot be considered drastically different in these two procedures.

In the NDA studies of EXPAREL, applicant evaluated EXPAREL 266 mg (highest dose) via local infiltration in hemorrhoidectomy procedure in adults. Based on discussion with clinical team, the hemorrhoidectomy is a highly vascular procedure and is likely to have the highest systemic drug exposure. A PK comparison is conducted between the highly vascular procedures in adults available so far for EXPAREL [hemorrhoidectomy (study in original NDA submission) and spine and cardiac surgeries (studies in this supplement)] in Table 1.3.4.1. The results show that the cardiac and spine procedures show comparable $AUC_{0\text{-}inf}$ values while slightly lower Cmax in comparison to hemorrhoidectomy (Table 1.3.4.1). Overall, since in adults, the cardiac and spine procedures being highly vascular procedures and showed comparable systemic exposure to hemorrhoidectomy, the systemic exposure from cardiac and spine procedures may represent worst case scenario for highest possible systemic exposure and thereby for worst possible systemic adverse events. Relating this to pediatrics, if in these highly vascular procedures of cardiac and spine procedures there is no concern of systemic adverse events, then in other pediatric surgical procedures, systemic safety is also unlikely to be a concern, since other less invasive, less vascular pediatric surgical procedures will result in lower systemic exposure.

The comparative mean plasma bupivacaine PK profiles of EXPAREL in cardiac versus spine procedures in adults is shown below in Figure 1.3.4.

Table 1.3.4.1: Mean PK parameters of EXPAREL in highly vascular procedures [spine and cardiac surgeries (studies in this supplement) and hemorrhoidectomy (study in original NDA submission)] in adults.

Parameter Mean (SD)	**This supplement S-035**		**Study submitted in original NDA (data from Exparel label)**
	EXPAREL 266 mg Cardiac, adults N=5 (study 118)	**EXPAREL 266 mg Spine, adults N=11 (study 117)**	**Hemorrhoidectomy 266 mg (20 mL) N=25**
Cmax (ng/mL)	445 (120)	513 (268)	867 (353)
$AUC_{0\text{-}24h}$ (ng.h/mL)	5515 (1000)	8229 (5572)	NE
$AUC_{0\text{-}36h}$ (ng.h/mL)	8823 (1227)	12023 (8111)	NE
$AUC_{0\text{-}48h}$ (ng.h/mL)	11585 (1840)	14619 (9860)	NE
$AUC_{0\text{-}last}$ (ng.h/mL)	14277 (3449) [1]	17214 (11621) [2]	16,867 (7868) [1]
AUC_{inf} (ng.h/mL)	15768 (4530)	17917 (12187)	18,289 (7569)
Tmax (h)	0.58 (0.55, 36.0)	0.6 (0.2, 37.0)	0.5 (0.25, 36)

*Arithmetic mean (standard deviation) except T_{max} where it is median (minimum, maximum)

[1] $AUC_{0\text{-}last}$, 0-72h ; [2] $AUC_{0\text{-}last}$, 0-96h.

NE: not evaluated

1.3.4.2 Cardiac (6 to <17 y) versus spine (12 to <17 y) procedures in pediatrics

As per 319 study design, the 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 y of

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age and Group 2 enrolled subjects 6 to <12 y of age. Group 1 (12 to <17 y) underwent only spine surgery, while Group 2 (6 to <12 y) underwent spine or cardiac surgery. As a result, all pediatric cardiac surgery patients were in the age group of 6 to <12 y age group (n=21), while none in 12 to <17 y age group. For pediatrics spine procedures, 15 subjects were in 12 to <17 y age group, while only two subjects were in 6 to <12 y age group. Since, mean PK values of 12 to <17 y age group were numerically similar to that of 6 to <12 y age group, both age groups were combined to represent 6 to <17 y (n=17).

When Cmax and the partial areas up to 40 h were compared between spine procedure (6 to 17 y) and cardiac procedure (6 to 12 y), the cardiac procedure showed 25% higher Cmax and ~30% higher $AUC_{0\text{-}40\ h}$ compared to spine procedure.

The $AUC_{0\text{-}last}$ or AUC_{inf} parameters in spine cannot be compared for the reasons mentioned above in section 1.3.2. The Tmax is not compared for the reasons mentioned above in section 1.3.2.

The mean PK parameters of EXPAREL in pediatrics cardiac and spine procedures is shown in Table 1.3.4.2. The comparative mean plasma bupivacaine PK profiles of EXPAREL in pediatrics' cardiac and spine procedures are shown below in Figure 1.3.4.

Table 1.3.4.2: Mean PK parameters of EXPAREL in cardiac and spine procedures in pediatrics.

PK Parameter *	**Pediatrics, EXPAREL 4 mg/kg (Study 319)**			
	Spine 6 to <12 y (N=2)[$]	**Spine** 12 to <17 y (N=15)	**Spine** 6 to <17 y (N=17)	**Cardiac** 6 to <12 y (N=21)
Cmax (ng/mL)	320 (203, 436)	357 (125)	353 (125)	447 (243)
$AUC_{0\text{-}24h}$ (ng.h/mL)	6469 (4207, 8732)	5800 (1482) (n,14)	5883 (1625) (n,16)	6617 (3107)
$AUC_{0\text{-}36h}$ (ng.h/mL)	8810 (5468, 12151)	8117 (2385) (n,14)	8203 (2545) (n,16)	10222 (4304)
$AUC_{0\text{-}40h}$ (ng.h/mL)	9365 (5739, 12990)	8699 (2681) (n,14)	8782 (2834) (n,16)	11286 (4791)
$AUC_{0\text{-}48h}$ (ng.h/mL)	NR[1]	NR[1]	NR[1]	13324 (5523)
$AUC_{0\text{-}60h}$ (ng.h/mL)	NR[1]	NR[1]	NR[1]	15856 (6974)
$AUC_{0\text{-}last}$ (ng.h/mL)	NR[1]	NR[1]	NR[1]	16776 (7936)[1]
AUC_{inf} (ng.h/mL)	NR[2]	NR[2]	NR[2]	NR[2]
Tmax (h)	7.4 (12.3, 2.4)	1.1 (0.30, 26.1)	1.1 (0.30, 26.1)	22.7 (0.21, 54.5)

*Arithmetic mean (standard deviation) except T_{max} where it is median (minimum, maximum)

[$] N=2, hence mean (individual values) are shown

[1] $AUC_{0\text{-}last}$, 0-72 h. The median last sampling time point is 69 h in pediatric cardiac surgery.

NR[1]: Not reported, since the last sampling time point varies among different patients.

NR[2]: Not reported, since the terminal elimination phase was not adequately characterized in sufficient number of patients.

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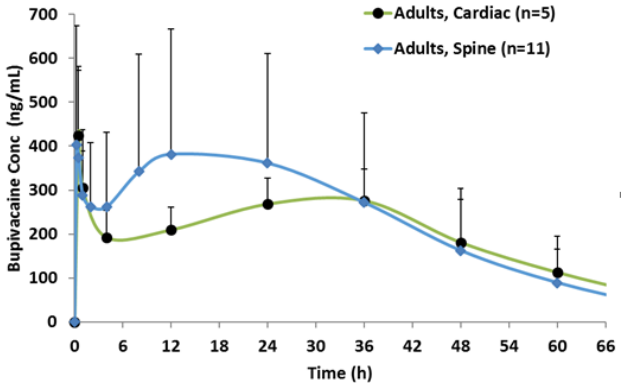
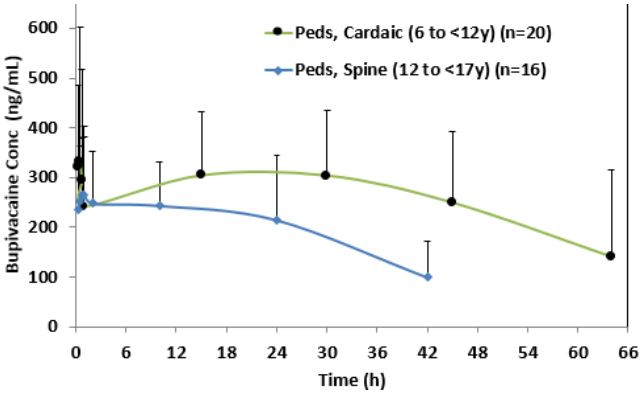
The comparative mean plasma bupivacaine PK profiles of EXPAREL in cardiac versus spine procedure in adults, and cardiac versus spine procedure in pediatrics are shown in Figure 1.3.4A.

Figure 1.3.4: Comparative mean plasma bupivacaine PK profiles of EXPAREL in cardiac versus spine procedure in adults, and cardiac versus spine procedure in pediatrics

Adults (cardiac versus spine)	**Pediatrics cardiac (6 to <12 y) versus spine (12 to <17 y)**
	

1.3.4.3 Comparison of PK parameters between EXPAREL and Bupivacaine HCl (in 12 to <17 y).

As per 319 study design, the Group 1 (12 to <17 y) underwent only spine surgery. The Group 1 included control arm, bupivacaine HCl at 2 mg/kg (not to exceed a maximum total dose of 175 mg). The EXPAREL 4 mg/kg (not to exceed a maximum total dose of 266 mg) PK parameters were compared to bupivacaine HCl 2 mg/kg.

The EXPAREL 4 mg/kg, at 2-fold higher dose compared to bupivacaine HCl at 2 mg/kg showed 37% lower Cmax and ~ 70% higher $AUC_{0\text{-}40\ h}$. The $AUC_{0\text{-}last}$ or AUC_{inf} parameters in cannot be compared for the reasons mentioned above in section 1.3.2. The Tmax is not compared for the reasons mentioned above in section 1.3.2.

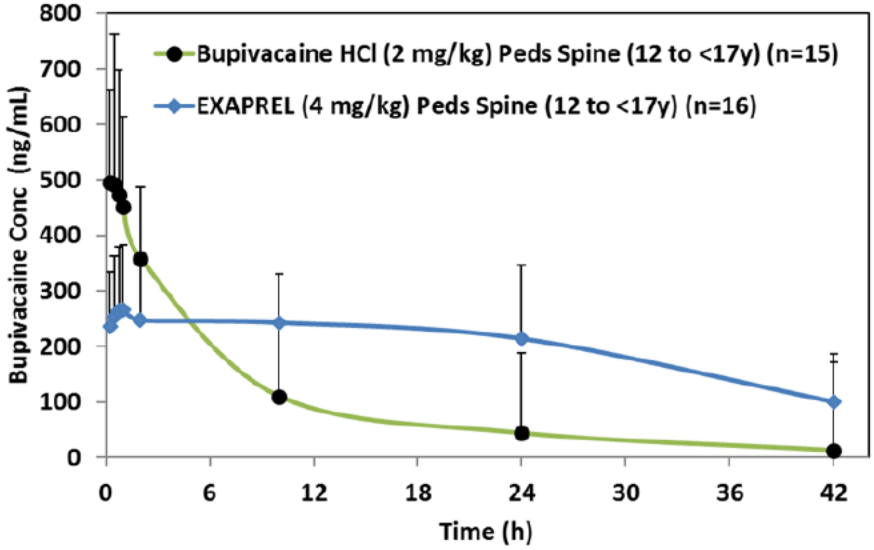
The mean PK parameters of EXPAREL and bupivacaine HCl is shown in Table 1.3.4.3. The comparative mean plasma bupivacaine PK profiles of EXPAREL 4 mg/kg and bupivacaine HCl 2 mg/kg in spine procedure in 12 to <17 y is shown in Figure 1.3.4.3.

Table 1.3.4.3: Mean PK parameters of EXPAREL 4 mg/kg and bupivacaine HCl 2 mg/kg in spine procedure in 12 to <17 y.

Parameter*	EXPAREL 4 mg/kg 12 to <17 Y (N=15)	Bupivacaine HCl 2 mg/kg 12 to <17 Y (N=15)	Ratio Exparel (4 mg/kg) / Bup HCl (2 mg/kg)
Cmax (ng/mL)	357 (125) (n,15)	564 (321)	0.63 (37% lower)
$AUC_{0\text{-}24h}$ (ng.h/mL)	5800 (1482) (n,14)	4561 (2035)	1.27 (27 % higher)
$AUC_{0\text{-}36h}$ (ng.h/mL)	8177 (2385) (n,14)	5021 (2373)	1.63 (63% higher)
$AUC_{0\text{-}40h}$ (ng.h/mL)	8699 (2681) (n,14)	5135 (2458)	1.69 (69 % higher)
$AUC_{0\text{-}last}$ (ng.h/mL)	NR[1]	5233 (2538)[1]	
AUC_{inf} (ng.h/mL)	NR[2]	5709 (3282)	
Tmax (h) [3]	1.1 (0.30, 26.1)	0.88 (0.33, 2.45)	

*Arithmetic mean (standard deviation) except T_{max} where it is median (minimum, maximum)
[1]$AUC_{0\text{-}last}$, 0-48h (median last sampling time point is 48h).
NR[1], Not reported, since the last sampling time point varies among different patients.
NR[2], Not reported, since the terminal elimination phase was not adequately characterized in sufficient number of patients.

Figure 1.3.4.3: Comparative mean plasma bupivacaine PK profiles of EXPAREL 4 mg/kg and bupivacaine HCl 2 mg/kg in spine procedure in 12 to <17 y.



1.3.4.4. Effect of surgical incision-length on the PK parameters

The effect of surgical incision-length on the absorption of EXPAREL (in terms of PK parameters Cmax and $AUC_{0\text{-}24}$) was evaluated in pediatric and adults in both spine and cardiac surgeries. Since the surgical incision-length will mainly affect the initial absorption phase, the correlation was compared between the variables', surgical incision-length and Cmax or partial $AUC_{0\text{-}24}$.

The R^2 values (coefficient of determination) for the variables' incision-length and Cmax or $AUC_{0\text{-}24}$ in both spine or cardiac procedures are low, ranging between 5E-6 to 0.27 in both adults

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and pediatrics. Similar R^2values were observed for incision-length and AUC_{inf} values in adult procedures or $AUC_{0\text{-}40h}$ for pediatric spine or $AUC_{0\text{-}60h}$ for pediatric cardiac procedures (data not shown).

Based on the low R^2 values between incision-length and Cmax or $AUC_{0\text{-}24}$ in both adults' and pediatrics' spine or cardiac procedures, it appears that there is no significant association between surgical incision length and the absorption of EXPAREL based on available data.
The surgical incision lengths and PK parameters in spine procedure and cardiac procedures is shown in Table 1.3.4.4A and Table 1.3.4.4B, respectively. The correlation between surgical incision lengths and Cmax or $AUC_{0\text{-}24}$ in spine and cardiac procedures is shown in Figure 1.3.4.4.

Table 1.3.4.4A: Surgical incision length and PK parameters in spine procedure in adults and pediatrics.

	Spine Surgery		
Population	Pediatrics, 12 to <17 y		Adults
Study Drug	EXPAREL 4 mg/kg (N=15)	Bupivacaine HCl 2 mg/kg (N=15)	EXPAREL 266 mg (N=11)
Incision length (cm)			
Mean (SD)	29 (7)	31 (4)	14 (6)
Min, Max	16, 37	21, 40	8, 30
PK parameter			
Cmax (ng/mL)	357 (125)	564 (321)	513 (268)
$AUC_{0\text{-}24h}$ (ng.h/mL)	5800 (1482) (n,14)	4561 (2035)	8229 (5572)

Table 1.3.4.4B: Surgical incision length and PK parameters in cardiac procedure in adults and pediatrics.

	Cardiac Surgery	
Population	Pediatrics, 6 to <12 y	Adults
Study Drug	EXPAREL 4 mg/kg (N=21)	EXPAREL 266 mg (N=5)
Incision length (cm)		
Mean (SD)	13 (4)	18 (13)
Min, Max	5, 21	1.2, 37
PK parameter		
Cmax (ng/mL)	447 (243)	445 (120)
$AUC_{0\text{-}24h}$ (ng.h/mL)	6617 (3107)	5515 (1000)

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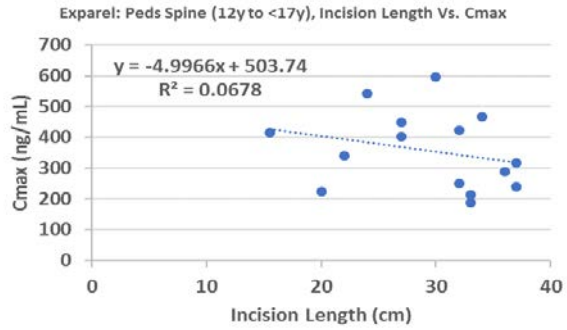
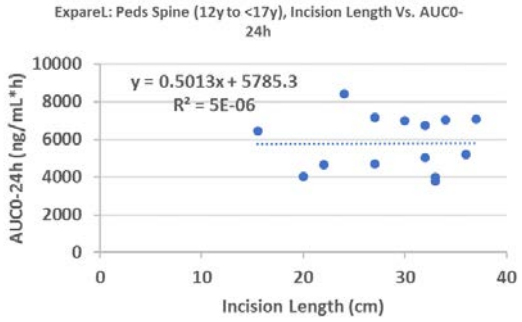
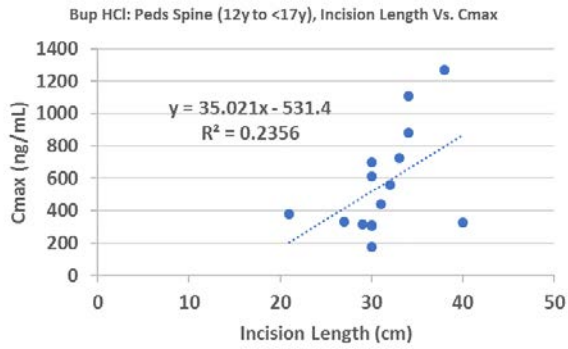
Figure 1.3.4.4: The correlation between surgical incision lengths and Cmax or AUC_{0-24} in spine and cardiac procedures.

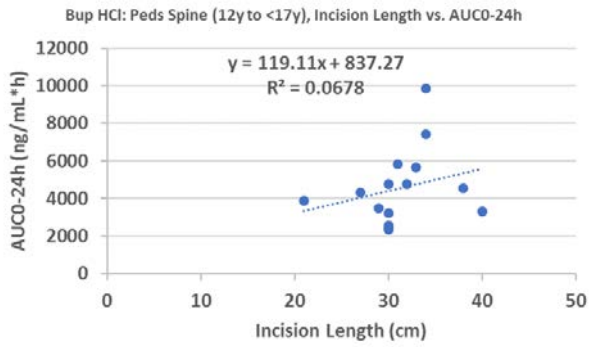
EXPAREL, Pediatric Spine



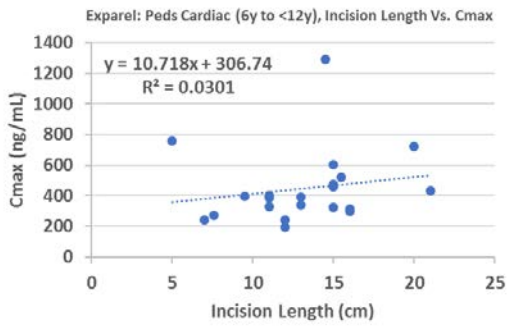


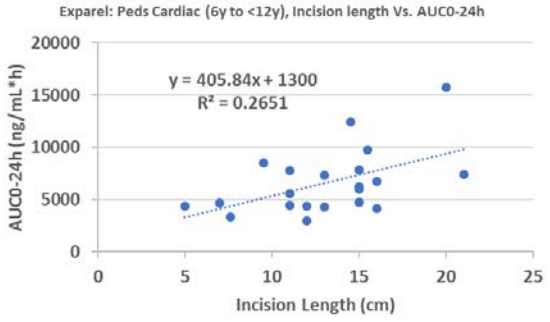
Bupivacaine HCl, Pediatric Spine



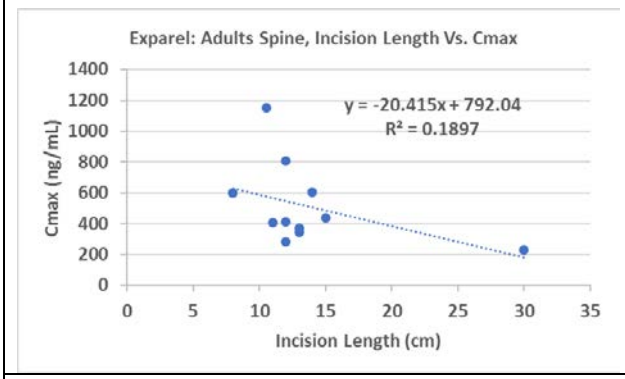


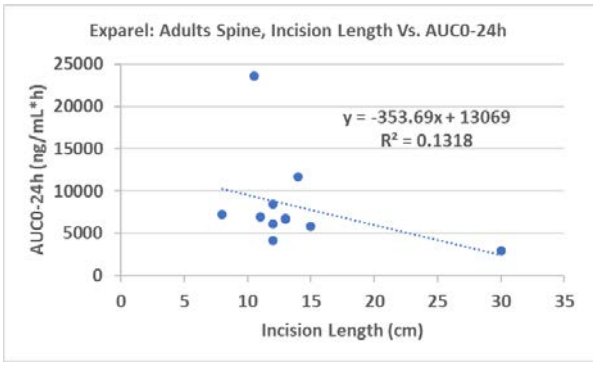
EXPAREL, Pediatric Cardiac



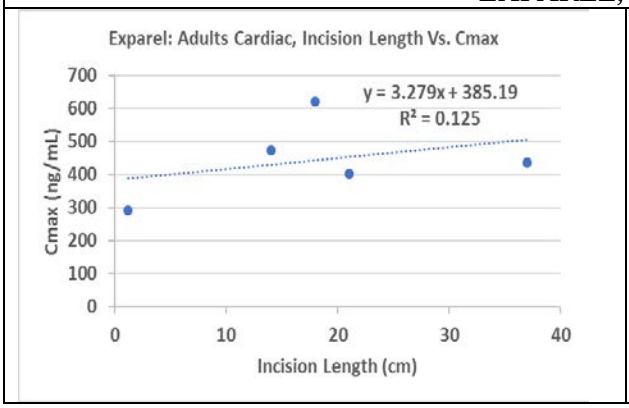


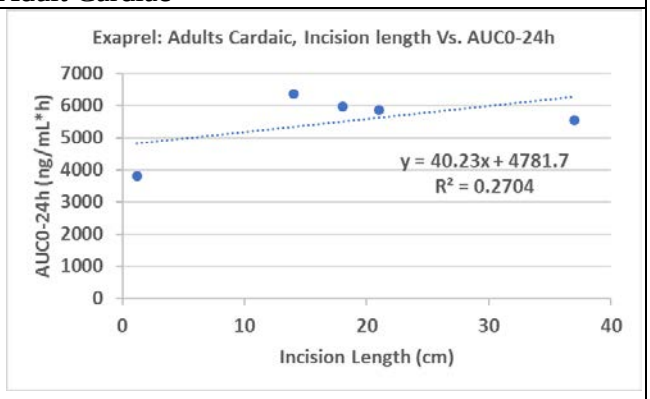
EXPAREL, Adult Spine





EXPAREL, Adult Cardiac





1.3.4.5 Maximum observed bupivacaine concentrations:

In this supplement, the bupivacaine concentrations of > 1000 ng /mL were observed in three subjects as follows:

- 1290 ng/mL (EXPAREL 4 mg/kg, pediatric cardiac procedure)
- 1270 ng /mL (BUPIVACAINE HCL 2 mg/kg, pediatric spine procedure)
- 1150 ng (EXPAREL 266 mg, adults spine procedure)

It was confirmed with the clinical team that none of subjects in this supplement were associated with local anesthetic systemic toxicity (LAST) related symptoms.

PK Comparison Conclusions:

In general, for peri-operative products like EXPAREL, the PK varies due to several factors, e.g., type of surgery, vasculature, surgeon and type of drug administration (number of infiltration spots), anatomical site etc. The following comparisons are made between adults and pediatrics in spine and cardiac surgical procedures.

- Comparison of EXPAREL PK between adults and pediatrics:
    - The pediatric subjects underwent matching surgical procedures in spine and cardiac as that of adults. In spine procedure, compared to the adults dosed at EXPAREL 266 mg, the pediatric subjects' (6 to <17 y) dosed at 4 mg/kg showed ~ 30% lower Cmax and 30% lower partial AUCs up to $AUC_{0\text{-}40h.}$ In cardiac

procedures, compared to the adults, the pediatric subjects (6 to <12 y) showed no change in Cmax and ~18% increase in $AUC_{0\text{-last}}$. Owing to a cross-study comparison and several factors that may affect absorption of EXPAREL, the observed PK differences between pediatrics dosed at 4 mg/kg and adults dosed at 266 mg cannot be considered significantly different. Hence, it is reasonable to say that the exposure in pediatrics in matching surgical procedures of cardiac and spine surgeries can be considered similar to the adults.

- Comparison of EXPAREL PK between cardiac and spine procedures:
    - Adults: In adults, for EXPAREL 266 mg, the cardiac procedure results in 13% lower Cmax, 10% lower AUC_{inf} compared to spine procedure.
    - Pediatrics: In pediatrics, for EXPAREL 4 mg/kg, the cardiac procedure (6 to 12 y) showed 25% higher Cmax and ~30% higher $AUC_{0\text{-}40\ h}$ compared to spine procedure (6 to 17 y).
- Comparison of EXPAREL (4 mg/kg) and Bupivacaine HCl (2 mg/kg) in 12 to <17 y in spine procedure:
    - The EXPAREL at 2-fold higher dose, 4 mg/kg compared to bupivacaine HCl at 2 mg/kg showed 37% lower Cmax and ~ 70% higher $AUC_{0\text{-}40\ h}$ in 12 to <17 y pediatrics spine procedure.
- Effect of surgical incision-length on the EXPAREL PK parameters:
    - Based on the low R^2 values between the variables, incision-length and Cmax or $AUC_{0\text{-}24}$ in both adults' and pediatrics' spine or cardiac procedures, it appears that there is no significant association between surgical incision-length and the absorption of EXPAREL based on available data.

1.4 Bioanalysis:

Since the extrapolation of pediatric efficacy may be based on PK exposure, the Office of Study Integrity and Surveillance (OSIS) inspection for Study 319 was requested. Following are the details of the sites that were requested for inspection.

- Bioanalytical Site: (b) (4)
- Clinical Site: Site 116 (Variety Children's Hospital db/a Nicklaus Children's Hospital, Miami, FL),
    - The Study 402-C-319 is a multicenter study in pediatrics, which was conducted across US. The highest number pediatric patients with PK data were evaluated in Site 116 (Variety Children's Hospital db/a Nicklaus Children's Hospital, 3100 SW 62nd Avenue, Miami, FL 33155), followed by Site 111 (Riley Hospital for Children, 705 Riley Hospital Drive, Indianapolis, IN 46202). Hence for clinical site inspection, we requested OSIS to investigate Site 116, which is preferred clinical site because of maximum number of subjects with PK data, and if feasible also to inspect Site 111.

The bioanalytical assay performance for pediatric and adult studies conducted in this supplement was evaluated, and it was found that the accuracy and precision of bupivacaine from EXPAREL were within the acceptance the range:

- Accuracy (expressed as % bias): < ± 15%
- Precision (expressed as % CV): < 15%

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OSIS inspection conclusion for bioanalysis portion of Study 319 (DARRTS review dated 01/05/2021):

"The Office of Study Integrity and Surveillance (OSIS) conducted a Remote Record Review (RRR) of the analytical portion of Study (b) (4)/15/19 (Protocol# 402-C-319) under NDA 022496/S035 (Bupivacaine Liposome Injection Suspension) conducted at (b) (4). An onsite inspection was not possible due to the disruption of inspectional activities by the COVID-19 global pandemic. We did not observe any objectionable conditions during the RRR that would impact reliability of study data".

Recommendation

"Based on our review of the RRR findings, we conclude that bioanalytical data from the reviewed study are reliable to support a regulatory decision".

OSIS inspection conclusion for clinical portion of Study 319:

Based on email discussion, OSIS is planning to conduct an RRR and submit a review by 2/26/2021. When this review is uploaded to DARRTS, the OSIS inspection conclusion for clinical portion of the review is still awaited.

1.5 Labeling

When this review is documented in DARRTS, the labeling changes are ongoing. The proposed labeling changes were made to the label based on studies conducted in pediatrics and adults.

Table 4: Summary of Pharmacokinetic Parameters for Bupivacaine after Administration of Single Doses of EXPAREL via Local Infiltration and Interscalene Brachial Plexus Nerve Block in Adult Patients

Parameters*	Surgical Site Administration via Local Infiltration				Interscalene Brachial Plexus Nerve Block
	Bunionectomy 106 mg (8 mL)	Hemorrhoidectomy 266 mg (20 mL)	Spine Surgery[1] 266 mg	Cardiac Surgery[2] 266 mg	Total Shoulder Arthroplasty 133 mg (10 mL)
	(N=26)	(N=25)	(N=11)	(N=5)	(N=12)
C_{max} (ng/mL)	166 (92.7)	867 (353)	513 (268)	445 (120)	207 (137)
T_{max} (h)	2 (0.5, 24)	0.5 (0.25, 36)	0.6 (0.2, 37)	0.6 (0.6, 36)	48 (3, 74)
$AUC_{0\text{-}40h}$ (h x ng/mL)	NE	NE	13035 (8782)	9867 (1332)	NE
$AUC_{(0\text{-}last)}$ (h x ng/mL)	5864 (2038)[3]	16,867 (7868)[3]	17214 (11621)[4]	14277 (3449)[3]	11484 (8615)[5]
$AUC_{(inf)}$ (h x ng/mL)	7105 (2283)	18,289 (7569)	17917 (12187)	15768 (4530)	11590 (8603)
$t_{½}$ (h)	34 (17)	24 (39)	9 (2)	14 (6)	11 (5)

* Arithmetic mean (standard deviation) except T_{max} where it is median (minimum, maximum).
[1] Subjects undergoing open posterior spinal fusion or reconstructive surgery
[2] Subjects undergoing posterolateral thoracotomy
[3] $AUC_{0\text{-}last}$, 0-72h ; [4] $AUC_{0\text{-}last}$, 0-96h ; [5] $AUC_{0\text{-}last}$, 0-120h
NE: Not evaluated

Table 5 : Summary of Pharmacokinetic Parameters for ~~Bupivacaine after~~ Administration of Single Doses of EXPAREL via Local Infiltration in Pediatric Patients Aged 6 to Less Than 17 Years Old.

Parameters*	Spine Surgery	(b) (4)	Cardiac Surgery
	EXPAREL 4 mg/kg (Maximum 266 mg)		~~EXPAREL~~ 4 mg/kg (Maximum 266 mg)
	6 to <17 years (N = 17)		~~6 to <12 years~~ (N = 21)
C_{max} (ng/mL)	353 (125)		447 (243)
T_{max} (h)	1.2 (0.3, (b) (4)		22.7 (0.2, (b) (4)
$AUC_{(0\text{-}40\ h)}$ (h x ng/mL)	8782 (2834)		11286 (4791)
$AUC_{(0\text{-}last)}$ (h x ng/mL)	NR[1]		16776 (7936)[1]
$AUC_{(inf)}$ (h x ng/mL)	NR[2]		NR[2]
$t_{½}$ (h)	NR[2]		NR[2]

Arithmetic mean (standard deviation) except T_{max} where it is median (minimum, maximum).
[1] $AUC_{0\text{-}last}$, 0-72h
NR[1] = Not reported, since the last sampling time point varies among different patients.
NR[2] = Not reported, since the terminal elimination phase was not adequately characterized in sufficient number of patients.

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