FDA Briefing Document

Anesthetic and Analgesic Drug Products Advisory Committee Meeting

February 14 and February 15, 2018

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought supplemental new drug application (sNDA) 022496/S-009, Exparel (bupivacaine liposome injectable suspension), submitted by Pacira Pharmaceuticals, Inc., to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Division Director Memo

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

M E M O R A N D U M

DATE: January 18, 2018

FROM: Sharon Hertz, MD
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members of the Anesthetic and Analgesic Drug Products Advisory Committee, and Invited Guests

RE: Overview of the February 14 and 15, 2018, AADPAC meeting to discuss NDA 022496 (Exparel)

At this meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), we will be discussing Pacira Pharmaceutical's supplemental NDA 022496 for bupivacaine liposome injectable suspension. The supplemental NDA (sNDA) was originally submitted on May 5, 2014, and the proposed indication was postsurgical analgesia via nerve block. The application was not approved after the first review cycle, and a Complete Response action letter was issued on February 27, 2015.

Pacira Pharmaceuticals (the Applicant) submitted a response to address the deficiencies noted in the action letter in October 2016. In this submission, the Applicant has submitted the following in support of their application:

- The results of two new clinical trials, Study 402-C-326, femoral blocks in the setting of a total knee arthroscopy, and Study 402-C-327, brachial plexus blocks in the setting of a total shoulder arthroplasty.
- A re-analysis of the safety data

In addition, Pacira has requested to change the indication from "administration into the surgical site to produce postsurgical analgesia" to "single-dose infiltration to produce local analgesia and as a nerve block to produce regional analgesia".

There are a lot of data for consideration with this supplemental NDA. The efficacy of Exparel is based on the local effects of bupivacaine while the safety is based on both local effects (e.g., time to return of motor function) and on systemic levels (e.g., risk of cardiac conduction effects). To support the request for an indication for use as a nerve block to produce regional analgesia, all of the nerve block studies conducted by Pacira will be presented, including the two new studies submitted in the supplemental NDA and nerve block studies previously submitted to the NDA. To support the request to change the indication from "administration into the surgical site to produce postsurgical analgesia" to "single-dose infiltration to produce local analgesia" the studies supporting the local infiltration along with the sponsor's rationale will be presented. The data on systemic exposure of bupivacaine will be presented including the extent of variability observed in the systemic pharmacokinetic profile based on the procedure, total dose, method of administration, and anatomical site of administration.

At the February 2018, meeting, the Committee will be asked to consider the following points:

1. **Whether the Applicant has provided sufficient information to support any of the proposed changes to the indication.**

2. **What data are necessary to adequately evaluate the benefit and risks of an extended-release local anesthetic, e.g., comparator arms.**

3. **Whether there are issues with this supplemental NDA that warrant additional studies and, if so, should these studies be conducted before or after approval.**

4. **Whether the efficacy, safety, and overall risk-benefit profile of Exparel support the approval of this supplemental application.**

The Division and the Agency are grateful to the members of the committee and our invited guests for taking time from your busy schedules to participate in this important meeting. Thank you in advance for your advice, which will aid us in making the most informed and appropriate decision possible.

Regulatory Summary

Exparel (bupivacaine liposome injectable solution) consists of microscopic liposomes (DepoFoam drug delivery system), forming a honeycomb-like structure of numerous non-concentric internal aqueous chambers containing bupivacaine. Each chamber is separated from adjacent chambers by lipid membranes. Bupivacaine, an amide-type local anesthetic, is the active ingredient released from the DepoFoam particles through reorganization of the barrier lipid membranes and subsequent diffusion of the drug over time.

Exparel was approved on October 28, 2011, based on the results of two Phase 3, placebo-controlled clinical trials – one in patients undergoing bunionectomy, and one in patients undergoing hemorrhoidectomy.

In May 2014, the Applicant submitted a supplemental NDA for the indication of post-surgical analgesia via the use of a nerve block. The Applicant submitted the results of two studies in support of this supplemental application. Study 402-C-322 (Study 322) evaluated the use of intercostal nerve block in subjects undergoing posterolateral thoracotomy Study 302-C-323 (Study 323) evaluated the use of femoral block in subjects undergoing total knee arthroplasty. The study had two parts: Part 1 was intended to provide dose-finding information and Part 2 to evaluate the magnitude and duration of the analgesic effect using the dose determined in Part 1.

Study 322 failed to demonstrate the efficacy of Exparel against placebo. Study 323 was able to demonstrate the efficacy of Exparel against placebo, but the trial was failed to demonstrate the duration of the femoral nerve block and, consequently, an adequate characterization of the safety profile of the proposed dose of Exparel in the setting of a femoral nerve block.

The supplemental application was not approved, and the Applicant was advised that, in order to pursue the proposed indication, the Applicant would need to provide evidence of efficacy from an adequate and well-controlled study in at least one additional clinical setting, and adequately characterize the safety profile of Exparel in this clinical setting.

The February 27, 2015 letter noted the following:

> 1. You have failed to adequately characterize the efficacy of Exparel for the proposed indication. You have submitted the result of one study demonstrating efficacy in the setting of femoral nerve block, but the second efficacy study failed to demonstrate efficacy for intercostal nerve block.
>
> To address this deficiency, provide evidence of efficacy from an adequate and well-controlled study in at least one additional clinical setting.
>
> 2. You have not adequately characterized the safety profile of Exparel in the setting of femoral nerve block for postsurgical analgesia, or for the broader indication of nerve block for postsurgical analgesia.

a) The pharmacokinetic evaluation of bupivacaine following administration of 266 mg of Exparel as a femoral nerve block, based on subjects with complete pharmacokinetic profiles, demonstrated that the median time of maximum concentration (T_{max}) was greater than the 72-hour period of assessment planned in the study protocol. Your assessments for systemic toxicity were intended to continue through T_{max}, but ceased at 72 hours for most patients.

b) There was inadequate capture of plasma bupivacaine concentrations at the time of cardiac or neurologic symptoms.

c) There was inadequate reporting of cardiac safety data. It appears that, although the study called for continuous Holter monitoring, the Holter assessments were limited to a maximum of three points in time for each subject. For example, analysis of the Holter data requested for subject 301-006 revealed a number of arrhythmias not previously reported or captured as adverse events. Furthermore, as specified in the protocol, 12-lead EKGs were not performed when either arrhythmias or other clinically relevant signs or symptoms occurred.

d) There are inadequate data to characterize the onset and duration of the femoral block.

a. In Study 402-C-323, sensory assessments were discontinued prior to the onset of the sensory deficit in a large proportion of patients.

b. You have not provided adequate support for the use of the walker-assisted 20-meter walk test as a measure of quadriceps femoris strength.

To address this deficiency, provide the following:

1. Conduct a clinical trial of Exparel in which clinical safety outcomes are followed until the upper limit of the expected Tmax, and/or resolution of the femoral nerve block. Include assessments of sensory and motor function that demonstrate the onset and resolution of the sensory and motor deficits from the nerve block.

2. Submit an analysis of all Holter data for all subjects collected in Studies 402-C-323 and 402-C-322. Cardiac arrhythmias noted on Holter or ECG should be identified and classified as adverse events. Bradycardia and tachycardia noted on the 72-hour Holter monitor should be incorporated into your assessment of incidence of potentially clinically significant abnormal vital signs.

In the current submission, the Applicant has submitted the results of two additional clinical trials, Study 402-C-326 (Study 326) and Study 402-C-327 (Study 327). Study 326 enrolled patients undergoing a total knee arthroplasty and administered a femoral block and Study 327 enrolled patients undergoing a total shoulder arthroplasty due for a rotator cuff repair, and administered a brachial plexus block.

Clinical Pharmacology Summary

Based on the clinical studies in the original NDA submission, it was known that:

1. The pharmacokinetic (PK) profile of EXPAREL varies with different surgical procedures and the rate of systemic absorption of bupivacaine from EXPAREL is dependent upon the total dose, the route, and the vascularity of administrated site. Hence, the time to maximum level (Tmax) and extent of exposure as area under the curve (AUC) of bupivacaine from EXPAREL vary with surgical procedures, and

2. EXPAREL 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.

The above two points were included in the EXPAREL approved label.

Supplement S-009

The details of the 2017-conducted nerve block studies are below:

Study 402-C-326- Femoral Nerve Block for Total Knee Arthoplasty:
Study 326 was a multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy, safety, and pharmacokinetics of femoral nerve block with EXPAREL for postsurgical analgesia in subjects undergoing total knee arthroplasty.

Subjects were randomized in a 1:1:1 ratio to receive a single 20 mL dose of one of the following treatments at least 1 hour prior to surgery using ultrasound guidance:

- EXPAREL 133 mg (10 mL EXPAREL + 10 mL normal saline)
- EXPAREL 266 mg (20 mL EXPAREL)
- Placebo (normal saline)

In addition to EXPAREL, 8 mL of bupivacaine HCl (0.5%) diluted with 8 mL of normal saline was administered as a periarticular infiltration before placement of the prosthesis in all three treatment groups. Therefore, the total bupivacaine dose in each group was:

- EXPAREL 133 mg + 40 mg bupivacaine HCl (0.5%) = 173 mg
- EXPAREL 266 mg + 40 mg bupivacaine HCl (0.5%) = 306 mg
- Placebo + 40 mg bupivacaine HCl (0.5%) = 40 mg

In this study, both partial and full PK sampling was conducted among different subjects. The PK parameters were calculated from subjects who had full PK sampling.

Results:

Postanesthesia Care Unit (PACU blood-draw):
The first blood sample drawn after the completion of surgery and then transfer to the PACU is termed as 'PACU PK blood-draw'. The time sequence of events between study- drug administration and PK-blood sampling in the study is as follows.

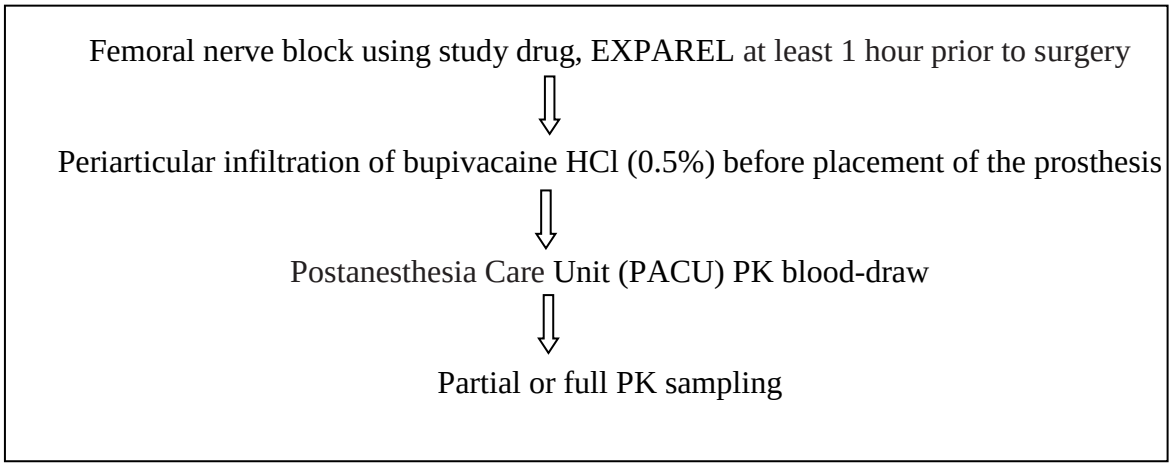


Table 1 shows the systemic levels of bupivacaine and the length of time between administration of study drug and periarticular bupivacaine HCl (0.5%) injection and the PACU PK blood draw, separated for US sites and sites outside the US [described as the Rest of the World (ROW)].

There was less time before blood was drawn at the ROW sites compared to the US sites by approximately 38, 23 and 35 minutes for EXPAREL-133 mg, EXPAREL-266 mg and placebo groups, respectively. The mean PACU bupivacaine concentrations are also lower for ROW sites compared to the US sites (Table 1).

Table 1: The time from study drug (EXPAREL/Placebo) administration and bupivacaine HCl (0.5%) injection to the PACU PK blood draw for US and Rest of the World (ROW).

	EXPAREL 133 mg		EXPAREL 266 mg		Placebo	
	US (n=38)	ROW (n=37)	US (n=38)	ROW (n=38)	US n=(40)	ROW (n=39)
PACU Bupivacaine Concentration						
n	34	37	37	38	32	39
Mean	224.4	75.3	242.1	113.4	129.5	72.1
(SD)	(232.4)	(34.7)	(192.2)	(81.8)	(83.4)	(38.3)
Range	41 – 1270	26 – 180	50 – 992	29 – 528	25.8 – 406	29 – 218
Time (hr) from Study Drug Injection						
n	35	37	38	38	34	39
Mean	3.51	3.93	3.60	3.88	3.55	3.97
(SD)	(0.78)	(0.89)	(0.78)	(0.61)	(0.59)	(0.75)
Median	3.47	3.83	3.63	3.87	3.60	3.83
Range	2.3 – 5.8	2.5 – 5.8	1.87 – 5.6	2.48 – 5.83	2.55 – 4.58	2.83 – 6.27
Time (hr) from bupivacaine injection						
n	33	37	36	38	28	39
Mean	1.48	0.84	1.31	0.93	1.48	0.89
(SD)	(0.88)	(0.31)	(0.84)	(0.26)	(0.62)	(0.25)
Median	1.30	0.82	1.33	0.92	1.37	0.83
Range	0.37 – 5.22	-0.17 – 1.4	-1.38 – 3.6	0.48 – 1.5	0.77 – 4.17	0.4 – 1.78

A scatter-plot showing the concentrations at each time point in all subjects with full and partial PK sampling by treatment in Study 326 is shown in Figure 1.

Figure 1: Bupivacaine concentrations at each time point in all subjects with full and partial PK sampling by treatment in Study 402-C-326.

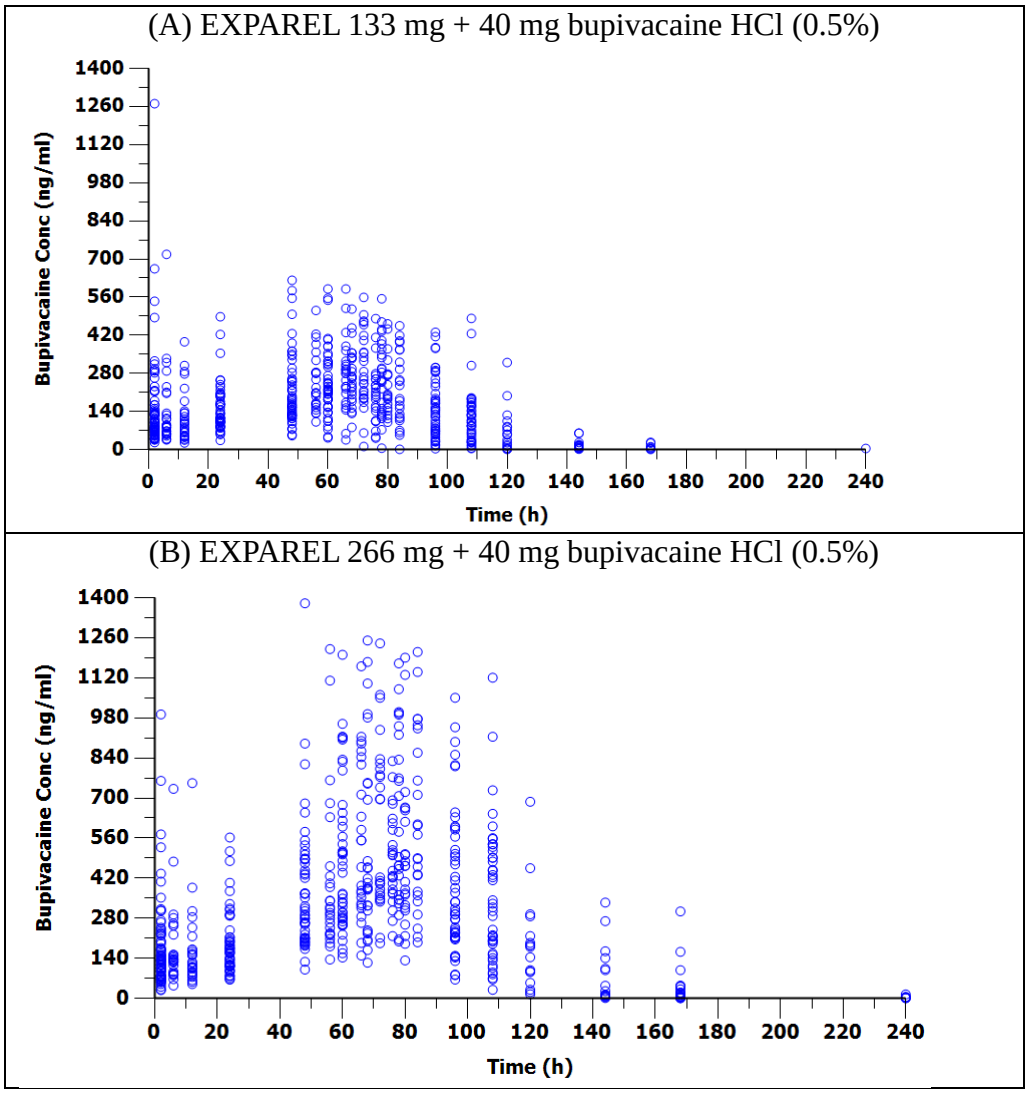
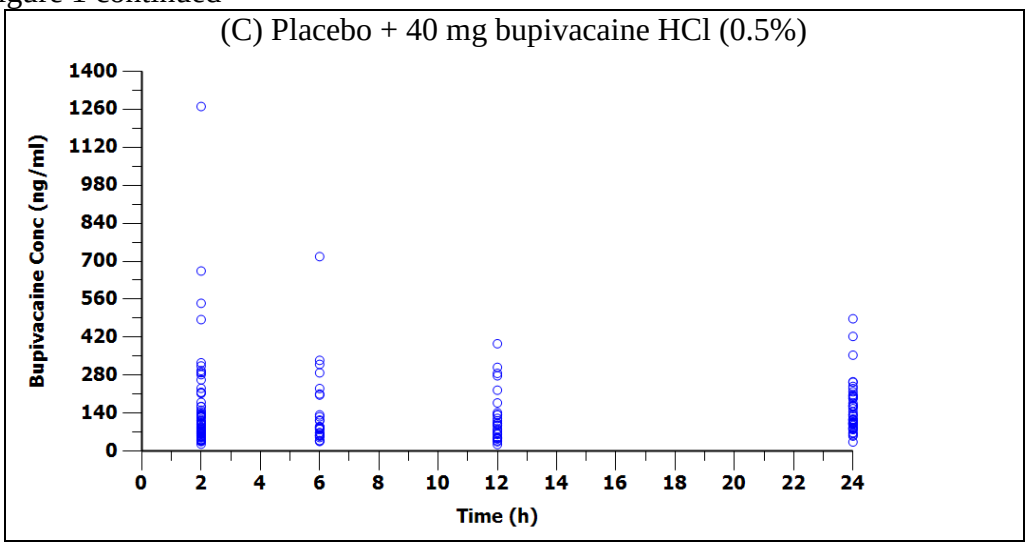


Figure 1 continued



The arithmetic mean ± SD bupivacaine plasma concentration profiles by treatment for subjects with full PK sampling and the corresponding PK parameters are in Study 326 are shown in Figure 2 and Table 2, respectively.

Figure 2: Mean bupivacaine plasma concentration profiles by treatment Study 402-C-326.

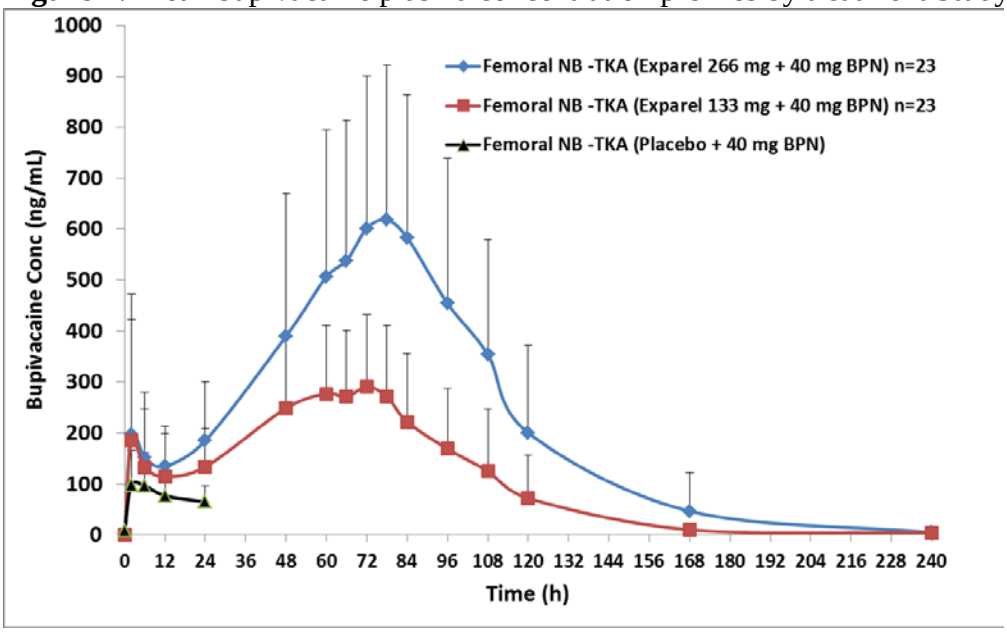


Table 2: PK parameters by treatment in Study 402-C-326

Parameter	**Arithmetic mean ± SD**	
	EXPAREL 133 mg + 40 mg bupivacaine HCl (0.5%) (N=24)	**EXPAREL 266 mg + 40 mg bupivacaine HCl (0.5%) (N=23)**
Cmax (ng/mL)	447 ± 227	743 ± 348
Tmax (h) [$]	64 [2 – 108]	72 [2.5 – 108]
$AUC_{(0\text{-}t,240h)}$ (h×ng/mL)	23022 ± 9017	48459 ± 21382
AUC(inf) (h×ng/mL)	23613 ± 9507 [a]	50514 ± 20978 [a]
Tlast	120 [84 – 240]	168 [100– 240]
t½ (h)	14 ± 9	18 ± 17 [a]

[$]Median [range]
[a] n=22

Study 402-C-327 Brachial Plexus Nerve Block for Total Shoulder Arthoplasty or Rotator Cuff Repair:
Study 327 was a multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy, safety, and pharmacokinetics of brachial plexus nerve block with EXPAREL for postsurgical analgesia in subjects undergoing total shoulder arthroplasty or rotator cuff repair.

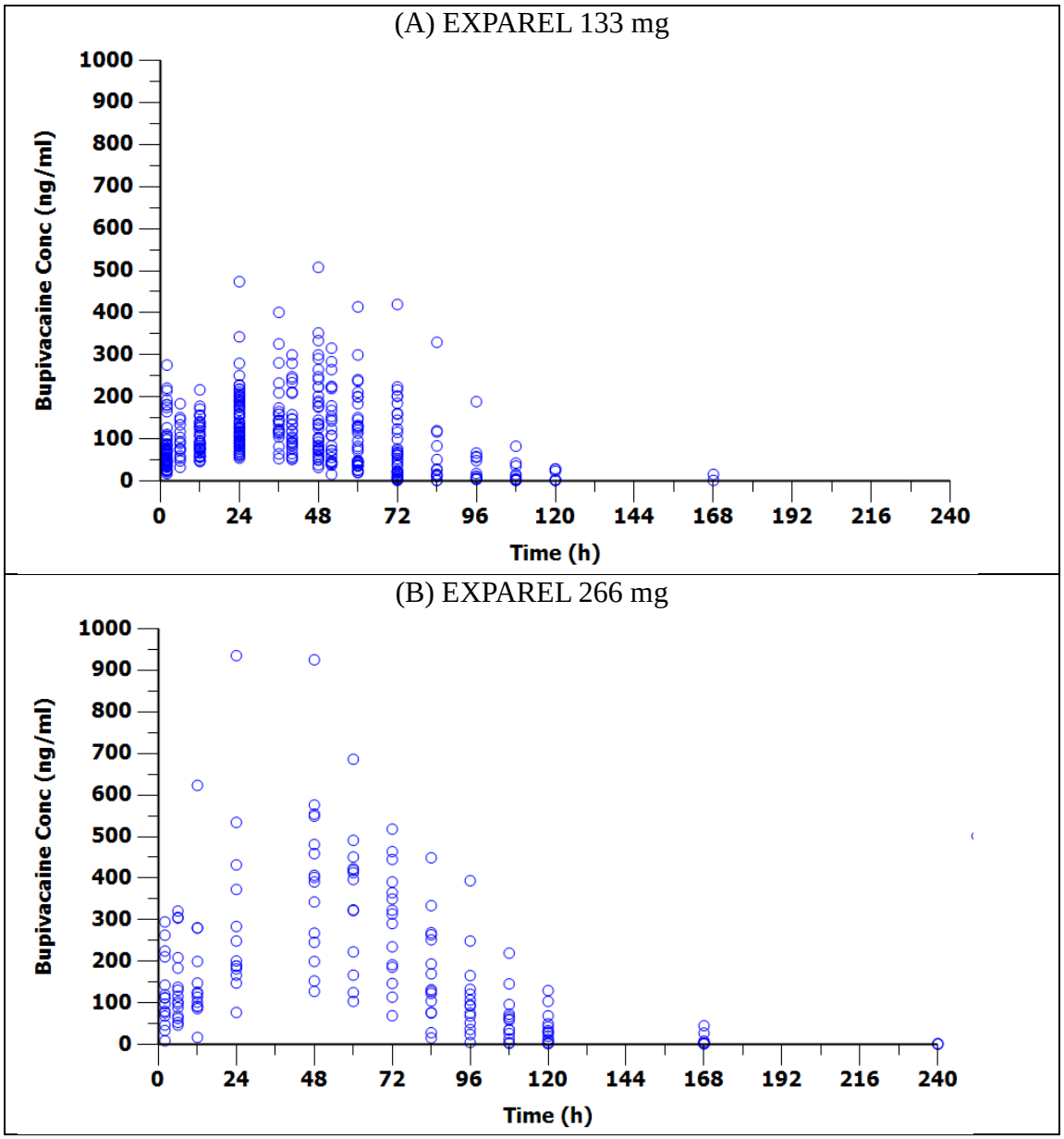
Subjects received a single 20 mL dose of one of the following into the brachial-plexus (interscalene or supraclavicular) via syringe at least 1 hour prior to surgery under ultrasound guidance:

- EXPAREL 133 mg (10 mL EXPAREL + 10 mL of normal saline)
- EXPAREL 266 mg (20 mL of EXPAREL).
- Placebo (normal saline)

In this study, both partial and full PK sampling were conducted for the different subjects. The PK parameters were calculated from subjects who had full PK sampling.

Results:
A scatter-plot showing the concentrations at each time point in all subjects with full and partial PK sampling by treatment in Study 326 is shown in Figure 3.

Figure 3: Scatter-plot showing the concentrations at each time point in all subjects with full and partial PK sampling by treatment in study 402-C-326 (brachial-plexus-nerve block).



The arithmetic mean ± SD bupivacaine plasma concentration profiles by treatment for subjects with full PK sampling and the corresponding PK parameters in Study 326 are shown in Figure 4 and Table 3, respectively.

Figure 4: Arithmetic mean ± SD bupivacaine plasma concentration profiles by treatment, Study 402-C-327 (brachial plexus nerve block).

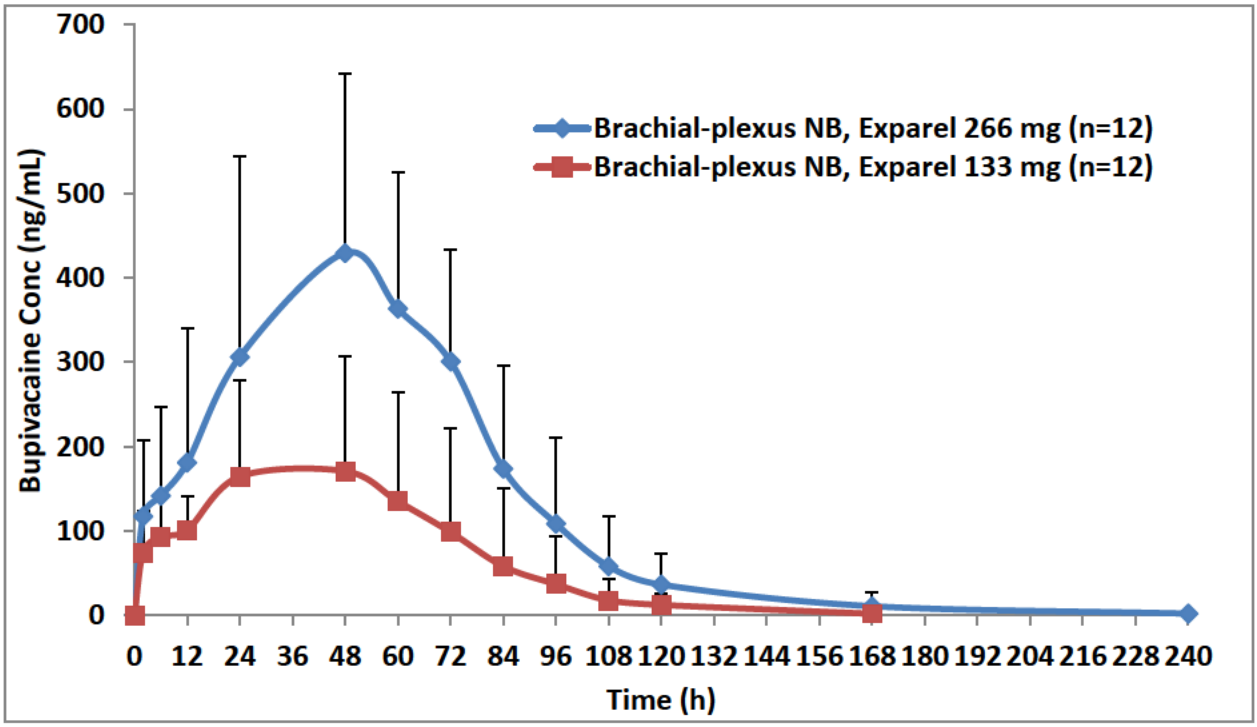


Table 3: PK parameters by treatment in Study 402-C-327 (brachial plexus nerve block).

Parameter	**Athematic mean ± SD**	
	EXPAREL 133 mg (N=12)	**EXPAREL 266 mg (N=12)**
Cmax (ng/mL)	207 ± 137	469 ± 194
Tmax (h) [$]	48 [3 – 74]	48 [24 – 72]
$AUC_{(0\text{-}t,240h)}$ (h×ng/mL)	11484 ± 8615	28857 ± 13351
AUC(inf) (h×ng/mL)	11590 ± 8603	28991 ± 13449
Tlast	108 [84– 168]	144 [108– 240]
t½ (h)	11 ± 5	14 ± 5

[$]Median [range]

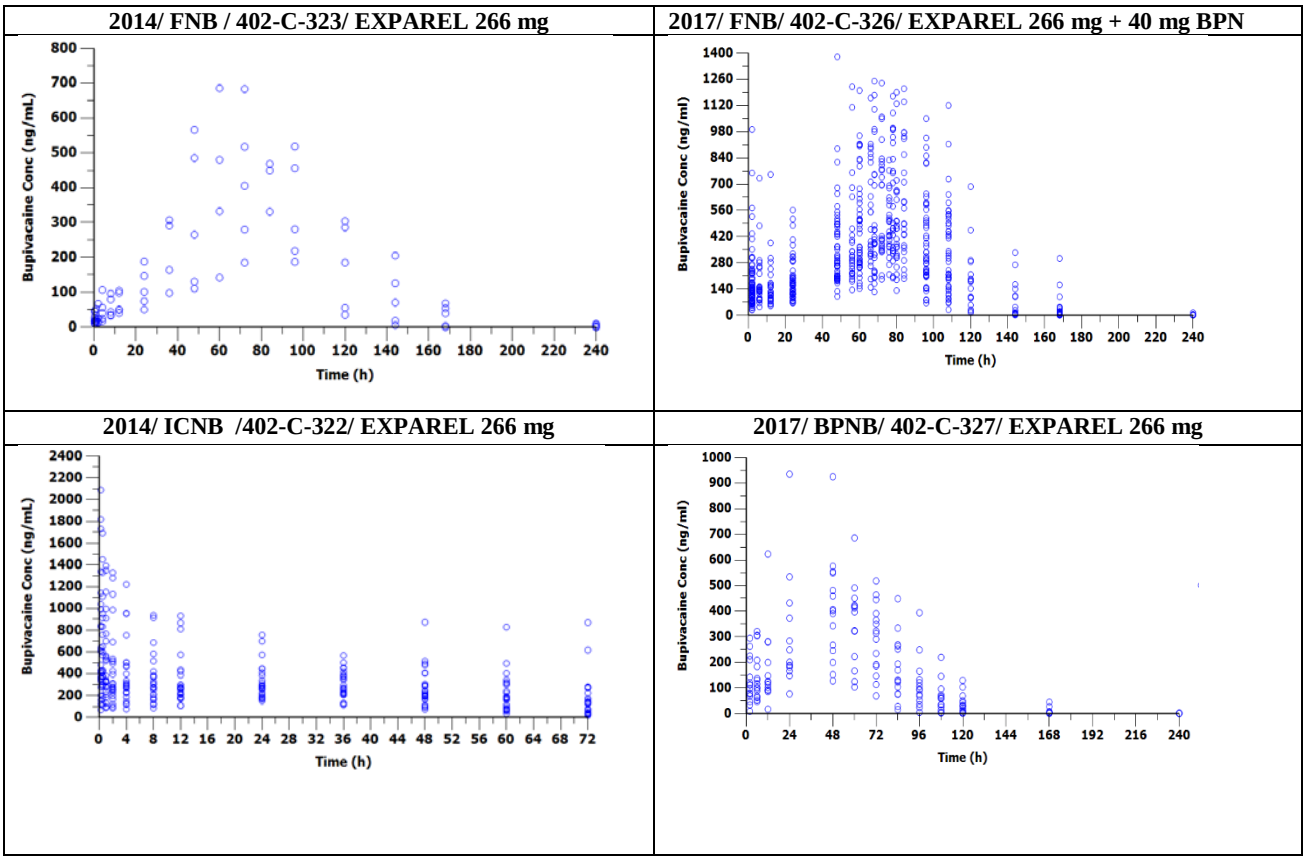
Comparison of PK between nerve block studies:

The nerve block studies were as follows:

Year	Study #	Procedure	Dose
2014	402-C-322	Intercostal nerve block in posterior-lateral thoracotomy	EXPAREL 266 mg
2014	402-C-323	Femoral nerve block in total knee arthoplasty	EXPAREL 266 mg
2017	402-C-326	Femoral nerve block in total knee arthoplasty	EXPAREL 266 mg + 40 mg bupivacaine (0.5%) (total dose 306 mg)
2017	402-C-327	Brachial Plexus nerve block in total shoulder arthoplasty or rotator cuff repair	EXPAREL 266 mg

A scatter-plot showing the concentrations at each time point in all subjects in all nerve block studies is shown in Figure 5. The PK profile comparison among four different nerve block studies is shown in Figure 6. The PK parameters from four nerve block studies are summarized in Table 4.

Figure 5: Bupivacaine concentrations at each time point in all subjects in all four nerve block studies. Note that Y axis scale is different among studies and is dependent on the observed concentrations.



ICNB -Intercostal NB in posterior-lateral thoracotomy; FNB- Femoral NB in total knee arthoplasty;
BPNB- Brachial Plexus NB in total shoulder arthoplasty or rotator cuff repair

Figure 6: Comparison of PK profile across the four nerve block studies

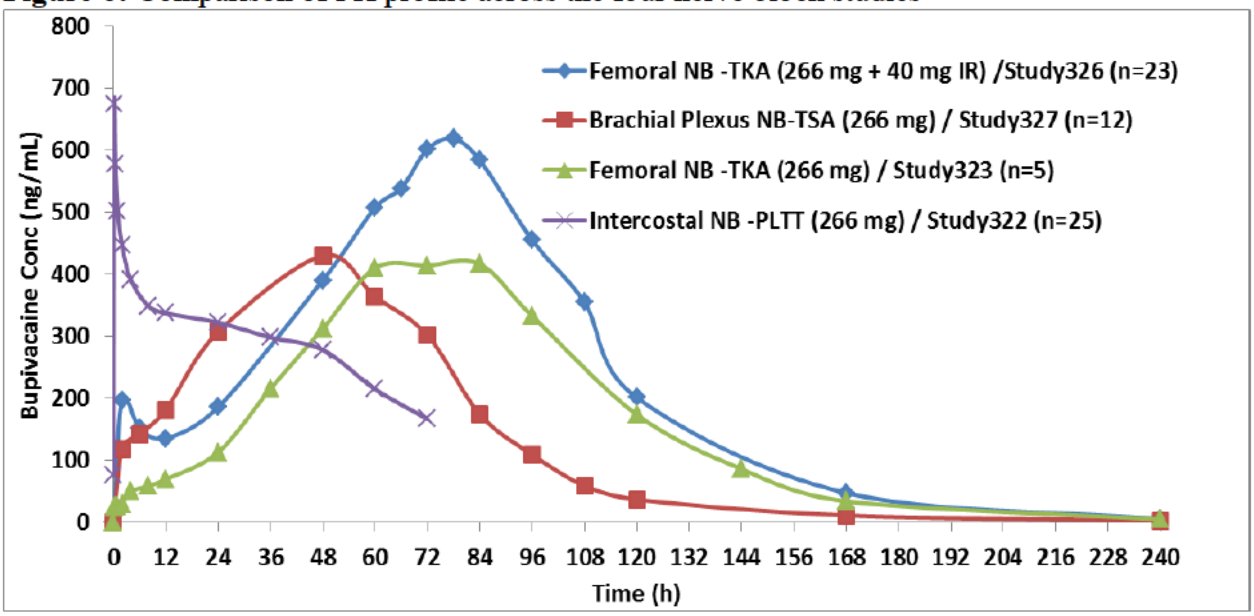


Table 4: Comparison of PK parameters across the nerve block studies

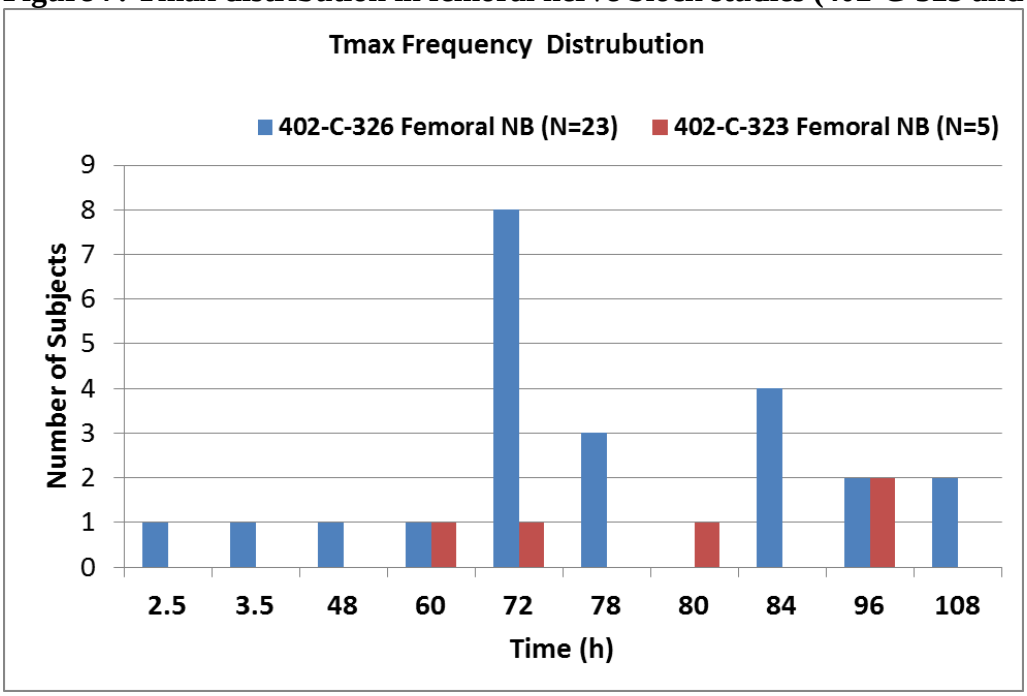
Parameter Mean ± SD	**2014 Intercostal NB PL Thoracotomy (402-C-322) N=25**	**2014 Femoral NB-TKA (402-C-323) N=5**	**2017 Femoral NB-TKA (402-C-326) N=23**	**2017 Brachial plexus NB- TSA (402-C-327) N=12**
Dose (mg) and volume	266 mg in 20 mL	266 mg in 20 ml	266 mg in 20 mL + 40 mg bupivacaine HCl (0.5%)	266 mg in 20 mL
How administered	Divided into three equal doses of 88 mg in 6.6 mL and administered to each of three nerve segments (index nerve, nerve above, and nerve below)	SD injection, femoral block under ultrasound guidance	SD injection, femoral block under ultrasound guidance + 40 mg IR	SD injection, brachial-plexus-nerve block under ultrasound guidance
Duration of PK sampling (h)	72	240	240	240
Cmax (ng/mL)	794 ± 510	498 ± 136	743 ± 348	469 ± 194
Tmax (h) Median [Range]	1.0 [0.5, 50]	80 [60, 96]	72 [3, 108]	48 [24, 72]
$AUC_{(0-t,72\ h)}$ (h×ng/mL)	21203 ± 8650	15377± 8294 [a]	22322 ± 11829 [a]	21994 ± 11642 [a]
AUCt (0-last time point)	21203 ± 8650 [b]	34326 ± 5262 [c]	48459 ± 21382 [c]	28857 ± 13351 [c]
AUC(inf) (h×ng/mL)	23264 ± 9210 [d]	34496 ± 5297	50514 ± 20978 [e]	28991 ± 13449
t½ (h)	23 ± 13 [d]	19 ± 7	18 ± 17 [e]	14 ± 5

[a] Partial AUC- AUC0-72 ; [b] AUC(0-t)- 0-72 h; [c] AUC(0-t)- 0-240 h; [d] n=19; [e] n=22; NC- not calculated ; SD- Single dose; TKA- Total Knee Arthroplasty ; TSA- Total Shoulder Arthroplasty; Dose NMZ- dose normalized

Femoral nerve block studies (402-C-323 and 402-C-326):

In both femoral nerve block studies, EXPAREL 266 mg was administered using ultrasound guidance. In Study 326, an additional 40 mg of immediate-release bupivacaine (0.5%) was administered by the surgeon to the periarticular space. This additional 40 mg IR bupivacaine in Study 326 can be observed as small initial peak (1st peak) at approximately 2.5 h in the mean PK profile. The median Tmax in Study 326 was 72 hours with a wide range of 2.5 to 108 hhoufx. The median Tmax in Study 323 was 80 hours with a range of 60 to 96 hhours. The distribution of Tmax in both femoral block studies is shown in Figure 7.

Figure 7: Tmax distribution in femoral nerve block studies (402-C-323 and 402-C-326)

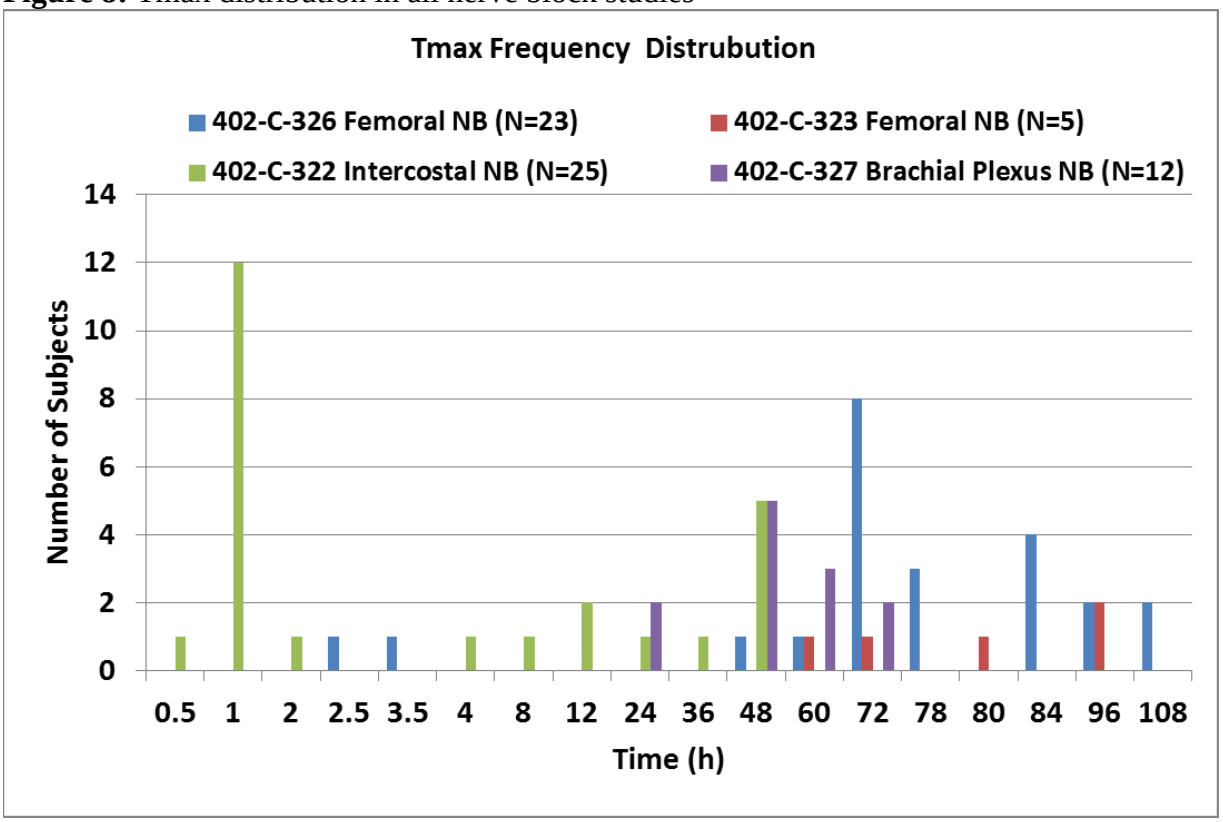


The Cmax in Study 326 is approximately 50% higher compared to the Study 323. The higher Cmax in Study 326 cannot be attributed to the additional 40 mg IR bupivacaine, beause the bupivacaine exposure from the IR bupivacaine should only last for up to 24 hours with the remainder of the bupivacaine levels from EXPAREL.

The AUCinf in Study 326 is approximately 46% higher compared to the Study323. The higher AUCinf in Study 326 can be attributed in part to the additional 40 mg IR.

Tmax comparison of across all nerve block studies:
The T_{max} observed across all of the nerve block studies was highly variable with a wide range of 0.5 to 108 hours (Figure 8). The differences in T_{max} were associated with the anatomical site, surgical procedure, and how the EXPAREL dose (i.e., single dose vs. divided doses of the dosage) was administered.

Figure 8: Tmax distribution in all nerve block studies



Overall clinical pharmacology conclusions:

- For Study 326, the mean PACU bupivacaine concentrations is lower for the non-US sites compared to the US sites, possibly due to differences in the timing of PK sampling.

- The Cmax and AUC values in Study 326 are approximately 50% and 46% higher, respectively, compared to the Study 323, possibly due to the additional 40 mg IR bupivacaine injection in Study 326.

- The T_{max} of bupivacaine from EXPAREL is highly variable with wide range of 0.5 hours to 108 hours across the different nerve block studies. The differences in T_{max} are associated with anatomical site, surgical procedure, and approach of EXPAREL administration (i.e., single dose vs. divided doses).

Clinical Summary

Efficacy
The sNDA included the results from four clinical trials: the previously-conducted trials on femoral nerve block (402-C-323, Part 2) and intercostal nerve block (402-C-322), and a repeated femoral nerve block trial (402-C-326), and an interscalene nerve block trial (402-C-327).

Key Study Characteristics of Phase 3 Pivotal Studies
(adapted from NDA submission; Table 4 of the Clinical Overview, page 25).

	Efficacy Study			
Study Characteristic	**402-C-327**	**402-C-323 (Part 2)**	**402-C-326**	**402-C-322**
Nerve block	Brachial plexus	Femoral	Femoral	Intercostal
Surgery type	TSA/RCR	TKA	TKA	Posterolateral thoracotomy
Study design	PC, DB, R, MC	PC, DB, R, MC	PC, DB, R, MC	PC, DB, R, MC
Doses studied	133 mg	266 mg	133 and 266 mg	266 mg
Randomization ratio	1:1	1:1	1:1:1	1:1
Region	United States and Western Europe	United States	United States and Western Europe	United States and Eastern Europe
Primary efficacy population	Intent-to-treat	Intent-to-treat	Intent-to-treat	Intent-to-treat
Primary efficacy endpoint	48-hour AUC of VAS	72-hour AUC of NRS-R	72-hour AUC of VAS	72-hour AUC of NRS-R
Rank of secondary efficacy endpoints				
Total opioid use	1	1	1	1
% opioid-free	2	Not ranked	2	Not ranked
Time to first opioid	3	2	3	2

AUC = area under the curve; DB = double-blind; MC = multicenter; NRS-R = numeric rating scale at rest; PC = placebo controlled; R = randomized; RCR = rotator cuff repair; TKA = total knee arthroplasty; TSA = total shoulder arthroplasty; VAS =visual analog scale.
Source: Study 402-C-327 CSR; Study 402-C-323 CSR; Study 402-C-326 CSR and Study 402-C-322 CSR

Two of the four trials (402-C-322 and 402-C-326) failed to meet their primary efficacy endpoints. The Sponsor proposes a broad indication of regional postsurgical analgesia when Exparel is administered as a nerve block. The proposed dose of up to 266 mg may be effective for interscalene block and possibly for femoral block, but it does not appear to be effective in any other blocks that have been evaluated by the Sponsor. In addition, contradictory study findings

in the two femoral nerve studies make it difficult to determine the efficacy of Exparel when administered as a femoral nerve block.

Statistical Significance Versus Placebo of Primary and Secondary Endpoints of Phase 3 Pivotal Studies (adapted from NDA submission; Table 5 of the Clinical Overview, page 26)

	Efficacy Study			
Study Characteristic	**402-C-327 Brachial plexus**	**402-C-323 (Part 2) Femoral**	**402-C-326 Femoral**	**402-C-322 Intercostal**
Primary Endpoint	<0.0001	<0.0001	133 mg: 0.4463 266 mg: 0.2749	0.5598
Rank of secondary efficacy endpoints				
Total opioid use	<0.0001	0.0016	NA	NA
% opioid-free	0.0080	Not ranked	NA	Not ranked
Time to first opioid	<0.0001	0.9556	NA	NA

NA = not appropriate for formal statistical testing.
Source: Study 402-C-327 CSR; Study 402-C-323 CSR; Study 402-C-326 CSR and Study 402-C-322 CSR

The study of intercostal nerve blocks (402-C-322) had a primary efficacy endpoint of an area under the curve analysis (AUC) for pain intensity at rest using a numerical rating scale (NRS-R) over 72 hours. The study did not win on its primary endpoint, which slightly favored placebo over Exparel in reducing NRS-R over 72 hours after thoracotomy. The Applicant stated that the drug may have been efficacious for the first 12 to 24 hours after administration, although they do not appear to have provided a rationale as to why the duration of analgesia would differ in the setting of intercostal nerve block as compared to femoral nerve block.

Study 402-C-323 (Part 2) clearly won in its primary endpoint, AUC for NRS-R over 72 hours. This outcome did not appear to be affected by drop-outs or imputation of pain scores. The study also won on its first secondary endpoint, total postsurgical opioid consumption over 72 hours, but did not win on its subsequent secondary endpoint, time to first opioid rescue. Exparel is demonstrated in this study to reduce pain at rest and opioid consumption over 72 hours after total knee arthroplasty, as compared to placebo. This result is not surprising because we know that immediate-release bupivacaine can provide excellent extended pain control via femoral nerve block, and therefore, subjects who received liposomal bupivacaine via femoral nerve block are expected to have superior pain control to those who received placebo. However, whether Exparel provides any additional benefit over immediate-release bupivacaine remains unanswered because an active control arm with immediate-release bupivacaine was not incorporated in this study. In addition, while the femoral nerve block clearly provided analgesia for 72 hours, its onset and duration beyond 72 hours was not characterized in this study, which did not permit an adequate assessment of the safety profile of Exparel when used as proposed in the sNDA. Furthermore, femoral nerve Study 402-C-326, failed to meet its primary efficacy endpoint, AUC of visual analog scale (VAS) pain intensity score through 72 hours.

Additional evidence that questions the benefit of Exparel over immediate-release bupivacaine for nerve blocks is found in the Applicant 's Phase 2 ankle block study (SKY0402-C-203). Exparel 350 mg was not more efficacious at providing post-surgical analgesia than bupivacaine HCl, and lower Exparel doses (225 and 175 mg) provided even less satisfactory pain control. Therefore, the dose proposed for labeling (up to 266 mg), administered via ankle block, would not be expected to provide satisfactory pain control.

The Applicant provided multiple reasons, which are discussed in the sections below, for the failure of Study 402-C-326 to demonstrate efficacy in the femoral nerve block. The rationale provided by the Applicant does not adequately explain the discrepancy in study results.

The Applicant proposed the following reasons for the failure of Study 402-C-326 (from the Integrated Summary of Efficacy and Study 402-C-326 Report Body):

> *1. "In order to ensure appropriate PK sampling, Study 402-C-326 was initially designed with a 5-day required hospital stay, which was a minimum of 3 days longer than the standard of care for TKA at the time the study began. The extended hospital stay required for this study led some investigators experienced with Exparel in the earlier study to decline participation in Study 402-C-326 and may also have led to some selection bias in the types of subjects willing to participate in the study (i.e., subjects willing to spend additional time in the hospital with the hopes of receiving opioid pain medications)."*

The Applicant indicated that the "standard of care" hospital stay after a TKA is 2 days. However, most recent literature indicates that the average length of stay in the hospital after a primary single joint arthroplasty is 3.7 days. (Youssef F. El Bitar, 2015) Multiple factors have been shown to impact the length of stay, and given that 50% of patients are routinely told to expect to stay four or more days, it seems unlikely that requiring a minimum of a five-day stay would lead to a selection bias, as the Applicant is suggesting. The Applicant also claims that if certain subjects at the Belgian site are removed from the analysis, then the study would meet its primary endpoint (see below). However, if a selection bias was responsible for the failure to establish efficacy in this study, then one would expect that it would occur at all sites, and therefore, one would not expect to see a difference in efficacy between US and ex-US study sites. In addition, the Sponsor does not define what they mean by "experienced" investigators. Although it would be advantageous to have investigators who are "experienced with Exparel" participate in the study, it is not clear which practitioners the Applicant is referring to. A femoral nerve block is one of the most frequently taught and performed nerve blocks in the anesthesia community worldwide. Therefore, any anesthesiologist who takes care of patients undergoing a TKA is likely both experienced and comfortable with femoral nerve block administration. Since these blocks were all done under ultrasound-guidance, there should be little to no difference in terms of visualizing the femoral nerve, the needle/catheter placement, or the perineural spread of the local anesthetic with Exparel versus the immediate-release bupivacaine, or any other local anesthetic, for that matter. Therefore, it seems very unlikely that the degree of experience with Exparel would make a difference in proper administration of the femoral nerve block. Furthermore, as Study 402-C-323, conducted from 2012-2013, was the first large Phase 3 study for femoral nerve block utilizing Exparel, the practitioners in that study also did not have "experience" with this drug via this

method of administration. As Study 402-C-323 met its primary efficacy endpoint, the experience of the practitioners with Exparel appears irrelevant.

2. Technique for administering Exparel

- *Study 402-C-323 included the use of a flexible epidural catheter placed through a needle into the space posterior to the femoral nerve under ultrasound guidance.*
- *In Study 402-C-326, the use of an epidural catheter was not required.*
- *Thus, there were likely some differences in technique between investigators that may have affected the overall efficacy of the study.*
- *Also changes in medical practice and the standard of care over the past 4 to 5 years may help to explain the inconsistent results seen in the two studies.*

As stated above, most anesthesiologists who take care of TKA patients on a routine basis are experienced at performing a femoral nerve block. As Exparel is administered as a one-time injection (not an infusion), and the injection is visualized with ultrasound guidance (drug spread), it should make little to no difference whether Exparel was delivered via a needle versus an epidural catheter. In fact, one could argue that placing a catheter under ultrasound guidance is more difficult and less frequently performed, whereas ultrasound-guided needle injection is more common and technically easier. Therefore, practitioners in Study 402-C-326 should have had an easier time visualizing the needle and the drug spread around the nerve. It is also unclear what particular changes in medical practice in the last 4 to 5 years the Applicant is referencing. The most clinically-significant change in the management of patients undergoing TKA is the replacement of the femoral nerve block with adductor canal blocks due to evidence of prolonged quadriceps weakness and increase in post-operative patient falls as a result of the femoral nerve block. (In Jun Koh, 2017). This new practice has no implications on the results of this study.

3. The overall treatment difference was highly dependent on consistency between the US and ex-US sites, as approximately half of all subjects (114 subjects; 49.6%) were enrolled at two sites in Belgium and Denmark (page 65 of Study Report)

- *Differences in both baseline subject characteristics between the US sites versus the ex-US sites (principally study Site 142 – Belgium)*
  - *Subjects in the US had a mean VAS score at baseline that ranged from 2.49 to 3.46 cm across treatment groups compared with 0.97 to 1.73 cm for subjects at the ex-US sites.*
  - *A larger percentage of subjects in the US than in the ex-US took at least one prior pain medication (43.1% versus 24.6%, respectively), with almost all prior opioid use occurring in the US.*
  - *These differences suggest that ex-US subjects were in less pain upon entering the study compared with subjects in the US.*
  - *The Applicant hypothesized that the pain difference might be due to lifestyle characteristics in Denmark and Belgium versus the US (e.g., lower body weight [range of 89.516 to 93.117 kg across treatment groups for US subjects compared to 83.872 to 84.027 kg for ex-US subjects] due to having a more active lifestyle) or knee replacement surgery being performed prior to the onset of more severe pain in ex-US subjects.*

- *It has been shown that baseline pain scores are predictive of postoperative outcome thereby showing the importance of having similar baseline pain characteristics across all treatment groups (Barbara A. Rakel, 2012).*

During the review of the original Supplement 9 submission, the Applicant was asked to provide a rationale for why the data collected in Europe was comparable and applicable to the US population. The Applicant provided the following rationale:

- That the practice of medicine in this specific clinical setting is similar between the US and non-US locations
- That extrinsic factors are not applicable
- That bupivacaine is widely used in the non-US locations and that eastern European clinicians there are adept at monitoring the effects of bupivacaine-containing drugs

However, per the End of Review meeting minutes dated April 21, 2015, the FDA indicated that they disagreed with the Applicant's justification for the comparability of the US population and ex-US populations. One of the reasons for the disagreement stated was, "In comparing study populations, beyond race and ethnicity, you must account for any differences in age, sex, and weight/BMI. Furthermore, 100% of the safety population of non-US subjects in the intercostal nerve block trial (Study 322) were Caucasian, in contrast to 82% of the safety population from the US femoral nerve block trial (Study 323, Part 2)." Therefore, the Applicant was aware of the potential problems which can occur when conducting their studies in both US and ex-US centers.

The Applicant hypothesized that lifestyle differences between the US and ex-US populations may have contributed to lack of treatment effect. In the Study 402-C-326 Report, the Applicant states, "…the pain difference might be due to lifestyle characteristics in Denmark and Belgium versus the US (eg, lower body weight [range of 89.516 to 93.117 kg across treatment groups for US subjects compared to 83.872 to 84.027 kg for ROW subjects] due to having a more active lifestyle) or knee replacement surgery being performed prior to the onset of more severe pain in ROW subjects." The Applicant notes that US subjects had higher baseline pain scores and more US subjects used preoperative opioids (defined as 30 days prior to study drug administration) than the ex-US subjects.

The Applicant has not provided an evidenced-based rationale to support the hypothesis that lifestyle difference, in particular patient weight, leads to higher preoperative pain scores and opioid consumption. Although it is plausible that obesity can contribute to or exacerbate other co-morbidities, including arthritis, many other genetic and environmental factors can also lead to a similar conclusion.

Prior use of opioid medications was also examined and is summarized in the table below:

Number (Percentage) of Subjects Reporting at Least One Prior Pain Medication and Number (Percentage) of Subjects Reporting at Least One Prior Opioid Pain Medication by Region (US vs Rest Of Word)

	Exparel 133 mg		Exparel 266 mg		All Exparel		Placebo		Total	
	US (n=38)	ROW (n=37)	US (n=38)	ROW (n=38)	US (n=76)	ROW (n=75)	US (n=40	ROW (n=39)	US (n=116)	ROW (n=114)
Subjects with at least 1 prior pain medication	22 (57.9%)	10 (27.0%)	12 (31.6%)	14 (36.8%)	34 (44.7%)	24 (32.0%)	16 (40.0%)	4 (10.3%)	50 (43.1%)	28 (24.6%)
Subjects with at least 1 prior opioid medication	13 (34.2%)	4 (10.8%)	8 (21.1%)	4 (10.5%)	21 (27.6%)	8 (10.7%)	13 (32.5%)	1 (2.6%)	34 (29.3%)	9 (7.9%)

ROW = Rest of the World
(Source: Sponsor's Efficacy Information Amendment dated December 9, 2017)

Although the etiology of the differences in preoperative opioid consumption remains in question, the table above confirms the overall statement that US subjects had a higher percentage of preoperative opioid consumption than the ROW subjects. However, it is noteworthy to point out that this difference was present in both the Exparel and the placebo groups.

The preoperative opioid consumption difference also appears to correlate to higher postoperative pain scores in the US population:

Study 402-C-326 AUC 0-72 US versus ROW

	US AUC (0-72)	ROW AUC (0-72)
Mean	368.70384	156.80536
Std Dev	163.82301	87.102262
Std Error Mean	15.210584	8.1578743
Upper 95% Mean	398.83308	172.96758
Lower 95% Mean	338.5746	140.64314
N	116	114

AUC = Area Under the Curve; ROW = Rest of Word

If the Sponsor's hypothesis is true, however, and the population differences were the cause of the failed study, then theoretically, the efficacy results should be positive if the two populations are analyzed separately. An analysis of the primary efficacy endpoint on US and Rest of the World (ROW) subjects separately, and are summarized in the table below:

Descriptive Results for US Only versus ROW Only Subgroups for AUC of VAS Pain Score 0-72 Hours

Statistic	Exparel 133 mg	Exparel 266 mg	Placebo
US Sites Only (N=116)			
N	38	38	40
Mean (SD)	365.9 (172.57)	339.3 (179.64)	399.3 (135.89)
Median (Min, Max)	334.3 (94.1, 663.2)	297.9 (94.7, 710.0)	427.7 (147.2, 667.0)
ROW Sites Only (N=114)			
N	37	38	39
Mean (SD)	140.3 (83.71)	166.7 (84.21)	162.9 (92.83)
Median (Min, Max)	134.2 (27.8, 335.9)	152.0 (0, 354.0)	156.5 (19.9, 383.2)

ROW = Rest of the World
From ANOVA model with terms for treatment, age, weight and height.

The placebo subjects in the US had slightly higher mean pain scores than the Exparel subjects, but the differences do not appear to be clinically meaningful. The placebo subjects in the ROW had similar mean pain scores to the Exparel 266 mg group, while the subjects in the Exparel 133 arm had the overall slightly lower pain scores than the other two groups. These differences also do not appear clinically meaningful.

At first it seems plausible that differences in patient weight, VAS score, activity status, and the timing of surgery between US and ROW may have masked the treatment effect. However, similar difference in baseline patient characteristics appeared in Study 402-C-327, where 25% of subjects came from the same European study sites as those in Study 402-C-326, which won on the primary efficacy endpoint. The Sponsor does not provide a justification why differences in study outcomes exist, while baseline patient characteristics across studies in US and ROW sites were the same.

In addition, since US subjects had overall higher baseline pain scores and higher postoperative pain scores, one would expect that the US subjects would also have greater postoperative opioid consumption. The table below summarizes total opioid consumption in morphine equivalent dose for Study 402-C-326.

Summary of Total Opioid Consumption (MED mg) through 72 hours by Site Efficacy Analysis Set

Sites	Statistic	Exparel 133 mg (N=75)	Exparel 266 mg (N=76)	Placebo (N=79)
101 118, 127, 152	N	29	28	28
	Geometric Mean	115.88	130.36	143.33
	Minimum	18.2	26.0	41.6
	Maximum	320.0	328.0	407.2
112, 148, 212, 248	N	7	7	8
	Geometric Mean	243.57	165.58	203.16
	Minimum	132.5	80.0	125.4
	Maximum	533.9	267.0	341.5
126	N	0	1	1
	Geometric Mean		319.85	154.32
	Minimum		319.9	154.3
	Maximum		319.9	154.3
151	N	2	2	3
	Geometric Mean	245.08	213.28	239.57
	Minimum	203.9	127.7	123.9
	Maximum	294.7	356.2	514.0
142 (Belgium)	N	36	37	36
	Geometric Mean	197.71	221.02	203.01
	Minimum	40.0	40.0	31.0
	Maximum	380.0	560.0	500.0
144, 150 (Denmark)	N	1	1	3
	Geometric Mean	300.0	130.0	138.97
	Minimum	300.0	130.0	98.5
	Maximum	300.0	130.0	201.8

MED = Morphine Equivalent Dose
(Source: Sponsor's Study 402-C-326 Study Report Body)

The table above demonstrates that opioid consumption was extremely variable across the investigational sites with no appreciable trend for more opioid use in either US or ROW population. In addition, per Sponsor's analysis in Study 402-C-326 Report, "Total postsurgical opioid consumption through 72 hours was not significantly lower in either EXPAREL group compared to the placebo group in the US and ROW."

Furthermore, preoperative opioid consumption may not play as large of a role on postoperative opioid consumption in subjects that are receiving a nerve block analgesia for a surgical procedure, assuming that the nerve block was properly administered. If the nerves that mediate pain perception to the anterior and posterior aspect of the knee joint are "blocked" from further transmission of pain, one would expect that no pain would be perceived, even in subjects with prior history of preoperative pain and prior opioid use. Opioid seeking behavior, however, cannot be "blocked" even with an excellent regional anesthetic, and thus could potentially confound this assumption.

Based on this data, it is questionable that the differences in subject baseline characteristics described above in US versus ROW sites contributed to the lack of efficacy seen in this study, particularly since no clinically meaningful differences exist when the two populations are analyzed separately.

4. Differences in study conduct between the US sites versus the ROW sites (page 66 of the Study Report)

- *A substantial number of ROW subjects had poor posterior capsule injections, as identified by both a number of protocol deviations identified on the final two monitoring visits, as well as low bupivacaine HCl concentrations in the PACU PK plasma samples post-surgery compared with subjects in the US.*
    - *In a post-hoc analysis, when subjects at Site 142 who had PACU bupivacaine plasma concentrations <70 ng/mL were eliminated from the analysis as noncompliant with the posterior capsule injection, statistical significance was achieved for the primary endpoint in the EXPAREL 266 mg treatment group (Data on File.*
- *Nurses at the ROW sites proactively managed the use of postsurgical rescue medication, specifically instructing subjects to take the rescue medication, rather than wait for the subject to request the pain medication as instructed in the protocol. In contrast, subjects in the US had to request rescue medication from the nurses.*
- *The first rescue dose of oxycodone at the ROW sites was double the protocol-specified dose (ie, four immediate-release 5 to10 mg tablets of oxycodone instead of two tablets for subjects in the US).*
- *Pain was assessed at some ROW sites by a 0 to 10 NRS scale (a Likert scale for which an integer pain score is selected) instead of the protocol-specified VAS scale. Thus, the data in this study were approximately evenly distributed between semi-continuous data from the VAS scale and ordinal data from the NRS scale.*

The most objective way to evaluate the effectiveness of a posterior capsule injection is by assessing the anatomical location of pain experienced by the subject. Pain in the posterior knee would most likely be attributed to ineffective posterior capsule injection, while pain in the lateral and anterior aspects of the knee would be attributed to ineffective or incomplete femoral nerve block. No data are available on the PK profile of immediate release bupivacaine injected into the posterior capsule of the knee. Given that multiple patient-related factors (e.g., blood pressure, tissue edema, size of the posterior capsule, etc.) could potentially affect the systemic absorption of the immediate-release bupivacaine from the posterior capsule, the plasma bupivacaine levels in the PACU are expected to vary from subject to subject. In addition, systemic bupivacaine levels seem to have little to no correlation to the efficacy of the local anesthetic at its injection site (see Section 6.1.10 below). Therefore, the argument that low PACU bupivacaine levels in certain subjects reflect poor posterior capsule injections is unsubstantiated.

Furthermore, per study protocol, Exparel was administered at least one hour prior to the surgical procedure. The timing of the first PACU PK sample draw after Exparel administration did not significantly differ between US and ROW study sites (see table below), whereas the timing of the first PACU PK sample draw after immediate-release bupivacaine was injected into the posterior capsule did differ between US and ex-US sites. This data is presented in the following table:

Time Interval From Study Drug Administration and Bupivacaine Injection to the PACU PK Blood Draw

	EXPAREL 133 mg		EXPAREL 266 mg		Placebo	
	US (n=38)	ROW (n=37)	US (n=38)	ROW (n=38)	US n=(40)	ROW (n=39)
PACU Bupivacaine Concentration						
n	34	37	37	38	32	39
Mean	224.4	75.3	242.1	113.4	129.5	72.1
(SD)	(232.4)	(34.7)	(192.2)	(81.8)	(83.4)	(38.3)
Range	41 – 1270	26 – 180	50 – 992	29 – 528	25.8 – 406	29 – 218
Time (hr) from Study Drug Injection						
n	35	37	38	38	34	39
Mean	3.51	3.93	3.60	3.88	3.55	3.97
(SD)	(0.78)	(0.89)	(0.78)	(0.61)	(0.59)	(0.75)
Median	3.47	3.83	3.63	3.87	3.60	3.83
Range	2.3 – 5.8	2.5 – 5.8	1.87 – 5.6	2.48 – 5.83	2.55 – 4.58	2.83 – 6.27
Time (hr) from bupivacaine injection						
n	33	37	36	38	28	39
Mean	1.48	0.84	1.31	0.93	1.48	0.89
(SD)	(0.88)	(0.31)	(0.84)	(0.26)	(0.62)	(0.25)
Median	1.30	0.82	1.33	0.92	1.37	0.83
Range	0.37 – 5.22	-0.17 – 1.4	-1.38 – 3.6	0.48 – 1.5	0.77 – 4.17	0.4 – 1.78

Source: Efficacy Information Amendment received on December 12, 2017

The above table demonstrates that the time of PACU blood draw from administration of study drug (i.e., Exparel or placebo) was fairly consistent between dose groups and between regions. Therefore, a difference in the timing of the PACU draw from the nerve block does not explain the difference in the systemic bupivacaine concentrations at the single PACU timepoint. However, the data demonstrate that there was less time from administration of immediate-release bupivacaine to the PACU blood draw in the ROW sites than in the US sites, indicating that the ROW sites administered the immediate-release bupivacaine later in the surgical procedure. This could explain the overall lower PACU bupivacaine levels in the ROW subjects. Thirty-four subjects were identified in the Protocol Deviations dataset using the verbatim descriptions "bupivacaine not given prior to placement of prosthesis" and "subject received 8 ml bupivacaine after placement of the prosthesis" at Site 142. The clinical significance of the bupivacaine injection being done after the prosthesis placement is unknown. However, a total of 68 subjects had documented PACU bupivacaine levels < 70 ng/ml (56 from Site 142). Therefore, the injection of the posterior capsule after prosthesis placement does apply to all the subjects who had low PACU bupivacaine levels.

Furthermore, since the orthopedic surgeons were the ones who were administering the immediate-release bupivacaine into the posterior capsule under direct visualization, it seems highly unlikely that this injection was done incorrectly at ROW sites, unless you assume that orthopedic surgeons in Belgium are not familiar with basic knee anatomy. Considering that orthopedic surgery training is similar between US and Europe, this assumption is not appropriate.

Lastly, given our current knowledge of the PK profile of Exparel, we would expect to see Exparel, in addition to the immediate-release bupivacaine reflected in the systemic plasma bupivacaine levels in the PACU at three hours after Exparel administration. At this time there is no known method of distinguishing plasma levels of bupivacaine from Exparel versus plasma levels of immediate-release bupivacaine, when given within several hours of one another.

The Study Report for Study 402-C-326 indicates that a post-hoc analysis was conducted in which subjects at Site 142 who had PACU bupivacaine plasma concentrations of 70 ng/mL or less were eliminated from the analysis of the primary efficacy endpoint. This post-hoc analysis demonstrated statistical significance for the primary endpoint in the Exparel 266 mg treatment group. The Sponsor was asked to provide additional information on this analysis and how the 70 ng/ml cut-off value was determined. On December 9, 2017, the Sponsor submitted the following table:

Analysis of AUC of VAS Pain Intensity Scores through 72 Hours. Efficacy Analysis Set Excluding Subjects at Site 142 Whose Bupivacaine Concentration at PACU Arrival is ≤ 70 ng/mL

Statistic	EXPAREL 133 mg (n=75)	EXPAREL 266 mg (n=76)	Placebo (n=79)
N	55	66	53
Mean	300.69	267.45	345.22
St Dev	181.256	169.731	158.944
Median	280.80	222.64	341.22
Min – Max	27.8 - 663.2	0 - 710.0	53.0 - 667.0
LS Mean	303.898	269.337	339.543
SE of LS Mean[a]	22.910	20.882	23.337
LS Treatment Difference[a,b]	-35.646	-70.206	
Treatment Difference 95% CI[a,b]	-99.969, 28.677	-131.636, -8.776	
Treatment Difference p value [a,b]	0.2774	0.0251	

a: From an ANOVA with age, weight, and height as covariates

b: Treatment difference is EXPAREL – Placebo

Source: Sponsor's Efficacy Information Amendment submitted on December 9, 2017

The ≤ 70 ng/ml cut-off was chosen because the median PACU bupivacaine concentration for placebo subjects across all sites was 70.7 ng/ml. In the Efficacy Information Amendment dated December 9, 2017, the Applicant indicated that "Because the placebo subjects received only a posterior capsule injection of bupivacaine, the PACU bupivacaine concentration was considered to be representative of the expected bupivacaine level solely from that injection and subjects with a PACU concentration lower than the median were classified as having received a "poor" injection (ie, their bupivacaine concentration was lower than expected)… In order to ensure that we did not create bias in choosing the ≤ 70 ng/mL cut-off, the analysis was repeated using additional cut-offs ranging from 60 ng/mL to 130 ng/mL (by 10 ng/mL increments). Results of the analyses using these additional cut-offs remained supportive of those using the ≤ 70 ng/mL cut-off."

Although, the Sponsor's post-hoc analysis presented in the table above demonstrates statistical significance, this is only seen in the Exparel 266 mg dose group. Statistical significance is not met when the analysis is repeated for the entire treatment arm (Exparel 133 mg and 266 mg) versus placebo. Descriptive results for multiple subgroups are summarized in the table below:

Descriptive Results for Multiple Subgroups Analyses for AUC of VAS Pain Score 0-72 Hours

Statistic	Exparel 133 mg	Exparel 266 mg	Placebo
Excluded Site 142 with PACU Bupivacaine Level < 70* ng/ml (N=230)			
N	55	66	53
Mean (SD)	300.7 (181.26)	267.5 (169.73)	345.2 (158.94)
Median (Min, Max)	222.6 (0, 710.0)	222.6 (0, 710.0)	341.2 (53.0, 667.0)
Exclude Site 142 (N=121)			
N	39	39	43
Mean (SD)	364.9 (170.40)	336.1 (178.35)	392.3 (134.18)
Median (Min, Max)	334.0 (94.1, 663.2)	294.3 (94.7, 710.0)	401.3 (147.2, 667.0)
PACU Bupivacaine Level (All Sites) ≥ 70* ng/ml (n=149)			
N	50	63	36
Mean (SD)	291.4 (175.79)	257.7 (157.20)	315.8 (159.34)
Median (Min, Max)	280.7 (27.8, 663.2)	222.1 (0, 646.4)	314.0 (53.0, 617.9)
PACU Bupivacaine Level (All Sites) < 70* ng/ml (n=71)			
N	25	13	43
Mean (SD)	181.1 (157.02)	230.1 (200.46)	254.7 (168.28)
Median (Min, Max)	135.4 (42.7, 645.0)	136.2 (74.6, 710.0)	231.6 (19.9, 667.0)

From ANOVA model with terms for treatment, age, weight and height.
*Subgroups defined by PACU bupivacaine levels are post-randomization groupings. Treatment assignment could be confounded with PACU grouping.

When subjects at Site 142 (Belgium) who had PACU bupivacaine levels less than 70 ng/ml were removed from the population analysis, or when all subjects at all sites who had PACU bupivacaine levels less than 70 ng/ml were removed from the population analysis, there is a small difference in mean pain scores, with placebo subjects having slightly higher pain scores than either of the Exparel arms. This difference is unlikely to be clinically meaningful. When all subjects at Site 142 were excluded from the analysis, even less clinically meaningful differences exist between the study groups. Similarly, when only subjects with PACU plasma bupivacaine levels ≥ 70 ng/ml were examined, no clinically meaningful differences between study groups were detected.

In addition, conducting a subgroup analysis is only appropriate when the primary efficacy endpoint has been achieved, and further examination of drug's efficacy across subpopulations in a more granular fashion is necessary. However, in this study, since the primary efficacy endpoint was not met across the entire treatment group, it is not appropriate to perform subgroup analyses because such subgroup analyses can provide spurious results, either by coincidence (multiple testing effects) or by unintended patient selection mechanisms. The ICH guidance for industry E9 Statistical Principles for Clinical Trials states, "In most cases…subgroup or interaction analyses are exploratory and should be clearly identified as such;…these analyses should be interpreted cautiously;…any conclusion of treatment efficacy (or lack thereof) or safety based solely on exploratory subgroup analyses are unlikely to be accepted."

Furthermore, the Sponsor did not plan to conduct this subgroup analysis prior to subject enrollment. A pre-planned subgroup analysis is superior to a post-hoc subgroup analysis because subgroups of interest are typically created by stratified randomization (i.e., randomization within the subgroup). Stratified randomization can create prognostic similarity within the strata, and when performed appropriately, can provide sufficient statistical power to detect a meaningful difference within the subgroup. The ICH guidance for industry E3 Structure and Content of Clinical Study Reports states, "… it is essential to consider the extent to which the analyses were

planned prior to the availability of data…This is particularly important in the case of any subgroup analyses, because if such analyses are not preplanned they will ordinarily not provide an adequate basis for definitive conclusions." Based on these guidelines, the post-hoc analysis performed by the Sponsor is inadequate to support efficacy of the primary efficacy endpoint.

Regarding the nurse administration of opioids, the use of oxycodone was examined between US and ROW sites because the Sponsor claimed that the nurses at ROW sites were administering double the doses of this particular drug.

Dose of Oxycodone Administered: ROW versus US

Statistic	ROW	US
N*	1777	1341
Max	20	15
Min	4	4
Mean	9.87	8.86
Median	10	10
SD	0.85	2.18

*Number of total doses (some subjects received multiple doses)

The above table demonstrates that the overall mean dose of oxycodone was not substantially different between the regions, and the median doses were the same. Other pain medications, including other opioids were not compared between study regions. Since opioid administration was a secondary efficacy endpoint, and the primary efficacy for this study was not met, additional evaluation of opioid use is unnecessary.

It is not clear why the Applicant chose to change the NRS pain scale utilized in Study 402-C-323 to the VAS pain scale utilized in Study 402-C-326. It is also unclear why some of the ROW sites utilized the NRS scale instead of the VAS scale. The Applicant did not list the difference in pain scale use at different sites as protocol deviations in the study report. When asked to provide additional detail regarding which subjects were evaluated with the NRS scale, the Applicant responded with the following on December 11, 2017 (verbatim):

> All study sites used the VAS provided by Pacira in the study binder for protocol-specified pain assessments…In addition to using the VAS provided by Pacira for assessment of pain, Site 142 used a different pain assessment method for some of the unscheduled assessments. This was a protocol deviation. At this site, the floor nurses used a site-specific numeric rating scale administered orally to collect pain assessment scores at the time unscheduled rescue medication was dispensed. When the numeric rating scale was used, the nurse asked the subject, "On a scale from 0 to 10, 0 being the least pain you ever experienced and 10 being the worst pain you ever experienced, what is your pain now?" The subject replied orally with a numerical score. The subject's numerical score was then entered into the VAS page of the subject's case report form. At other times, the same subject may have used the provided VAS to report their pain score. Of the 109 subjects treated at Site 142, 107 have a documented deviation indicating use of this oral numeric rating scale for at least one of the unscheduled pain assessments.

> For the purposes of the primary endpoint analysis, all data recorded in the case report forms from Site 142 were treated as VAS data and were used in the analysis without any scaling or standardizing of the scores from the two different assessment methods.

On December 8, 2017, the Applicant also stated, "The specific instrument used was not captured on a by-subject level and, thus, identification of the specific scale used by an individual subject for a particular assessment timepoint cannot be ascertained from the study data base."

Given that the Applicant cannot verify which pain scale instrument was utilized at any specific time point for any specific study subject at Site 142, it becomes very difficult to analyze the primary efficacy endpoint data. As a result, the study data was analyzed for the primary efficacy endpoint excluding Site 142. (Refer to Table 32) Even with exclusion of Site 142 from the analysis, there does not appear to be sufficient evidence to demonstrate a difference in treatment effect between the Exparel groups and the placebo.

Furthermore, as the study data do not show a difference in treatment effect for the primary efficacy endpoint, additional secondary endpoint analyses are unnecessary.

Of note, the same study site (Site 142) was utilized in Study 402-C-327 (N=19). Since both studies were conducted at approximately the same time, one could envision that the same nurses were likely taking care of the study subjects in the postoperative period for both studies. Therefore, similar protocol violations (higher doses of oxycodone and different pain scale utilization) would be expected in Study 402-C-327 for that study site. The Applicant indicated that the NRS scale was also used on eight subjects in Study 402-C-327 in their response to an Information Request dated December 9, 2017. This information was originally not provided by the Sponsor in the study report or in the Protocol Deviations dataset. Additionally, the Protocol Deviations dataset does not appear to list increased oxycodone dosage as protocol deviations in Study 402-C-327. The Applicant did not provide justification for this discrepancy in nurse conduct between the studies.

One possibility that the Applicant did not address is the use of immediate-release bupivacaine as one commonality that is shared between all failed Exparel studies for infiltration and for peripheral nerve block (with the exception of the intercostal nerve study, which failed to show efficacy over placebo). Although the Applicant designated Study 402-C-326 as a placebo-controlled trial, the protocol also included 40 mg of immediate-release bupivacaine via injection into the posterior capsule for all study arms. Therefore, the placebo group received the immediate-release bupivacaine and not just normal saline. Although the posterior capsule injection would not be expected to provide analgesia to the anterior portion of the knee, may have provided enough analgesia to mask the contribution of Exparel to analgesia .

Safety

Several safety concerns were conveyed to the Applicant after the review of the original Supplement 9 submission, outlined below:

- Cardiac manifestations of systemic bupivacaine toxicity
    - No analysis provided of the cardiac Holter monitor data

    - Many of the protocol-specified ECGs (baseline and Tmax) were not provided and not incorporated in the Applicant 's analysis for change in ECG parameters
    - Arrhythmias noted on ECGs were not counted as adverse events
    - Holter monitoring was discontinued before mean T_{max} in Study 402-C-323
- Neurologic manifestations of systemic bupivacaine toxicity
    - Neurologic questionnaire was discontinued before Tmax in Study 402-C-323, and therefore may have failed to identify subjects with neurologic symptoms.
- Block onset and duration
    - The Applicant has not characterized the onset and duration of sensory and motor block after femoral nerve block and nerve blocks in general. This puts patients at risk for falls and for unrecognized nerve injury.
    - Incidence of falls in the Exparel subjects in Study 402-C-323 was 2.6%, whereas there were no falls among the placebo subjects.
    - Evaluation of motor function consisted of a 20-meter walk test, which likely has very low sensitivity and specificity for motor block in the post-TKA population.
- Rationale for the safety of all nerve blocks
    - PK profile of Exparel is very different with the different blocks and administration techniques that have been evaluated.
    - PK profile may correlate with the risk of systemic toxicity.
    - The Applicant has not provided a rationale as to how the PK and safety data applies to other commonly performed nerve blocks.

In order to further examine the possibility of cardiac manifestations of systemic bupivacaine toxicity, the Applicant submitted re-analyzed Holter monitor and ECG data from Studies 402-C-322 and 402-C-323. The re-analyzed data, and the additional new ECG data from Studies 402-C-326 and 402-C-327, did not reveal any evidence of cardiac toxicity associated with Exparel.

With regard to neurologic manifestations of systemic bupivacaine toxicity, the neurologic questionnaire in Studies 402-C-326 and 402-C-327 was continued beyond the identified T_{max} of the drug in each study. Therefore, it is reasonable to believe that most adverse events associated with neurologic toxicity were captured. The examination of these adverse events neither confirmed nor ruled out the possibility of delayed neurological toxicity of the study drug. The difficulty in making this determination stems from the types of surgical procedures that were enrolled in these studies (e.g.., knee arthroplasty, shoulder arthroplasty, and rotator cuff repair). Because all of these procedures carry an inherent risk of muscle and nerve injury that may manifest with similar symptoms to local anesthetic toxicity, the true etiology of some of these adverse events is debatable. In addition, concomitant intraoperative anesthetic drugs and postoperative medications could lead to adverse events which present similarly to local anesthetic toxicity (e.g., nausea, dizziness, hypotension, etc.). Therefore, although at this time no clear signal for neurological manifestations of delayed local anesthetic toxicity is apparent, further monitoring of this important adverse event is warranted in additional surgical models.

The Applicant also monitored both sensory and motor function through T_{max} and until resolution of the nerve block in Studies 402-C-326 and 402-C-327. The PK profiles varied significantly in each study, which is not surprising given the known variability of the PK profile of Exparel

previously demonstrated with different nerve blocks, as well as, with different sites of infiltration. Additionally, nadir of both sensory and motor loss did not correlate with T_{max} of the Exparel in each study, indicating no correlation between local drug efficacy and systemic levels of bupivacaine. Furthermore, in Study 402-C-326, adverse events of fall only occurred in the Exparel treatment arms. Because the Applicant chose not to incorporate an immediate-release bupivacaine femoral nerve block as a comparator arm into their study, it is unclear whether prolonged femoral nerve block-induced quadriceps weakness from any local anesthetic would result in increased incidence of falls, or whether Exparel further increases this risk. An additional study where Exparel femoral nerve block is compared to immediate-release bupivacaine femoral nerve block would help to make this differentiation.

The Applicant contends that they have provided adequate safety and PK data for several peripheral blocks, and therefore a general nerve block indication is appropriate. However, the data presented to date only further demonstrate the great variability in the PK profile of Exparel with different nerve block and administration techniques. The PK profile at sites that have not been evaluated is still unknown, and the Applicant has not provided an adequate rationale to support extrapolation of the PK and safety data to other commonly performed nerve blocks. In addition, it is critical to understand the PK profile in order to ascertain the proper dose of Exparel (i.e., Study 402-C-327 discontinued the 266 mg cohort based on the delayed T_{max} of this dose when administered via an interscalene or supraclavicular nerve block).

Local Anesthetic Systemic Toxicity

Local anesthetic systemic toxicity (LAST) was initially described in the late 1800's in association with the use of cocaine. Thereafter, new local anesthetics were developed to replace cocaine as the most commonly used local anesthetic, however, systemic toxicity continued to be a significant concern. Until the 1960's, the management of LAST emphasized optimization of oxygenation and ventilation. However, with the introduction of bupivacaine (Marcaine, NDA 016964, approved October 3, 1972), a long-acting, lipid-soluble local anesthetic, episodes of local anesthetic systemic toxicity became more difficult to treat. Several cases of cardiac arrest following regional anesthesia with bupivacaine were reported in the literature requiring "cardiac massage for 45 minutes or longer." (Albright, 1979) The toxicity of bupivacaine was attributed to its high lipid solubility and to inadvertent intravascular injection. Strategies were developed to minimize the risk of intravascular injection causing immediate cardiotoxicity, such as, adherence to dosing guidelines, intermittent aspiration and injection of local anesthetics, utilization of a "marker" (epinephrine) in a test dose of local anesthetic, and the use of electrical nerve stimulation for placement of regional blocks. In recent years, ultra-sound guidance of peripheral nerve block has gain a prominent role in regional anesthetic techniques by providing visualization of the anatomy of nerve, adjacent vascular structure, location of the regional needle tip, and distribution of the local anesthetic during injection.

While these strategies have reduced the incidence of intravascular injections there are several published articles that have reviewed the timing and progression of LAST. The classic clinical presentation of local anesthetic toxicity (Figure 1.a.) described a progression from prodromal symptoms (e.g., tinnitus or agitation), usually seen immediately after an intravascular injection of local anesthetic, to seizures, reflecting the plasma levels of the local anesthetic. Thereafter, if plasma levels of the local anesthetic continue to rise, ventricular arrhythmias and cardiac arrest

could occur. An article by Di Gregorio (Di Gregorio, 2010), reviewed published cases of LAST from 1979 to 2009 to determine if the presentation of LAST followed this progression. Of note, Di Gregorio found that almost 50% of the cases occurred under one minute. However, he also found that 25% of the cases occurred after five minutes, with one case presenting after 60 minutes. The delayed presentations of toxicity were predominantly associated with continuous infusions. He also reported that neurologic toxicity (CNS) occurred in 89% of these cases (45% were CNS only with no cardiovascular systems). Furthermore, the most common presenting CNS event was seizure in 68% of cases. Symptoms of cardiovascular toxicity (CV) occurred in 55% of cases, with isolated cardiovascular symptoms in 11% of cases. Bradycardia and hypotension were the first change in vital signs noted. Di Gregorio noted that 41% of the cases did not follow the classic progression of symptoms (Figure 1.b).

Figure 1.a. Classic Progression of Signs and Symptoms of LAST

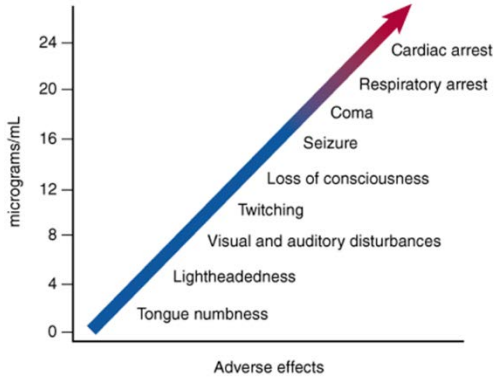


Figure 1.b. Spectrum of Presenting Signs (Di Gregorio 2010)

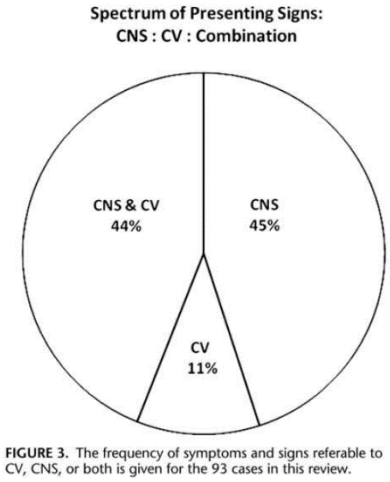


FIGURE 3. The frequency of symptoms and signs referable to CV, CNS, or both is given for the 93 cases in this review.

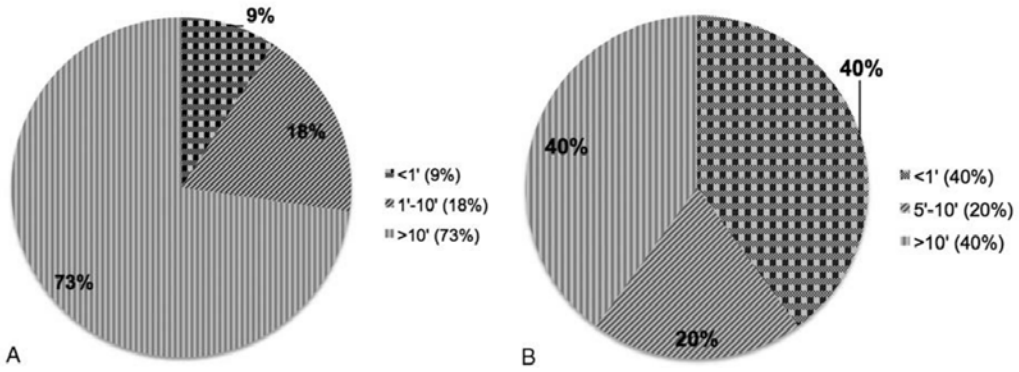
In 2015, Vasques (Vasques, 2015), published a follow up to the Di Gregorio article. He examined reports of LAST published between March 2010 to March 2014, with 67 separate LAST events reported. Of the 67 cases, 50 cases occurred after a single injection of LA, 8 cases occurred during a continuous infusion of LA, 8 cases followed topical administration of LA, and 2 cases were after

inadvertent intravascular injection through a venous cannula. The most common signs and symptoms of LAST were broken down into the following categories:

- Isolated CNS toxicity - 50% of cases (most common sign was seizure)
- Isolated CV toxicity - 14% of cases (most common sign was bradycardia, hypotension, and shock)
- Combined CNS and CV toxicity - 36% of cases

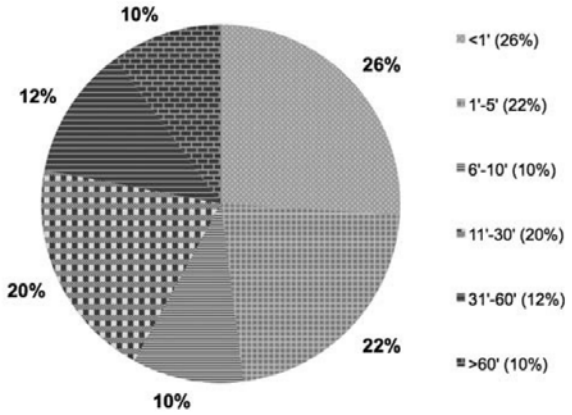
Single-shot ultrasound guided regional anesthesia (Figure 2. A) compared to single-shot regional anesthesia performed with electric nerve stimulation guidance (Figure 2. B) demonstrated the following shift in timing of onset of signs and symptoms (Vasques, 2015).

Figure 2. Onset time of LAST comparing ultrasound (A) to electric nerve stimulation (B) guidance



Furthermore, Vasquez, summarizes the onset time of LAST after all single-shot regional anesthetics (Figure 3).

Figure 3. Onset time of LAST after single-shot regional anesthesia



These data support the likelihood that the timing of the onset of LAST may be delayed and may present during the anesthetic (general or sedation) when symptoms may be masked or occur after a patient is discharged to a lower level of care with less frequent monitoring.

Di Gregorio (Di Gregorio, 2010) made another observation is his paper, stating that "pre-existing cardiac or neurologic disease might lower the threshold for symptomatic local anesthetic toxicity." This highlights the importance of knowing the risk factors that increase the risk of LAST to facilitate early recognition and treatment of LAST. Patient factors (e.g., extremes of age, end organ dysfunction, carnitine deficiency, and other metabolic derangements) can increase the free plasma concentration or increase sensitivity to local anesthetics. With an underappreciation of delayed onset of LAST and increased risk in patients with neurologic or cardiac conditions, it is likely that LAST, especially delayed onset, may not be considered in the differential diagnosis. Instead, symptoms are attributed to the patients' comorbid condition(s); therefore, no consideration is given to specific treatment of LAST in the management of the events.

The Office of Surveillance and Epidemiology (OSE) was consulted for a review of the LAST case reports from FDA's Adverse Event Reporting System and published medical literature that are associated with Exparel and injectable immediate-release local anesthetics. Immediately following is a summary of OSE's findings.

Summary of the Office of Surveillance and Epidemiology (OSE) Pharmacovigilance and Drug Utilization Review of Local Anesthetic Systemic Toxicity

On September 27, 2017, the Office of Surveillance and Epidemiology (OSE) completed a review that assessed local anesthetic systemic toxicity (LAST) case reports from FDA's Adverse Event Reporting System (FAERS) and the published medical literature associated with Exparel (bupivacaine liposome injectable suspension) and injectable immediate release (IR) local anesthetics (LAs). The review also included drug utilization analyses to provide context for the case reports. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested the review over concern that Exparel may cause a delayed onset of LAST due to its unique formulation, in comparison with a rapid onset of LAST with IR LAs. All LA labels include varying language that describe signs and symptoms of LAST (generally within 1 hour of injection) or list "systemic toxicity" as an adverse event; however, labels do not describe – explicitly – the potential for delayed onset of LAST. The OSE review defined rapid onset LAST as occurring ≤1 hour after LA administration and delayed onset LAST as occurring greater than1 to 96 hours after LA administration.

OSE's analysis identified 93 cases of LAST reported with Exparel and IR LAs through July 26, 2016. Exparel use was reported in 36 cases (including 21 cases of Exparel alone and 15 cases of Exparel with a concomitant IR LA), and IR LA use was reported in 57 cases (including 19 cases with more than one IR LA). Of the 93 cases, 11 reported Exparel with delayed onset LAST, and three cases reported IR LAs with delayed onset. The time to onset among the delayed onset cases for Exparel and the IR LAs differed, with a range of 65 minutes to 72 hours for Exparel and 80 minutes to 12 hours for IR LAs; however, OSE identified medical literature that suggests other factors (e.g., age, renal dysfunction, hepatic dysfunction, cardiac disease, pregnancy, block site

and technique) may delay the onset of LAST for several days after the initiation of an IR LA. Rapid onset LAST was reported for both Exparel and IR LAs; however, a greater proportion of the IR LA cases occurred within five minutes. The clinical presentation of LAST can be highly variable and predominantly involves cardiac and neurologic toxicities. However, the reported cardiac and neurologic clinical symptoms were similar among the Exparel and IR LA cases and among the rapid and delayed onset cases. Eight cases reported a fatal outcome, and all but one case reported a serious[a] outcome. Approximately one third of the Exparel cases and more than half of the IR LA cases reported the off-label use of lipid emulsions to treat the LAST symptom(s). Cases generally involved hospital or outpatient settings; only one case reported LA administration in a dental setting.

Based on the case report and drug utilization findings, the OSE review suggests that LAST appears to be rarely reported with Exparel and IR LAs relative to its use. In the non-federal hospital setting alone, analyses of the drug utilization data showed a nationally estimated number of 28 million patients had an inpatient or outpatient discharge billing for local anesthetic injectable products in 2015.[i] Of this population, approximately 23 million patients and 7 million patients had an inpatient or outpatient discharge billing for single-ingredient lidocaine or bupivacaine injectable products (brand and generic products grouped together), respectively. The number of patients who had an inpatient or outpatient discharge billing for single-ingredient bupivacaine injectable products increased by 52% from 2002 to 2015. Moreover, the sales data showed that in 2015, Exparel® accounted for 4% of sales of single-ingredient bupivacaine injectable products sold from manufacturers. The sales of Exparel® increased from approximately 40,000 vials in 2012 to 781,000 vials in 2015.[ii]

On November 8, 2017, in preparation for this advisory committee meeting, OSE searched FAERS and the medical literature to identify additional cases of LAST with Exparel and IR LA use reported since the previous OSE review. OSE identified and evaluated 18 additional cases from FAERS (n=12) and the medical literature (n=6). Three cases reported Exparel and LAST and 15 cases reported one or more IR LA and LAST. All 18 cases reported either rapid onset LAST (n=15) or did not report a time to onset of LAST (n=3). No additional cases reported delayed onset LAST with either Exparel or an IR LA. All but three cases reported administration of lipid emulsion to treat LAST. Ten cases reported measures to prevent LAST (i.e., ultrasound, aspiration, nerve stimulation). Seventeen of the 18 cases reported the patient recovered from LAST, and the remaining case did not report an event outcome.

In summary, the OSE review concluded that analyses of FAERS and the medical literature supports an association between the use of Exparel and all injectable IR LAs and LAST, with variable time of onset and clinical presentation. The FAERS case series supports that Exparel is associated with both rapid and delayed onset LAST. The FAERS case series and medical literature support the premise that IR LAs are also associated with rapid and delayed onset LAST. Although unapproved for the treatment of LAST, lipid emulsion administration is frequently described in the medical literature in treatment and successful reversal of LAST.

[a] Serious adverse drug experiences per regulatory definition (21 CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

Reference List

Vasques F, et al. (2015) A Review of Local Anesthetic Systemic Toxicity Cases Since Publication of the American Society of Regional Anesthesia Recommendations. Reg Anesth Pain Med 40: 698–705.

[i] IQVIA, Hospital Visit Analyzer (HVA). Years 2002-2015. Data extracted July 2016.
[ii] IQVIA, National Sales Perspectives (NSP). Years 2006-2015. Data extracted July 2016.