CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	22-496/0000
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Indication(s):	Postsurgical analgesia
Applicant:	Pacira Pharmaceuticals
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Keywords: clinical studies, NDA review, double-blind, foreign clinical data

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1. EXECUTIVE SUMMARY

Pacira Pharmaceuticals has submitted an application evaluating Exparel, an extended release formulation of bupivacaine, for the treatment of post-surgical pain. Based on my review of the data from two placebo-controlled clinical trials, SKY0402-C-316 (hemorrhoidectomy) and SKY0402-C-317 (bunionectomy), there is evidence to support the efficacy of Exparel in treating post-surgical pain. For both studies, the analyses of the predefined primary efficacy endpoints were statistically significant in favor of Exparel. The evidence of an analgesic effect was further supported by the analyses of secondary endpoints such as the proportion of patients that were pain free and time to first use of rescue medication.

The treatment effect for Study SKY0402-C-317 was much smaller than that in Study SKY0402-C-316. To explore this, I examined mean pain intensity (PI) scores by time. In the hemorrhoidectomy study, patients randomized to Exparel had stable pain scores following surgery, Figure 1. However in the bunionectomy study, this effect was not observed, Figure 2. In fact, following surgery, mean PI scores increased from mild to moderate for patients randomized to both Exparel and placebo, but there was less of an increase in pain for those patients treated with Exparel when compared to placebo-treated patients. The clinical relevance of the treatment effect observed in the bunionectomy study will need to be determined.

(b) (4)

Additionally, Study SKY0402-C-316 was conducted entirely in Eastern Europe. The clinical review team has requested the Applicant explain the generalizability of these results to patients in the Unites States. The Applicant's response was not available prior to the finalization of my review.

2. INTRODUCTION

2.1 Overview

The Applicant states that bupivacaine is one of the longer acting local anesthetics; its duration of action is usually limited to no more than 12 hours when administered via local infiltration. Exparel is an extended-release liposomal formulation of bupivacaine that is to be administered as a single dose by local infiltration into the surgical wound at the end of the surgical procedure.

(b) (4)

The development program for Exparel was conducted under IND 69,198. The Applicant submitted the results of two placebo-controlled Phase 3 studies (b) (4) (b) (4) These were randomized, double-blind, parallel-group trials designed to demonstrate superiority of Exparel over the control group, either placebo or standard release

bupivacaine. [redacted] (b) (4)

Table 1. Phase 3 clinical studies

Study	Phase	Placebo/ active	Region	Exparel Dose (mg)	Surgical Procedure
[redacted] (b) (4)					
SKY0402-C-316	3	Placebo	Eastern Europe	300	Hemorrhoidectomy
SKY0402-C-317	3	Placebo	United States	120	Bunionectomy

Source: Reviewer

Study SKY0402-C-316 (C-316) was conducted from May 2009 to August 2009 at sites in the Republic of Georgia, Poland, and Serbia. The protocol for this study was reviewed by me in September 2009. Concerns noted were the Applicant's definition of the analysis population, the proposed number of measurements needed to calculate an AUC, and the lack of incorporation of rescue medication into the primary analysis.

Study SKY0402-C-317 (C-317) was conducted from April 2009 to September 2009 at three sites in Texas and one site in Utah. The protocol for this study was also reviewed by me in September 2009. I had concerns regarding the Applicant's definition of the analysis population, number of measurements required to calculate an area-under-curve (AUC), and incorporation of the use of rescue medication in the primary analysis. The statistical analysis plan (SAP) for this study was reviewed by me in November of 2009. The SAP indicated only two measurements were needed to calculate an AUC, not four as was stated in the reviewed protocol.

2.2 Data Sources

All data was supplied electronically by the Applicant as SAS transport files and can be found at the following location in the CDER electronic document room (EDR):

\\cdsesub1\evsprod\NDA022469\0000\m5\datasets

3. STATISTICAL EVALUATION

Studies C-316 and C-317 were of similar design; however, the dose was different for each procedure and the primary efficacy endpoint (AUC for PI scores) was evaluated at different times post-surgery. These studies will be evaluated separately under Sections 3.2.1 and 3.2.2.

3.1 Data and Analysis Quality

The electronic data submitted by the Applicant for the two Phase 3 studies was of sufficient quality to allow a thorough review of the data. I was able to derive the primary and secondary

endpoints for each study. The statistical analyses of my derived endpoints were in agreement with the Applicant's analyses.

DSI audits of the sites in the Republic of Georgia from Study C-316 did not reveal any findings that suggested compromised data integrity. The overall inspection results indicate that the study data were collected according to the protocol and applicable good clinical practice regulations.

3.2 Evaluation of Efficacy

My review (b) (4) focuses on the two placebo-controlled studies that demonstrated a significant treatment effect in favor of Exparel.

3.2.1 Study C-316

In this New Drug Application, the Applicant appropriately addressed some of the concerns conveyed during the development process. Use of rescue medication was accounted for in the primary analysis and a revised protocol stated that only two measurements would be required to calculate an AUC. However despite the Division's advice, the Applicant's analysis population excluded patients that did not have at least two post-treatment pain measurements. Upon review, I concluded that this was not a concern as only two patients were excluded based on a lack of post-treatment measurements.

Study Design and Endpoints

Eligible patients that were to undergo a hemorrhoidectomy were randomized to either placebo or Exparel 300 mg in a 1:1 ratio. Following surgery, a single dose of the study drug was administered into the surgery site via infiltration. Rescue analgesia for break-through pain was morphine every 4-6 hours over the first 72 hours. No other analgesic agents were allowed during the first 72 hours. Subjects were discharged 72 hours after surgery. Post-operative efficacy assessments included PI at rest and during bowel movement, use of rescue medication, time of first bowel movement, post-operative nausea and vomiting, and occurrence of constipation. PI was assessed using an 11-point scale with 0 being no pain and 10 the worst pain and was measured at baseline (prior to surgery), end of general anesthesia, before first dose of rescue medication, and at 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after surgery.

The pre-specified primary efficacy outcome was the AUC of PI scores out to 72 hours (AUC_{72}). Secondary efficacy outcomes included AUC at other time points, the proportion of patients who were pain free, defined as a PI score of 0 or 1, and time to first use of rescue.

Based on the results of a Phase 2 hemorrhoidectomy study, the Applicant estimated that a sample size of 90 subjects per treatment arm would provide 90% power to detect a treatment effect.

Patient Disposition, Demographic and Baseline Characteristics

This study screened 235 patients in order to randomize 190 eligible subjects, 94 placebo and 96 Exparel. One patient, a 61 year old Caucasian female, was randomized to Exparel but was not treated due to an existing medical condition. Demographics for all randomized and treated patients are shown in Table 2.

Table 2. Patient demographics for Study C-316

Characteristic	
Number of Patients (n)	189*
Age in years	
Mean (SD)	48(12)
Median	48
[range]	[18, 86]
Gender (%)	
Female	59 (31)
Male	130 (69)
Race (%)	
Caucasian	189 (100)

Source: Reviewer
*excludes one patient that was randomized but not treated

Since this was an inpatient study, there was a high completion rate, greater than 98%. In fact, only three patients withdrew consent and did not complete the study, two subjects in the placebo group and one in the Exparel group. Only two of these subjects were missing all observations and were not included in the Applicant's analysis population.

Statistical Methodologies

The Applicant defined the analysis population as the full analysis set (FA). The FA population included all subjects that underwent the surgical procedure, received study drug, and had at least two post-treatment PI scores. An AUC, similar to a time-weighted average, was calculated for each patient using PI scores measured at 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours post-dose. The Applicant proposed the following strategy to handle missing data.

- Missing scores before the first non-missing score would be replaced by the median score from other subjects in the same treatment group.
- Missing scores after the last non-missing score would be replaced by the last recorded observation. This is analogous to a last observation carried forward strategy for study dropouts.
- Missing scores between two non-missing scores would use linear interpolation.

Use of rescue medication was accounted for by using the worst observation carried forward within a specified window (wWOCF). If a patient received morphine at time x, for any time point within $x + 4$ hours, the highest score from time 0 up until time x was used. If the PI score for the windowed observation was higher than the worst observed score, it was not replaced.

To evaluate efficacy, the Applicant compared the primary efficacy outcome, AUC_{72}, for Exparel to placebo using an analysis of variance (ANOVA) model with treatment and country as main effects. The AUCs at other time points were analyzed using the same ANOVA model. Time to first post-operative use of rescue medication was analyzed using Kaplan-Meier methods. A log-rank test was used to compare the survival curves between Exparel and placebo, and the median time to first use of rescue medication was reported. Overall, the statistical

methodologies utilized by the Applicant for the analyses of the primary and secondary efficacy outcomes were acceptable.

To calculate the percentage of pain free patients, the Applicant used the wWOCF method which resulted in patients requiring rescue to be classified as pain free. For example, if a patient used rescue medication at 18 hours post-surgery and had a PI score < 2 at 24 hours, the patient would be classified as pain free. I did not find this to be appropriate and did not consider such a patient as being pain free since they had used rescue medication. I determined pain free status as a patient that had a PI score < 2 and had not used rescue medication at any time prior to that time point. The Applicant used a CMH test adjusted for country to compare the percentage of patients that were pain free. I used a Chi-square test or Fisher Exact test when the numbers of events were less than five, to compare the proportion of patients that were pain free at each time point.

I also examined the amount of rescue medication used through 72 hours. The total amount of morphine consumed was compared between treatment groups using an ANOVA model with treatment as fixed effect.

Results and Conclusions

The results of the Applicant's primary efficacy analysis and mine are shown in Table 3. My analysis differed from the Applicant's as I included the baseline PI score as a covariate in the ANOVA model. However, my results are consistent with the Applicant. There was a significant treatment effect in favor of Exparel.

Table 3. Results from the primary efficacy analysis from Study C-316

	AUC_{72hrs} (pi*hr) – mean (stderr)		Diff [95% CI]*	p-value
	Placebo (N=93)	Exparel (N=94)		
Applicant	202 (11)	142 (11)	60, [31, 90]	< 0.0001
Reviewer	207 (10)	144 (11)	62, [33, 92]	<0.0001

Source: Reviewer
* difference in LSMEANS

Based on the electronic data submitted by the Applicant, missing data was not an issue. This was not unexpected as the study was conducted in an inpatient setting and patients only received a single dose of treatment. There were two patients with intermittent missing data at the one hour post-treatment assessment. While the Applicant imputed this data using last observation carried forward, I used the mean PI score of the other patients in the same treatment group. This had no impact on the conclusion of the study. There was still a significant treatment effect in favor of Exparel.

The Applicant's analysis population excluded two randomized and treated patients that did not have at least two post-treatment PI scores. Even though the exclusion of two patients from the analysis likely did not bias the results, I examined the impact of this exclusion. I re-analyzed the data including these two patients. I used the mean score from the placebo group to impute the PI scores at each time point. My conclusion did not change; there was still a significant treatment effect in favor of Exparel for the primary efficacy endpoint. It is important to note that this

approach may not be acceptable in every setting, such as a study with a large amount of missing data or a chronic indication. However, since this study had very little missing data and was for an acute indication, this approach was acceptable.

The Applicant also examined several secondary endpoints. Although all of the secondary endpoints discussed below demonstrated an apparent treatment effect in favor of Exparel, there were no pre-specified adjustments to the analyses to account for multiple comparisons. These results are only supportive of the primary efficacy endpoint and should not be included as label claims.

The Applicant examined AUC values at 12, 24, 36, 48, and 60 hours post-surgery. The results for comparison of the two treatment groups are shown in Table 4. These are the results from my analysis where I included the baseline PI score as a covariate. My conclusion was the same as the Applicant's. There was a significant difference in favor of Exparel at each time point.

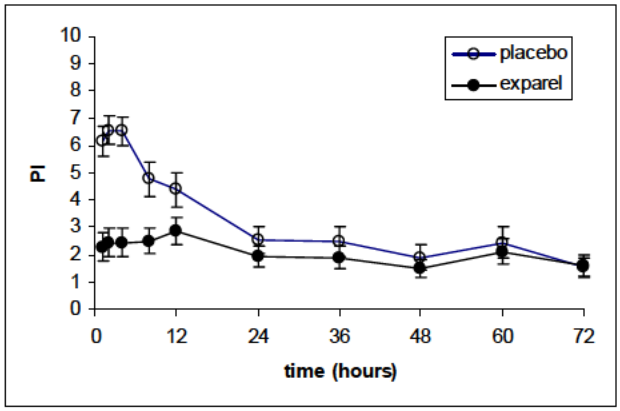
Table 4. Comparison of AUCs at all time points in Study C-316

Time point	AUC (pi*hr) – mean (stdev)		diff	p-value
	Placebo	Exparel		
2	6 (2)	2 (2)	4	<0.0001
4	19 (7)	7 (7)	12	<0.0001
8	42 (16)	17 (15)	25	<0.0001
12	60 (25)	28 (22)	32	<0.0001
24	102 (48)	57 (40)	45	<0.0001
36	132 (65)	80 (56)	52	<0.0001
48	158 (81)	100 (69)	58	<0.0001
60	184 (97)	121 (81)	63	<0.0001
72	144 (96)	207 (111)	63	< 0.0001

Source: Reviewer

As an AUC is cumulative and derived from the PI scores measured at each time point, I examined the mean PI scores by treatment group at each time point, Figure 1. To account for the use of rescue medication, I applied the Applicant's wWOCf method. Error bars indicate the 95% confidence interval of the point estimate. This approach may help with the clinical interpretation of the effect size observed with the primary endpoint, AUC_{72}.

Figure 1. Mean PI scores at each measured time point in Study C-316



Source: reviewer

In the above figure, there is separation between the two curves out to approximately 24 hours post-surgery. After 24-hours, the mean PI scores for the placebo group have diminished and are at levels similar to that of Exparel. Of note, the significant difference demonstrated in the comparison of AUC of PI scores at 36, 48, 60, and 72 hours (Tables 3 and 4) is most likely influenced by the early separation in the curves. Based on this information, the benefit of Exparel after 24 hours post-surgery is unclear.

The percentage of patients that were pain free was determined at each time point. The Applicant's method utilized their wWOCF imputation when a patient used rescue medication. My approach considered any patient using rescue medication prior to the assessed time point as not being pain free. The results from both approaches are shown in Tables 5 and 6.

Table 5. Percentage of patients that were pain free in Study C-316, Applicant's method

Treatment	Percentage of patients pain free at each time point									
	1	2	4	8	12	24	36	48	60	72
placebo	10	14	14	20	25	44	55	67	61	63
SKY0402	48*	52*	51*	51*	49*	59*	62	60	59	57

Source: Modified from Applicant's Table 14.2-2.2.1, page 62 of CSR
* p-value < 0.01 (CMH test adjusted for country)

Table 6. Percentage of patients that were pain free in Study C-316, Reviewer's method

Treatment	Percentage of patients pain free and did not use rescue medication prior to that time point									
	1	2	4	8	12	24	36	48	60	72
placebo	9	4	2	2	3	6	8	8	6	5
SKY0402	48	45	46	39	30	23	24	20	17	16
p-value	*	*	*	*	*	0.001	0.002	0.01	0.02	0.02

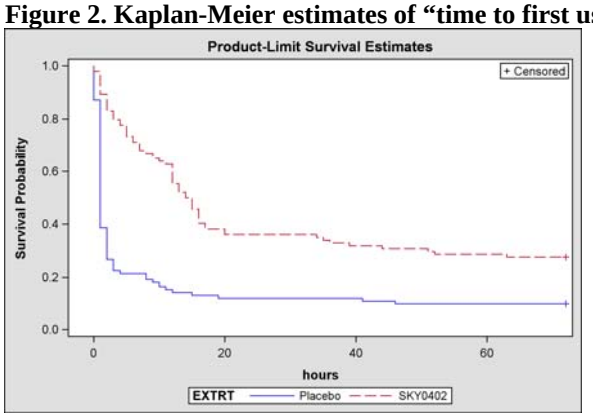
Source: Reviewer
* p-value < 0.0001 (Chi-square test)

Regardless of the method utilized to analyze the data, more patients on Exparel were pain free for a longer period of time than patients that received placebo. In my analyses, there was a

significant treatment effect observed out to 72 hours post-dose while the Applicant's analyses only reported significance out to 24 hours. However, the analyses do not account for multiple comparisons. If I applied a conservative method such as a Bonferroni correction to my analyses, significance would be established using an alpha of 0.005. Using this method statistical significance would only be demonstrated out to 36 hours post-surgery.

The median time to first use of post-operative rescue medication was 1 hour in placebo patients and 15 hours in patients treated with Exparel. Using Kaplan-Meier methods, the survival curves for time to first use of rescue medication for patients on placebo and Exparel are shown in Figure 2.

Figure 2. Kaplan-Meier estimates of "time to first use of rescue medication" for Study C-316



Source: Reviewer

Based on the log-rank test, p-value < 0.0001, a significant difference exists in the distributions of time to first use of rescue medication for the two treatment groups in favor of Exparel.

When I examined total amount of rescue medication (morphine) used through 72-hours post-surgery, there was a significant difference between treatment groups. Placebo-treated patients used a mean amount of 29 mg versus 22 mg for Exparel-treated patients.

There was a statistically significant difference between treatment arms for the primary efficacy endpoint, AUC_{72}. This finding was supported by the mean PI scores by time, Figure 1. Further evidence was provided by the analyses of the percentage of patients pain free, time to first use of rescue medication, and total amount of rescue medication used post-surgery.

3.2.2 Study C-317

The Applicant did address most of the concerns noted in my review of the protocol and SAP in 2009. The primary analysis was revised to account for the use of rescue medication and stated only two measurements are required to calculate an AUC. However, the analysis population still excluded patients that lacked post-treatment efficacy assessments.

Based on the results of a Phase 2 study that evaluated capsaicin in treating post-operative pain associated with a bunionectomy surgery, the Applicant estimated 93 subjects per treatment arm would provide 90% power. This calculation was based on a difference of 22 points in AUC and a pooled standard deviation of 46.

Study Design and Endpoints

Eligible patients that were to undergo a unilateral first metatarsal osteotomy (bunionectomy) were randomized to either placebo or Exparel 120 mg in a 1:1 fashion. Following surgery, a single dose of the study drug was administered intraoperatively by local infiltration. Subjects were then transferred from the surgery center to the inpatient unit. Allowed rescue medication was Percocet and if needed, a single IV dose of ketorolac. Staff at the inpatient unit were blind to a subject's treatment. During the inpatient stay, PI was measured (11-point NRS) prior to surgery (baseline), before first use of rescue, and 2, 4, 8, 12, and 24 hours post-treatment. Patients were discharged after 24 hours but were instructed to record pain scores and any use of rescue medication at approximately 36, 48, 60, and 72 hours post-treatment.

Patient Disposition, Demographic and Baseline Characteristics

Study C-317 enrolled 195 patients but only 193 received treatment, 96 placebo and 97 Exparel. Two randomized patients were not treated due to existing medical conditions; one subject had elevated blood pressure and one had unstable vital signs. Demographics for randomized and treated patients are shown in Table 7.

Table 7. Patient demographics for Study C-317

Characteristic	
Number of Patients (n)	193*
Age in years	
Mean (SD)	43 (13)
Median	44
[range]	[18, 72]
Gender (%)	
Female	159 (82)
Male	34 (18)
Race (%)	
Caucasian	138 (72)
Black	46 (24)
Multiple	5 (2)
Asian	3 (1.5)
American Indian or Alaska Native	1 (0.5)

Source: Reviewer
*excludes two patients that were randomized but not treated

There were eight randomized and treated subjects that did not complete the study, four in the placebo group and four in the Exparel group, Table 8. One patient in the placebo group withdrew from the study due to a serious adverse event, deep vein thrombosis. Protocol violations accounted for the three discontinuations classified as "other".

Table 8. Disposition of patients that discontinued in Study C-317

Reason for Discontinuation	Placebo	Exparel	Total
Death	0	0	0
Adverse event	1	0	1
Withdrew consent	3	1	4
Other	0	3	3

Source: Reviewer

Statistical Methodologies

The statistical methods utilized in Study C-317 were similar to those used in Study C-316 except that the primary endpoint was the AUC out to 24 hours (AUC_{24}) instead of AUC_{72}. To account for rescue medication, the window used for the wWOCF imputation strategy was six hours instead of four. The Applicant used an ANOVA model with treatment, site, and baseline PI score as fixed effects in the model. This same model was used to compare the AUC at other time points. Although the Applicant's definition of the analysis population excluded patients that did not have at least two post-treatment PI scores, there were no patients that met this criterion.

As I did for Study C-316, I used a different method to establish the percentage of patients that were pain free at each time point. I determined "pain free" status as a patient that had a PI score of 0 or 1 at each time point and had not used rescue medication prior to that time point. The Applicant used a CMH test adjusted for site to compare the percentage of patients that were pain free. I used a Chi-square test or Fisher Exact test when the numbers of events were less than five, to compare the proportion of patients that were pain free at each time point.

As with Study C-316, I examined the amount of rescue medication used through 72 hours. Percocet was converted to morphine equivalents (mg) and compared between treatment groups using an ANOVA model with treatment as a fixed effect. Since there is no available method to convert ketorolac to morphine equivalents, this data was analyzed separately as the proportion of patients that received ketorolac using a Chi-square test.

There was a pre-planned interim analysis in Study C-317 that occurred when approximately 20% of the subjects had completed the 72 hour visit. The purpose of this interim analysis was to verify the assumptions used to estimate the sample size and was conducted by an un-blinded statistician not involved in any other aspect of the study. There were no adjustments incorporated into the final analysis to preserve the over all Type I error. It was pre-specified that the sample size could not be reduced and could only be increased up to a maximum of 225 patients.

Similar to Study C-316, missing data was not an issue as patients were hospitalized for 24 hours following surgery and received a single injection. Four patients withdrew consent, but only one of these patients withdrew consent prior to the 24 hours. Two patients withdrew consent after 72 hours post-surgery so there was no missing efficacy data for these two patients. Table 9 lists each patient with missing data, the Applicant's explanation of why the data was missing, and the imputation method utilized in the analyses.

Table 9. Patients with missing data in Study C-317

Subject ID	Missing time points (hr)	explanation	Imputation	
			Applicant	Reviewer
1000028	36, 48, 60, 72	WD consent	LOCF	WOCF
1000048	24, 36, 48, 60, 72	WD consent	LOCF	WOCF
2000056	36,48,60,72	protocol violation	WOCF/LOCF	WOCF
3000005	48, 60, 72	protocol violation	WOCF/LOCF	WOCF
3000050	36,48,60,72	AE	LOCF	WOCF
4000012	36	intermittent missing	linear interpolation	mean of 24 and 48 hour

Source: Reviewer

Results and Conclusions

Based on the results of the Applicant's interim analysis, the sample size was not increased. An interim analysis that is estimating a pooled standard deviation does not need to unblind the treatment assignment, however the treatment assignments were revealed to the statistician that conducted the Applicant's analysis. While this is not ideal, the statistician that conducted the interim analysis was not involved in any other aspects of the study and the Applicant had pre-specified that the sample size could not be reduced. They had also specified the sample size could only be increased to a maximum of 225 patients. Based on this information, I agreed with the Applicant, no adjustment to the overall significance level was required.

Analysis of the primary efficacy outcome measure, AUC_{24}, demonstrated a significant treatment effect in favor of Exparel. The mean AUC_{24} for the Exparel group was lower than that of the placebo group. The Applicant's results along with mine are shown in Table 10.

Table 10. Results from the primary efficacy analysis from Study C-317

	AUC_{24hrs} (pi*hr) – mean (stderr)		Diff [95% CI]*	p-value
	Placebo	Exparel		
Applicant	146 (4)	125 (5)	22 [10, 35]	0.0005
Reviewer	146 (4)	123 (5)	24 [11, 37]	0.0002

Source: Reviewer
*difference in LSMEANS

AUC values at other time points were also compared using the same ANOVA model as used for the primary endpoint. These results are shown in Table 11.

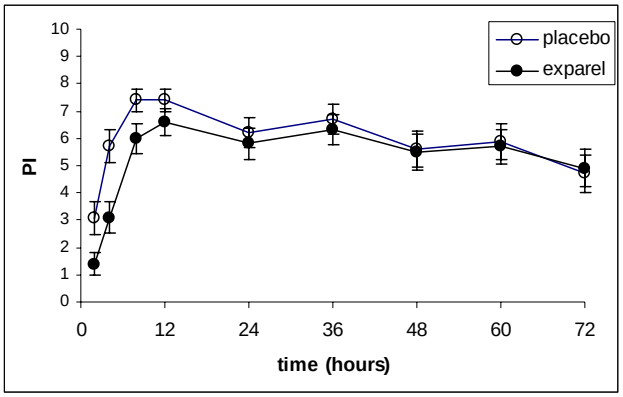
Table 11. Comparison of AUCs at all time points in Study C-317

Time point	AUC (pi*hr) – mean (stdev)		diff	p-value
	Placebo	Exparel		
4	9 (5)	4 (5)	5	<0.0001
8	35 (14)	23 (14)	12	<0.0001
12	64 (20)	48 (23)	16	<0.0001
24	146 (41)	123 (49)	23	0.0002
36	223 (67)	195 (78)	28	0.005
48	297 (94)	266 (108)	31	0.03
60	366 (123)	334 (139)	32	0.08
72	429 (153)	398 (171)	31	0.16

Source: Reviewer

In addition, the mean PI scores for each treatment group were plotted against time, Figure 2. To account for the use of rescue medication, the Applicant's wWOCF method was utilized. The error bars indicate the 95% CI for the point estimate.

Figure 3. Mean PI scores at each measured time point in Study C-317.



Source: reviewer

Even though there is separation in the curves out to approximately 24 hours post-surgery, this separation may or may not be clinically relevant as mean PI scores for all patients increased from mild, score between 1 and 3, to moderate, score between 4 and 7.

The percentage of patients that were pain free at each time point is shown in Tables 12 and 13. The Applicant's wWOCF method was utilized to account for the use of rescue medication. My method considered any use of rescue medication prior to that time point as an indication of pain.

Table 12. Percentage of patients that were pain free in Study C-317, Applicant's method

treatment	Percentage of patients pain free at each time point								
	2	4	8	12	24	36	48	60	72
placebo	46	15	3	4	17	20	19	26	35
Exparel	68*	38*	13*	11	18	21	35*	35	33

Source: Applicant (modified from Table 14.2-2.2.2.1 in CSR)
* p-value < 0.01 (CHM test adjusted for site)

Table 13. Percentage of patients that were pain free in Study C-317, Reviewer's method

treatment	Percentage of patients pain free and did not use rescue medication prior to that time point								
	2	4	8	12	24	36	48	60	72
placebo	42	14	0	0	1	0	1	1	2
Exparel	68	37	7	2	3	3	3	3	3
p-value	*	*	0.007	0.5	0.6	0.2	0.6	0.6	1.0

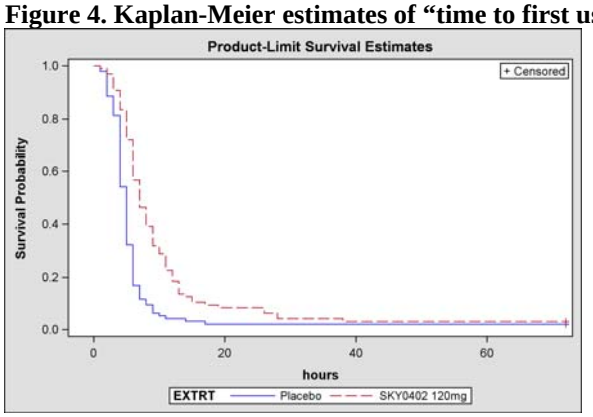
Source: Reviewer

* p-value < 0.001 (Chi-square or Fisher's Exact test)

After eight hours post-surgery, regardless of the method, there was no longer a significant difference in the percentage of patients that were pain free.

The median time to first use of rescue was 5 and 7 hours for the placebo and Exparel groups, respectively. Using Kaplan-Meier methods, the survival curves depicting the time to first use of rescue medication for patients on placebo and Exparel are shown in Figure 4.

Figure 4. Kaplan-Meier estimates of "time to first use of rescue medication" for Study C-317



The log-rank test comparing the two survival curves was significant, p-value < 0.0001. This suggests that subjects treated with Exparel do not require rescue medication as soon as placebo-treated patients.

When I examined the mean total amount of morphine equivalents (mg) used through 72 hours post-surgery, there was not a significant difference; 82 mg versus 85 mg for placebo and Exparel, respectively. In addition, there was not a significant difference in the percentage of patients that used ketorolac, 43% versus 31% for placebo and Exparel, respectively.

Even though there was a statistically significant difference for the primary efficacy endpoint and various secondary endpoints, the clinical interpretation and meaningfulness of the effect size observed with the primary endpoint, AUC_{24} is not clear. When I examined mean PI scores by time, Figure 2, Exparel did not seem effective at controlling post-operative pain associated with bunionectomy. Further, there was not a significant difference for total amount of rescue medication used through 72 hours-post surgery.

3.3 Evaluation of Safety

The primary medical officer, Dr. Arthur Simone, reviewed the safety data for this application.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The Applicant examined the primary efficacy endpoint in both studies for any differences due to age, gender, or racial subgroup. Age was categorized as less than 40 years old, at least 40 but less than 65, and older than 65 years in age. Racial subgroups were categorized as Caucasian or not Caucasian. For Study C-316, country was examined for any differences in the primary endpoint. For Study C-317, site was examined for any differences in the primary endpoint. Each study will be discussed separately below.

For age and sex, the Applicant summarized the primary endpoint for each subgroup. Country (Study C-316) or site (Study C-317) was included as a fixed effect in the primary analysis (ANOVA). To further explore the efficacy within subgroups, I examined the primary endpoint for a treatment interaction with age, gender, and country. Using an ANOVA model, I included a treatment interaction for age, racial subgroup, sex, and country or site.

Study C-316

Since all patients in this study were classified as Caucasian, racial subgroups were not summarized. The results for the other subgroups are shown in Table 14.

Table 14. Subgroup analysis for age, gender, and country in Study C-316

Subgroup		Mean AUC_{72} (stdev)	
		Placebo	Exparel 300 mg
Gender	Female (n=58)	200 (105)	122 (97)
	Male (n=129)	210 (114)	154 (94)
Age	< 40 (n=41)	247 (114)	162 (109)
	40 ≤ age < 65 (n=127)	205 (108)	140 (94)
	≥65 (n=19)	151 (107)	126 (74)
Country	Republic of Georgia (n=72)	250 (108)	121 (92)
	Poland (n=50)	176 (92)	157 (109)
	Serbia (n=65)	185 (115)	158 (86)

Source: Reviewer

While there was not a significant treatment interaction for gender or age, there was a significant treatment interaction with country. The magnitude of the treatment effect in the Republic of Georgia was much larger than the treatment effect observed in Poland or Serbia. However, I was not concerned with this as there was a treatment effect observed in all countries and the study was not powered to detect treatment effects in individual countries.

Study C-317

The results of the primary efficacy analysis, AUC_{24}, were evaluated for any treatment interactions with sex, age, or using the ANOVA model described above. The results are shown in Table 15.

Table 15. Subgroup analysis for age, gender, race, and site in Study C-317

Subgroup		Mean AUC_{24} (stdev)	
		Placebo	Exparel 120 mg
Gender	Female (n=159)	144 (41)	120 (49)
	Male (n=34)	157 (42)	132 (50)
Age	< 40 (n=83)	148 (41)	125 (53)
	[40, 65) (n=104)	141 (41)	122 (47)
	≥ 65 (n=6)	165 (43)	70 (-)
Racial Subgroup	Caucasian (n=138)	146 (40)	126 (51)
	Not Caucasian (n=55)	144 (46)	114 (46)
Site	Austin, TX (n=59)	150 (38)	112 (42)
	San Marcos, TX (n=43)	144 (39)	144 (46)
	Houston, TX (n=58)	153 (43)	120 (52)
	Salt Lake City, Utah (n=33)	126 (44)	115 (54)

Source: reviewer

This study was conducted mainly in female patients as bunions are more common in women than men. There were no significant interactions of treatment with any of the subgroups examined. However, it is interesting to note there was not a treatment effect observed at the site in San Marcos, TX. The Applicant did not provide an explanation as to why there was not a treatment effect observed at this site. I performed an exploratory analysis of baseline characteristics (age, gender, race, and baseline pain score) but did not find any significant differences in this site from the other sites.

4.2 Other Special/Subgroup Populations

For Study C-317, no other subgroups of interest were identified or analyzed. However for Study C-316, the reviewing medical officer observed that nine patients had pain scores that were denoted as "completed with a hand of the investigator based on verbal interview with patients." As an exploratory analysis, I removed these patients from the primary analysis. My conclusions did not change; there was still a significant treatment effect in favor of Exparel.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

I reviewed two Phase 3 clinical trials to evaluate the efficacy of Exparel in treating post-operative pain. There was a significant treatment effect for the pre-defined primary efficacy endpoint and various supportive secondary endpoints in both studies. There were no concerns regarding the analysis populations, statistical analyses, or imputation of missing data that could

not be addressed. The Applicant's approach to handling use of rescue medication in the primary analysis was appropriate. Each study is discussed separately below.

For Study C-316, the analysis of the primary efficacy endpoint, AUC of PI scores out to 72 hours, demonstrated a significant treatment effect in favor of Exparel. This was supported by the analyses of various secondary endpoints such as percentage of patients that were pain free and time to first use of rescue medication. (b) (4) Furthermore, since this study was conducted entirely in Eastern Europe, the Applicant was requested to provide evidence that the surgical procedures in Europe are similar to those conducted in the United States.

In Study C-317, there was a significant treatment effect noted for the primary efficacy endpoint, AUC of PI scores out to 24 hours, and secondary endpoints, percentage of patients that were pain free and time to first use of rescue. However, there was not a significant difference in the total amount of rescue medication used through 72 hours post-surgery. Furthermore, I questioned the treatment effect when I examined mean PI scores by time. Exparel did not seem effective at controlling post-surgical pain associated with a bunionectomy as mean pain scores for patients treated with Exparel increased from mild to moderate following surgery. This effect was not observed in the hemorrhoidectomy study.

5.2 Conclusions and Recommendations

The analyses of the AUC_{24} and AUC_{72} yielded significant differences between Exparel and placebo for both studies and were supported by various secondary endpoints. Although an AUC is acceptable as the primary efficacy endpoint, differences in AUCs have little clinical interpretation when considering treatment effect size. One can examine the pain scores that make up an AUC to aid in the clinical interpretation. Figures 1 and 3 are graphs of the mean PI scores by time. For Study C-316, Figure 1 supports the statistical significance of the primary efficacy endpoint, AUC_{72}. The mean PI scores for patients on Exparel were maintained a mild level (score between 1 and 3) while placebo treated patients were not. However, for Study C-317, Figure 3 indicates that Exparel was not able to moderate post-surgical pain. Since this effect was also noted for placebo treated patients, I conclude that even though pain was increased following surgery, there was less of an increase for those patients treated with Exparel when compared to placebo treated patients.

(b) (4) In both figures, the separation between placebo and Exparel was diminished after 24 hours.

In conclusion, the efficacy of Exparel was demonstrated by treating post-surgical pain as indicated by the significance of the pre-specified primary endpoints and was supported by the significance of various secondary endpoints. The clinical significance of the treatment effect observed in Study C-317 will need to be determined by other members of the review team.

5.3 Label Review

Using the label provided in the submission, I have the following comments from Section 14. My comments and suggestions follow the Applicant's proposed wording and are italicized. It may be beneficial to include the graphs of mean PI scores by time, Figures 1 and 3, in the label.

The efficacy of EXPAREL™ was evaluated in Bunionectomy and Hemorrhoidectomy in two multicenter, randomized, double-blind, placebo-controlled studies. (b) (4)

(b) (4)

14.1 Bunionectomy

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluated the safety and efficacy of (b) (4) EXPAREL™ in 193 patients undergoing bunionectomy. The mean age was 43 years (range 18 to 72). Study medication was administered directly into the wound at the conclusion of the surgery, prior to wound closure. Pain intensity was rated by the patients on a 0-10 numeric rating scale (NRS). Post-operatively, patients were allowed rescue medication (5 mg oxycodone/325 mg acetaminophen orally every 4-6 hours as needed) or, if that was ineffective within the first 24 hours, ketorolac (15-30 mg IV).

The above is consistent with the study report.

(b) (4)

The above sentence is not readily interpretable by a clinician. I recommend deletion of this sentence.

(b) (4)

I recommend deletion (b) (4) *Since an AUC may not be readily interpretable, a statement such as "Patients randomized to Exparel experienced less post surgical pain compared to patients randomized to placebo" may be more appropriate.*

(b) (4)

(b) (4)

14.2 Hemorrhoidectomy

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluated the safety and efficacy of (b) (4) EXPAREL™ in 189 patients undergoing hemorrhoidectomy. The mean age was 48 years (range 18 to 86). Study medication was administered directly into the wound (≥3 cm) at the conclusion of the surgery. Pain intensity was rated by the patients on a 0-10 NRS at multiple time points up to 72 hours. Post-operatively, patients were allowed rescue medication (morphine sulfate 10 mg IM every 4 hours as needed).

The above is consistent with the study report.

(b) (4)

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(b) (4)

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/s/

DAVID M PETULLO
09/23/2011

DIONNE L PRICE
09/23/2011
Concur

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

NDA Number:	22-496
Drug Name:	Exparel
Indication(s):	For single-dose local administration into the surgical wound to produce postsurgical analgesia
Applicant:	Pacira Pharmaceuticals, Inc.
Date(s):	Received on June 1, 2011
Review Priority:	Standard
Biometrics Division:	VI
Statistical Reviewer:	Youngsook Jeon, Ph.D.
Concurring Reviewers:	Yi Tsong, Ph.D.
Project Manager:	Swati Patwardhan

Distribution: Yi Tsong, Ph.D.
ONDQA/Arthur B Shaw, Ph.D.
Swati Patwardhan

Table of Contents

1. EXECUTIVE SUMMARY

This review describes statistical findings on Pacira Pharmaceuticals' [redacted] (b) (4) stability data so that FDA Office of New Drug Quality Assessment can make informed decisions on the sponsor's proposal of 24-month shelf life.

The FDA statistician conducted a stability analysis to estimate a shelf life for [redacted] (b) (4) of Exparel based on 24-month stability data. Two acceptance criteria - [redacted] (b) (4) - are used. The estimated shelf lives are beyond the period covered by the data. Therefore, 24-month shelf life is supported by the stability data.

2. INTRODUCTION

This review describes statistical findings on Pacira Pharmaceuticals' stability data for [redacted] (b) (4) so that FDA Office of New Drug Quality Assessment (ONDQA) can make informed decisions on the sponsor's proposal of 24-month shelf life.

FDA statistician received 24-month stability data for [redacted] (b) (4) (see Table 1). The stability data were collected following the 2003 ICH guideline on the testing frequency: every 3 months over the first year, every 6 months over the second year, and annually thereafter throughout the proposed shelf life.

Table 1 Stability Data for [redacted] (b) (4) (microg/mL)

Vial	Batch	Available Data (month)
10	08-2508B	0, 3, 6, 9, 12, 18, 24
	08-2509B	0, 3, 6, 9, 12, 18, 24
	08-2510B	0, 3, 6, 9, 12, 18, 24
20	08-2508A	0, 3, 6, 9, 12, 18, 24
	08-2509A	0, 3, 6, 9, 12, 18, 24
	08-2510A	0, 3, 6, 9, 12, 18, 24

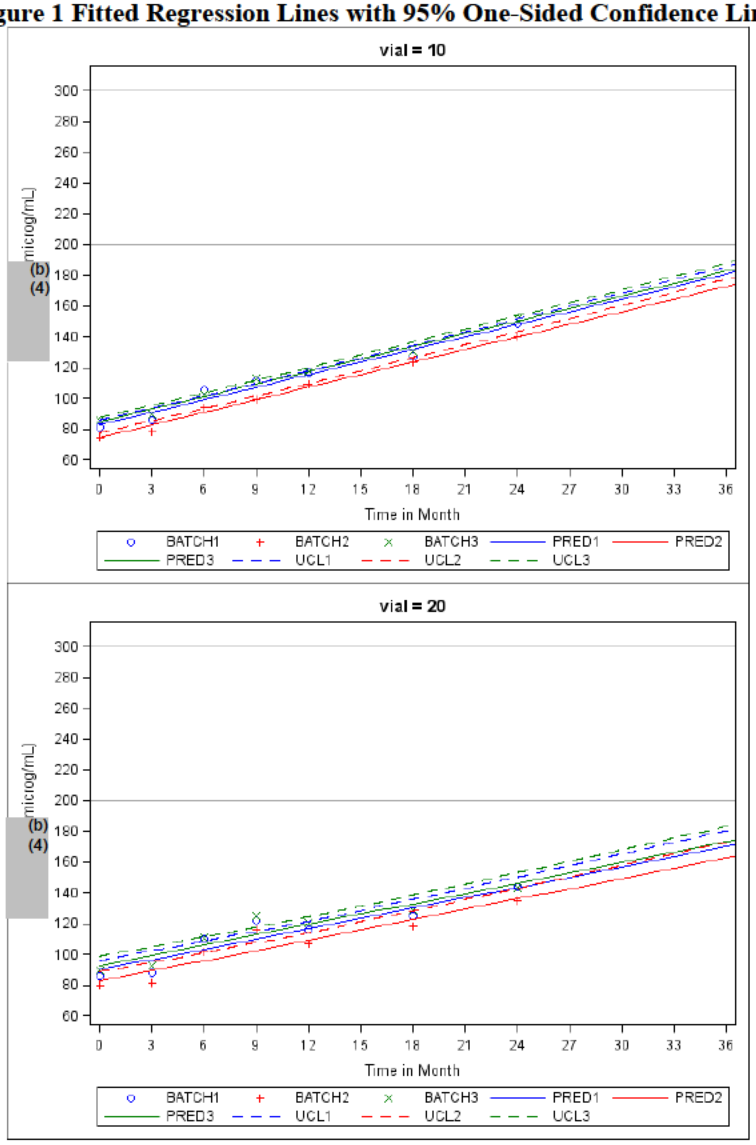
The sponsor proposed 24-month shelf life based on the proposed acceptance limit, [redacted] (b) (4) However, the sponsor's acceptance limit was not justified. The FDA chemist suggests [redacted] (b) (4) as a specification limit instead. The FDA statistician conducted an independent stability analysis using two specification limits – [redacted] (b) (4) and reported in the next section.

3. REVIWER'S ASSESSMENT

The reviewer evaluated the sponsor's 24-month stability data in accordance with the 2003 ICH Guidance for Industry: Q1A(R2) Stability Testing of New Drug Substances and Products. The reviewer conducted an ANCOVA analysis to estimate a shelf life of the drug for each vial separately using Statistical Analysis Software, SAS.

First, the reviewer performed batch poolability tests. For both vial configurations, only slopes are pooled and, as a result, the fitted regression lines are parallel lines with different intercepts. The Figure 1 displays the stability data with both the fitted regression lines (solid lines) and one-sided 95% confidence limits of the regression means (dashed lines).

Figure 1 Fitted Regression Lines with 95% One-Sided Confidence Limit



Second, the reviewer estimated the shelf life by comparing the 95% confidence limits shown above using the two acceptance criteria, (b) (4) Table 2 shows the shelf life estimates for two criteria.

Table 2 Shelf Life Estimation for (b) (4) (microg/mL)

Vial	Batch (Batch Name in Figure 1)	Fitted Regression		Estimated Shelf Life (Month)	
		Intercept	Slope	(b) (4) microg/mL	(b) (4) microg/mL
10	08-2508B (BATCH1)	82.78	2.72	75	41
	08-2509B (BATCH2)	74.63	2.72	78	43
	08-2510B (BATCH3)	84.86	2.72	75	40
20	08-2508A (BATCH1)	90.07	2.23	82	43
	08-2509A (BATCH2)	82.64	2.23	85	46
	08-2510A (BATCH3)	92.87	2.23	81	42

When [redacted] (b) (4) acceptance criterion is used, the shortest estimated shelf life is 75 months. When [redacted] (b) (4) acceptance criterion is used, the shortest estimated shelf life is 40 months. In both cases, the estimated shelf lives are longer than the period covered by the data, 24 months. Therefore, 24-month shelf life is supported by data for both acceptance criteria.

4. CONCLUSIONS AND RECOMMENDATIONS

The FDA statistician conducted a stability analysis to estimate a shelf life for [redacted] (b) (4) of the drug product based on 24-month stability data. Two acceptance criteria - [redacted] (b) (4) - are used. The estimated shelf lives are beyond the period covered by the data for both criteria. Therefore, 24-month shelf life is supported by the data.

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/s/

YOUNGSOOK JEON
06/08/2011

YI TSONG
06/08/2011

STATISTICS FILING CHECKLIST FOR NDA (b) (4)

NDA Number: 22-496 **Applicant: Pacira Pharmaceuticals** **Stamp Date: Sept 13, 2010**

Drug Name: bupivacaine ER **NDA/BLA Type: Standard**

On **initial** overview of the NDA/BLA application for RTF: **Studies SKY0402-C-316 and SKY0402-C-317**

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			X	**Dropouts were not an issue as these were inpatient clinical trials.**

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/s/

DAVID M PETULLO
12/10/2010

DIONNE L PRICE
12/10/2010
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