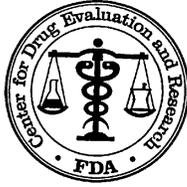


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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 # 21-446
Supplement # S-028
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Applicant: Pfizer
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1. EXECUTIVE SUMMARY

Pfizer has submitted an efficacy supplement for Lyrica (pregabalin) to add an indication for the management of neuropathic pain associated with spinal cord injury. Based on my review of the data from two placebo-controlled clinical trials, A0081107 and 1008-125, there is evidence to support the efficacy of Lyrica for the proposed new indication. For both studies, the analyses of the efficacy endpoints of primary interest to the division were statistically significant in favor of Lyrica. The evidence of an analgesic effect was further supported by the analyses of secondary endpoints such as a 30% reduction in baseline pain and patient global impression of change.

2. INTRODUCTION

2.1 Overview

Lyrica has been approved for marketing in the United States since December 2004 for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia. In June 2005, Lyrica was approved as an add-on therapy for epilepsy, and in June 2007, it was approved for the management of fibromyalgia. According to the applicant, chronic pain following spinal cord injury (SCI) is experienced in approximately 65-70% of individuals, with about a third of those reporting severe pain. There are no approved products for the treatment of pain associated with SCI.

The development program for Lyrica was conducted under IND 53,763. The applicant submitted the results of two placebo-controlled Phase 3 studies, A0081107 (1107) and 1008-125 (125), to support the efficacy of this application. These were randomized, double-blind, parallel-group trials designed to demonstrate superiority of Lyrica over placebo. Based on the Agency's advice that the duration of treatment in neuropathic pain studies should be 12-weeks of fixed dosing, Study 1107 consisted of 12-weeks of fixed dosing. Study 125 was conducted prior to this advice and only contained 9-weeks of fixed dosing.

Study 125 was conducted from June 2002 to July 2004 at eight centers in Australia. The protocol for this study was not submitted for review. In fact, it appears that this study was not conducted under an IND. At a pre-NDA meeting held on September 30, 2011, the applicant was advised that last observation carried forward (LOCF) would not be acceptable as an imputation strategy for their primary efficacy endpoint and that the duration of the fixed-dose portion was insufficient. The applicant stated that the study was conducted prior to receiving the Agency's advice regarding study duration.

Study 1107 was conducted from January 2007 to February 2011 at 60 centers in Chile, China, Columbia, Czech Republic, Hong Kong, India, Japan, Philippines, Russia, and the United States. A special protocol assessment (SPA) for this study was requested in January, 2006. An agreement was not reached, and the following comments related to the statistical review of the SPA were sent to the applicant.

- We encourage you to use the change in pain intensity at the end of the fixed dose phase compared to the baseline pain assessment rather than the proposed duration adjusted average change as the primary endpoint. If an analysis of the change from baseline to 12 weeks does not support the finding based on the duration adjusted average change, the study may not be considered capable of supporting a finding of efficacy.
- We also recommend that you perform continuous responder analyses by calculating the proportion of responders for each treatment arm using multiple cutoffs to define responders. Any patients who drop out or discontinue regardless of the reason of dropout should be classified as non-responders (i.e. treatment failures).
- We recommend that the primary efficacy analysis include all randomized patients who received at least one dose of study medication. Any patients who drop out or who have missed visits should be included in the primary analyses.
- Specify the “clinically relevant covariates” you intend to include in the tests for treatment effect.
- We recommend that you provide a plan, as well as standard operating procedure (SOP) for design modifications due to sample size re-estimation, and provide a plan on how you would control any possible inflation of Type 1 error rate due to this modification.

In April 2006, the applicant again requested a SPA with the duration average adjusted change (DAAC) as the primary endpoint. The applicant argued that the proposed primary endpoint appropriately accounted for the treatment effect over the trial duration, and since the division did not agree, they requested a formal dispute resolution in November 2006. The division’s response was that the applicant should conduct a landmark analysis with a conservative imputation strategy for missing data. They could use DAAC but must also win on the change in baseline pain intensity (PI) at Week 12 using a conservative strategy such as the baseline observation carried forward (BOCF). At a pre-NDA meeting held in September 2011, the applicant was again informed that a win on DAAC by itself would not support efficacy, and they must use a conservative imputation strategy for missing data. The applicant was advised that LOCF was not acceptable.

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\NDA021446\0130\m5\datasets>

3. STATISTICAL EVALUATION

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. 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.

The Office of Scientific Investigation (OSI) inspected two of the sites from Study 1107, Sites 1072 and 1100, and two sites from Study 125, Sites 004 and 006. For Study 1107, there were no notable deficiencies found at Site 1100. However, the inspection of Site 1072 resulted in the issuance of a Form 483 notifying the company of potential objectionable conditions. Three patients were found to have consumed concomitant analgesics and/or muscle relaxants during the study but were not reported as protocol violations. In light of this finding, the reviewing Medical Officer identified an additional 26 Lyrica patients and 33 placebo patients that consumed concomitant analgesics during the study. To assess the influence of these patients, I reanalyzed the data considering them treatment failures. There was still a significant treatment effect noted in favor of Lyrica. I deemed the data from these patients did not drive the significant treatment effect. See Section 4.2 for full details of these analyses.

The inspection of Sites from Study 125 was not completed at the time my review was finalized. Any concerns noted will be addressed as an amendment to my review.

3.2 Evaluation of Efficacy

My review focused on the two Phase 3 studies that were submitted to support efficacy and are reviewed separately in Sections 3.2.1 and 3.2.2

3.2.1 Study 125

Study Design and Endpoints

This randomized, double-blind, placebo-controlled, multi-center study consisted of three phases; a three week dose-adjustment phase, a nine week fixed-dose phase, and one week taper phase. Eligible patients were randomized in a 1:1 ratio to either placebo or Lyrica. At baseline, patients must have completed at least 4 evaluations and have an average pain score of 4 or higher. Patients were allowed to take analgesics, tricyclic antidepressants, serotonin-reuptake inhibitors, and NSAIDS but must have been on a stable dose. Benzodiazepines were allowed as needed but not within six hours of a clinic visit.

Pain and pain-related sleep interference scores were measured daily and recorded in the patient's diary. PI was measured using an 11-point numerical rating scale where 0 indicated no pain and 10 indicated the worst pain possible. Sleep interference was assessed also using an 11-point numerical rating scale. A score of 0 indicated that pain did not interfere with sleep, and a score of 10 indicated the pain completely interfered with sleep. Patient global impression of change (PGIC) was measured using a 7-point scale where 1 indicated 'very much improved' and 7 indicated 'very much worse'.

The pre-specified primary efficacy outcome was the endpoint weekly mean PI score and was defined as the mean of the last seven post-randomization pain scores including the day after the last day of dosing. Secondary efficacy endpoints evaluated in my review included weekly mean pain-related sleep interference scores, percentage of patients that achieved at least a 30% reduction in baseline PI at Week 12, and patient global impression of change (PGIC).

Based on previous studies and the literature, the applicant estimated that a sample size of 132 patients, 66 per treatment arm, would provide greater than 90% power to detect a clinically

meaningful difference of 1.3 points in endpoint mean pain scores assuming a standard deviation of 2.12.

Patient Disposition, Demographic and Baseline Characteristics

This study screened 165 patients in order to randomize 137, 67 randomized to placebo and 70 randomized to Lyrica. Demographics and baseline pain scores for all randomized and treated patients are shown in Table 1.

Table 1. Patient demographics for Study 125

Characteristic	placebo	Lyrica
Number of Patients (n)	67	70
Age in years		
Mean (SD)	50 (14)	50 (14)
[range]	[21, 80]	[23, 78]
Gender (%)		
Female	13 (19)	10 (14)
Male	54 (81)	60 (86)
Race (%)		
Caucasian	66 (99)	67 (96)
Asian	1 (1)	2 (3)
Other	0 (0)	1 (1)
Baseline Pain Score		
Mean (SD)	6.7 (1.3)	6.5 (1.3)
[range]	[3.9, 10]	[3.6, 9.6]

Source: Reviewer

There were two patients that did not meet the eligibility criteria of having a baseline pain score greater than 4.0; one patient was missing the baseline pain score and one had a mean score of 3.6. Regardless, these two patients would not have a significant impact or change the conclusions drawn from this study.

There was a fairly high discontinuation rate regardless of treatment, 45% and 30% in the placebo and Lyrica groups, respectively. The reasons for discontinuations are shown in Table 2.

Table 2. Disposition of patients that discontinued in Study 125

Reason for Discontinuation	Number (%)		
	Placebo, n=67	Lyrica, n=70	Total, n=137
Lack of efficacy	20 (30)	5 (7)	25 (18)
Adverse event	9 (14)	15 (22)	24 (18)
Other	1 (1)	1 (1)	2 (1)

Source: Reviewer

The percentage of patients discontinuing was not insignificant, 45% in the placebo group and 37% in the active group. Not unexpected, there were more dropouts due to lack of efficacy in the placebo arm than in the Lyrica arm. However, there does not appear to be any obvious trends for dropouts due to adverse events, 14% in the placebo group versus 22% in the Lyrica group.

Statistical Methodologies

As previously stated, the protocol and Statistical Analysis Plan (SAP) for this study was not submitted to the Agency for review prior to submission of the NDA. The applicant's primary efficacy endpoint was defined as "endpoint mean pain score". Endpoint was defined as the mean pain score of the last seven post-randomization entries. This type of approach is analogous to a LOCF strategy to account for missing data. In my analyses, I focused on the change in baseline PI at Week 12 as it had the most relevance based on advice consistently given by the division over the past several years. I utilized both a BOCF and a modified or hybrid approach (mBOCF) to account for missing data at Week 12. The mBOCF approach utilized LOCF for discontinuations due lack of efficacy and BOCF for all other reasons. In July 2010, the National Academy of Sciences issued a report on the prevention and treatment of missing data. The NAS report discourages single imputation methods; however, I justified the use of single imputation strategies in this study since it was conducted prior to the NAS report. Although it is unclear which alternative methods are most desirable, I conducted a cumulative responder analysis which may address some of the concerns outlined in the report. Further, the methods I utilized were unlikely to impute a treatment effect for a patient that withdrew due to an undesirable outcome, i.e. adverse event.

The applicant defined the intent-to-treat (ITT) population as all randomized patients that received at least one dose of study drug and had at least one post-randomization efficacy assessment. Patients were analyzed as randomized regardless of the treatment actually received. All efficacy analyses conducted by the applicant used the ITT population.

To evaluate efficacy, the applicant compared the endpoint mean pain score for the Lyrica group compared to the placebo group using an analysis of covariance (ANCOVA) model with treatment and center as main effects and the baseline PI score as a covariate. If less than seven observations were available, the applicant used what data were available. In my analysis, a patient had to have at least 4 pain scores during Week 12, otherwise the Week 12 pain score was considered missing and was imputed according to the above rules. This approach was not explicitly stated in the protocol for Study 125; however, it was stated for Study 1107.

Secondary outcomes were also evaluated. The percentage of patients that achieved at least a 30% reduction in baseline PI at the end of the study were analyzed using logistic regression with treatment, center, and baseline PI score in the model. PGIC scores were compared between treatment groups using a Cochran-Mantel-Haenszel (CMH) test. Mean sleep interference scores were analyzed using the same ANCOVA model used for the primary endpoint. Treatment and center were included as main effects and the baseline PI score as a covariate.

Results and Conclusions

Even though I was concerned that the applicant's definition of the ITT population excluded patients that lacked post-treatment efficacy assessments, this was not an issue as it applied to only one patient. I included all 137 patients in my analyses.

Although the endpoint and strategy for handling missing data were not those generally recommended by the division, I included the applicant's results in Table 3 for thoroughness.

Table 3. Applicant's primary efficacy analysis for Study 125

	Placebo	Pregabalin	Treatment Difference (Placebo - Pregabalin) ^a		
			Estimate (S.E.)	95% CI	p-value
Baseline					
N	67	69			
Mean (SD)	6.727 (1.446)	6.540 (1.253)			
LS Mean (S.E.)	6.615 (0.174)	6.430 (0.170)	0.185 (0.230)	-0.27, 0.641	0.423
Endpoint					
N	67	69			
Mean Change	-0.454	-1.917			
LS Mean (S.E.)	6.199 (0.235)	4.665 (0.231)			
LS Mean Change	-0.433	-1.967	1.533 (0.312)	0.916, 2.150	<0.001

LS Mean = Least squares mean; S.E. = Standard error; LS Mean Change = Least squares mean of change from baseline; SD = Standard deviation; Mean Change = Mean change from baseline, 95% CI = 95% Confidence Interval.

^a Placebo - Pregabalin difference in LS Means from the ANCOVA Model with Treatment, Center, and Baseline (Baseline not included at baseline time point) as factors.

Source: Table 11 from applicant's clinical study report

To address concerns regarding the LOCF imputation strategy, I considered the change in baseline PI to Week 12 using the same ANCOVA model as the applicant but imputing missing data using BOCF and mBOCF. My results are shown in Table 4.

Table 4. Reviewer's primary efficacy analysis for Study 125

Imputation	Treatment	N	Mean Pain Intensity (SE)			
			Baseline	WK12	Change	p-value
BOCF	Placebo	67	6.7 (0.2)	6.4 (0.2)	0.3 (0.1)	
	Lyrica	70	6.5 (0.2)	5.3 (0.3)	1.2 (0.2)	< 0.001
mBOCF	Placebo	67	6.7 (0.2)	6.4 (0.2)	0.3 (0.2)	
	Lyrica	70	6.5 (0.2)	5.3 (0.3)	1.3 (0.2)	< 0.001

Source: Reviewer

There was a significant treatment effect observed in favor of Lyrica regardless of how missing data was imputed.

As an exploratory analysis, I considered a responder approach. If a patient had a reduction from moderate pain at baseline to mild pain at Week 12, the patient was considered a responder. Mild pain was defined as a pain score between 3 and 7, and moderate pain was defined by a pain score between 1 and 3. The proportion of responders in each treatment group was compared using a Chi-square test. Results are shown in Table 5.

Table 5. Responder analysis based on a reduction from moderate to mild pain for Study 125

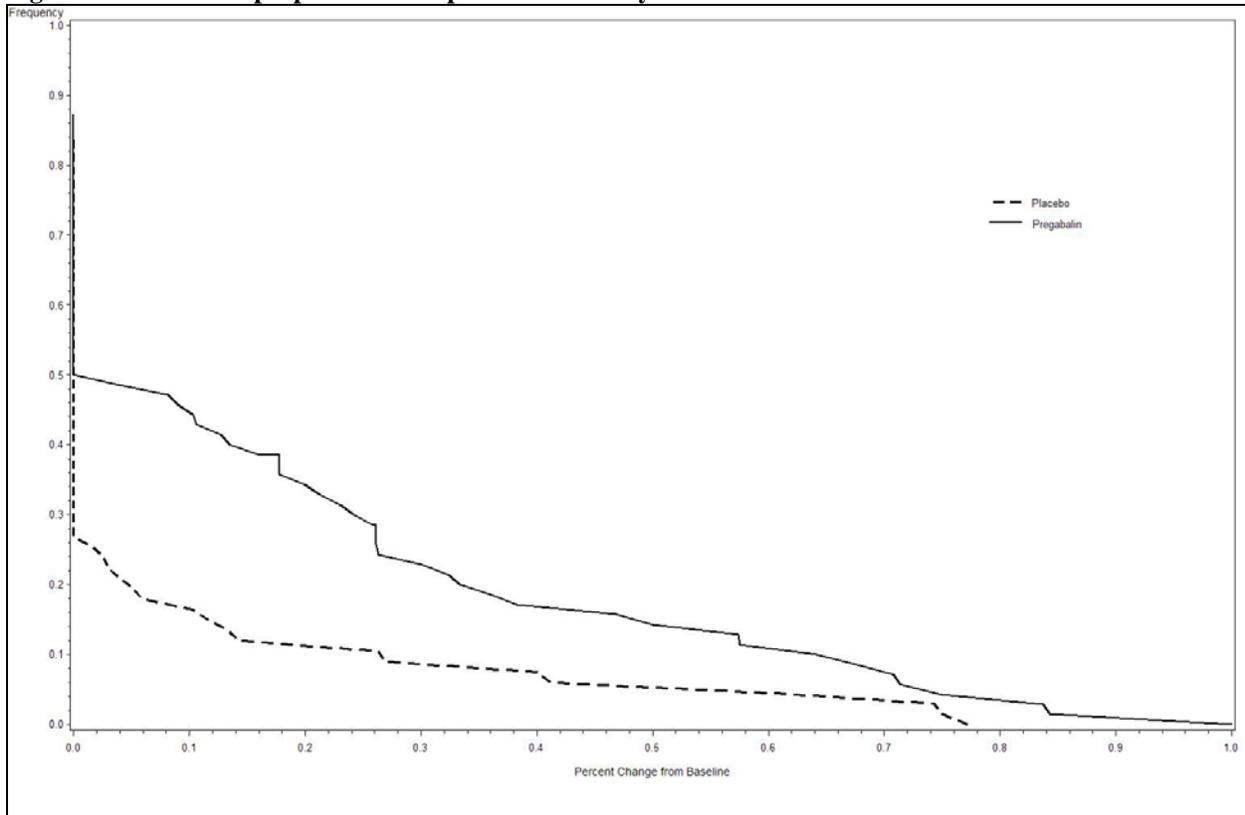
Treatment	Number of responders (%)	p-value
Placebo, n=67	5 (7)	-
Lyrica, n=70	17 (24)	0.007

Source: Reviewer

Even though there were relatively few patients, 22 out of 137, that meet this criteria, there were significantly more in the Lyrica treatment arm than in the placebo arm, and the difference was significant.

To further explore the pain response profile, I examined the data using a cumulative response approach. Patients missing the Week 12 assessment were considered non-responders. This analysis is presented as a cumulative responder curve and is shown in Figure 1.

Figure 1. Cumulative proportion of responders for Study 125



Source: Reviewer

There was clear separation in the two curves with Lyrica having a better response profile. To test for significance, I performed two different statistical tests, the Van der Waerden test and Wilcoxon Ranks Sum test. The Van der Waerden test converts the ranks of the Wilcoxon test to quantiles of the standard normal distribution. It should have more power than the Wilcoxon test. Both tests were more sensitive to differences in the left tail of the distribution. Results are shown in Table 6.

Table 6. Statistical comparison of cumulative responder curves for Study 125

Test	p-value
Van der Waerden	< 0.001
Wilcoxon Ranks Sum	0.004

Source: Reviewer

Not unexpected, the two curves were significantly different, p-value < 0.05. At each response level, there were more responders in the Lyrica arm compared to the placebo arm. The applicant looked specifically at patients that achieved at least a 30% reduction in baseline PI at the study endpoint. Note in the applicant's analyses, study endpoint was not Week 12 for all patients. My analysis evaluated the proportion of responders at Week 12 using a BOCF approach for missing data. Results are presented in Table 7.

Table 7. Proportion of patients with at least a 30% reduction in baseline pain at Week 12 for Study 125

Imputation	Proportion of responders (%)		p-value
	placebo	Lyrica	
Applicant	11/67 (16)	29/69 (42)	0.001
Reviewer	6/67 (9)	18/70 (26)	0.02

Source: Reviewer

As observed with the continuous responder curves, there were more responders in the Lyrica arm than the placebo arm, and the difference was statistically significant.

Patient global impression of change (PGIC) was evaluated at study completion. Again in the applicant's analyses, study completion may not be Week 12. To account for this, I utilized a responder approach. Only patients that had a score of 1 or 2 were considered responders at Week 12. This corresponded to a score of "much improved" or "very much improved". All other patients, either missing a Week 12 assessment or had a score greater than 2, were considered non-responders in my analyses. The proportion of responders in each treatment group was compared using a Chi-square test. Results are shown in Table 8.

Table 8. Responder analysis based on PGIC for Study 125

Treatment	Number of responders (%)	p-value
Placebo, n=67	10 (15)	-
Lyrica, n=70	32 (46)	<0.001

Source: reviewer

As observed with assessments for pain, there were more responders in the active group than placebo. Patients randomized to Lyrica reported better self assessments than patients randomized to placebo.

Mean sleep interference scores at Week 12 were compared using ANCOVA with treatment, center, and baseline PI scores in the model. Results are shown in Table 9.

Table 9. Comparison of mean sleep interference scores for Study 125

Treatment	N	Mean Sleep Interference Score (SE)			
		baseline	Wk12	Change	p-value
Placebo	66	5.1 (0.3)	4.8 (0.3)	-0.3 (0.1)	-
Lyrica	70	4.3 (0.3)	3.3 (0.3)	-1.0 (0.2)	0.002

Source: Reviewer

The mean baseline sleep score was lower in the Lyrica group, but since it was included as covariate in the analyses, it was not a concern. There was more of a change in the active group than placebo. The clinical relevance of this change should be evaluated.

3.2.2 Study 1107

Study Design and Endpoints

This was a 17-week randomized, double-blind, placebo-controlled, parallel-group, multi-center study that consisted of a 4-week double-blind dose adjustment phase, a 12-week double-blind treatment period, and a 1-week taper period. Eligible patients were randomized to either Lyrica or placebo in a 1:1 ratio. During the dose adjustment phase, patients were optimized to an effective dose of Lyrica or placebo and remained at this dose for the duration of the study. However, patients were allowed one dose reduction during the fixed dose phase if the optimized dose was not well tolerated. Note, the dose adjustment phase was added as an amendment to the protocol on February 12, 2008. Prior to the amendment, eight patients were randomized to a fixed dose of Lyrica.

Patients were allowed to use acetaminophen up to 4 g/day, NSAIDs, and COX-2 inhibitors as rescue medication. Analgesics were allowed if the patients were on a stable dose 30 days prior to the start of the study.

PI, pain-related sleep interference scores, and PGIC were measured as in Study 125. However, the applicant's predefined primary efficacy outcome was the DAAC instead of the mean pain at study end. The DAAC was defined as the mean of all post-baseline visits adjusted by the proportion of the study duration that the patient was enrolled in the study. However, the applicant was advised that this was not acceptable as patients that dropped out early due to adverse events may contribute a positive treatment effect even though they had a bad outcome. In light of this advice, I focused on the change in baseline PI after 12 weeks of stable treatment since it had the most relevance based on advice consistently given by the division over the past several years. Secondary endpoints considered in my review were the cumulative proportion of responders, proportion of patients achieving at least a 30% reduction in baseline PI, PGIC, and sleep interference score.

Based on the results of previous studies with Lyrica, the applicant estimated 100 patients per treatment arm would provide 82% power to detect a 0.9 point treatment difference in change from baseline to endpoint mean pain score using a mBOCF analysis. This calculation assumed a pooled standard deviation of 22.

Patient Disposition, Demographic and Baseline Characteristics

A total of 220 patients entered the screening phase with 219 patients being randomized, 107 to placebo and 112 to Lyrica. Demographics and baseline pain scores for all randomized and treated patients are shown in Table 10. One patient, 11081001, was randomized to placebo but received Lyrica. This patient was treated as having been randomized to placebo in my analysis but is included in the Lyrica group in Tables 10 and 11.

Table 10. Patient demographics for Study 1107

Characteristic	placebo	Lyrica
Number of Patients (n)	107	112
Age in years		
Mean (SD)	46 (14)	46 (13)
[range]	[19, 81]	[22, 72]
Gender (%)		
Female	16 (15)	27 (24)
Male	91 (85)	85 (76)
Race (%)		
Caucasian	42 (39)	43 (39)
Black	8 (7)	6 (5)
Asian	53 (50)	57 (51)
Other	4 (4)	6 (5)
Baseline Pain Score		
Mean (SD)	6.5 (1.4)	6.5 (1.4)
[range]	[3.4, 10]	[3.3, 10]

Source: Reviewer

There were four patients, two in each treatment arm, who had mean baseline pain scores less than four. This violation of the entry criteria did not impact the conclusion drawn from this study. When I excluded these patients from the analysis, there was still a significant treatment effect in favor of Lyrica. The discontinuation rate in this study was moderate, 15% and 17 % in the placebo and Lyrica groups, respectively. The reasons for discontinuations are shown in Table 11.

Table 11. Disposition of patients that discontinued in Study 1107

Reason for Discontinuation	Number (%)		
	Placebo, n=107	Lyrica, n=112	Total, n=219
Lack of efficacy	2 (2)	1 (1)	3 (1)
Adverse event	8 (7)	8 (7)	16 (7)
Protocol violation	3 (3)	5 (4)	8 (4)
Other	-	2 (2)	2 (1)
Withdrew Consent	3 (3)	3 (3)	6 (3)

Source: Reviewer

There was no obvious trend observed in the disposition of these patients.

Statistical Methodologies

There were several lengthy reviews of this protocol by the Agency that resulted in a formal dispute resolution regarding the primary efficacy endpoint. The Agency deemed that the DAAC was not an acceptable as primary efficacy endpoint for a chronic pain trial. Pfizer was informed that a landmark analysis would be required, i.e. change in baseline PI at Week 16. While the applicant did not change the primary endpoint, the landmark analysis was included as a key secondary endpoint only to be tested if their primary was significant. My review focuses on the change in baseline PI at Week 16

The applicant defined the ITT population as all randomized patients who received at least one dose of study treatment. There was one patient that was randomized but did not receive study drug. The modified intent to treat (mITT) population excluded the eight patients that were randomized under the fixed dose paradigm and was the applicant’s primary analysis population.

The applicant’s primary endpoint, DAAC, was compared between treatment groups using an ANCOVA model with baseline pain and pain catastrophizing scores (PCS) as covariates. By definition, DAAC does not impute missing data. Key secondary endpoints included change in PI from baseline to Week 16, 30% reduction in baseline PI, PGIC, and pain related sleep interference scores. The analysis of the change in PI mimicked that of the primary endpoint. Missing data at Week 16 was imputed using three separate approaches, BOCF, mBOCF, and LOCF. The results for PGIC were analyzed via a CMH test adjusting for center. Responder status (30%) was analyzed using a logistic regression model with treatment, center, and baseline PI and PCS. The results for sleep interference scores were compared between treatment groups utilizing an ANCOVA model with baseline pain as a covariate. Missing data was imputed using LOCF.

If the applicant’s primary analysis was significant, the key secondary endpoints were tested sequentially; change in PI from baseline to Week 16, 30% reduction in PI at Week 16, PGIC, and change from baseline in the pain related sleep interference score.

Results and Conclusions

The applicant’s primary analysis used the mITT population that excluded the eight patients that were randomized to a fixed dose of Lyrica. Since these were randomized and treated patients, I did not exclude these patients from my analyses, i.e. I used the ITT population.

The applicant was informed that a significant result on the DAAC by itself would not be sufficient evidence of efficacy. For completeness, the applicant’s results for the analyses of DAAC are shown in Table 12.

Table 12. Applicant’s primary efficacy analysis for Study 1107

	N	n	Mean (SD)	Min, Max	I.S Mean (SE)	Difference From Placebo		
						Diff (SE)	95% CI	p-value
Pregabalin	105	105	-1.64 (1.465)	-5.9, 1.5	-1.66 (0.157)	-0.59 (0.198)	(-0.98, -0.20)	0.0032
Placebo	106	106	-1.05 (1.446)	-4.7, 3.1	-1.07 (0.149)	NA	NA	NA

Source: Table 14 from applicant’s study report

My review focused on the change in baseline PI at Week 16. Results for my analyses are shown in Table 13. The patient that was randomized to placebo but received Lyrica is included in the below tables as a placebo patient.

Table 13. Reviewer's primary efficacy analysis for Study 1107

Imputation	Treatment	N	Mean Pain Intensity (SE)				
			baseline	Wk16	Change	Diff	p-value
BOCF	Placebo	108	6.5 (0.1)	5.4 (0.2)	1.1 (0.2)	-	-
	Lyrica	111	6.4 (0.1)	4.7 (0.2)	1.7 (0.2)	0.6	0.014
mBOCF	Placebo	108	6.5 (0.1)	5.4 (0.2)	1.1 (0.2)	-	-
	Lyrica	111	6.4 (0.1)	4.7 (0.2)	1.7 (0.2)	0.6	0.015

Source: Reviewer

As expected, there was very little difference in my analysis using BOCF and mBOCF since there were only three patients that discontinued due to lack of efficacy. Results indicate a significant treatment effect in favor of Lyrica.

Similar to Study 125, I looked at the number of patients that had a reduction in pain from moderate at baseline to mild at Week 16. Since I only considered patients that had a moderate baseline pain score, the four patients that had a baseline pain score less than four were excluded even if they had a mild pain score at Week 16. Results are shown in Table 14.

Table 14. Responder analysis based on a reduction from moderate to mild pain for Study 1107

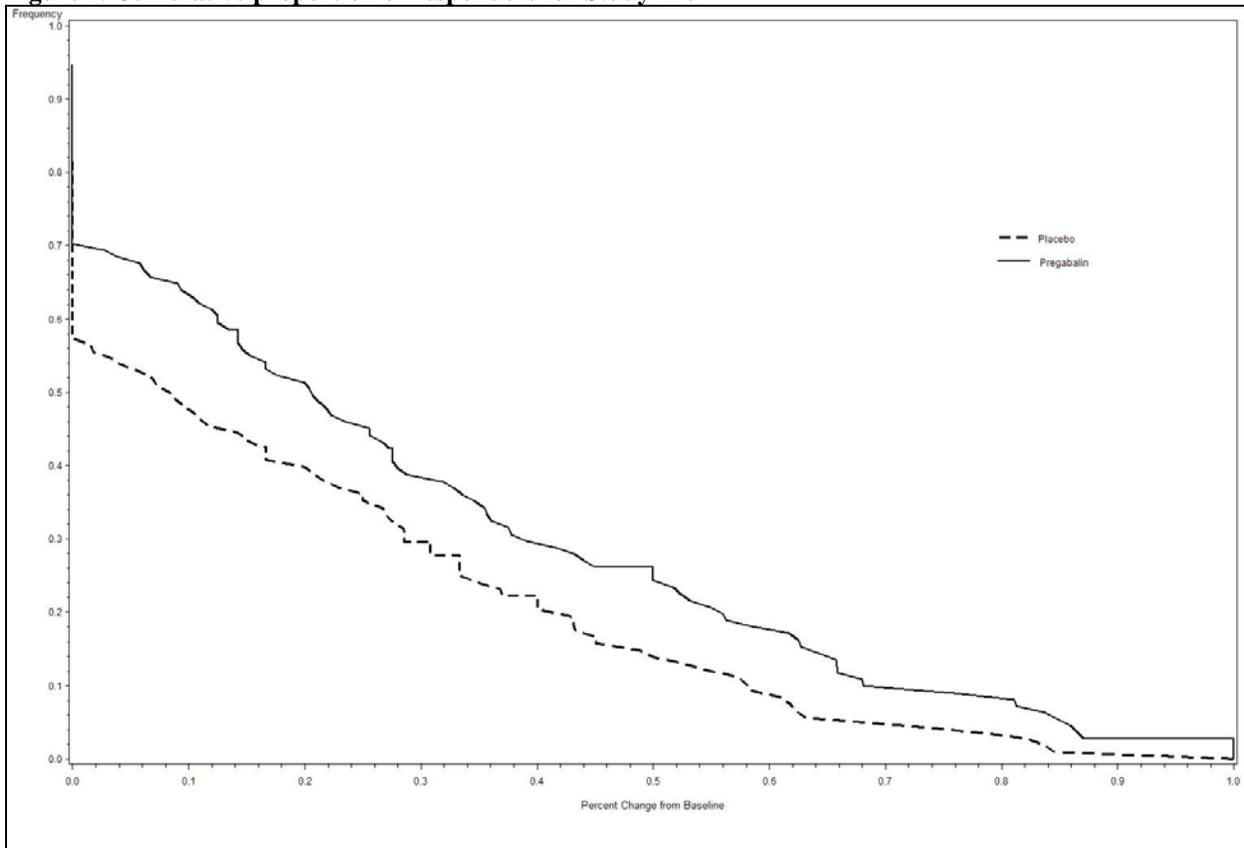
Treatment	Number of Responders (%)	p-value
Placebo, n=108	26 (24)	-
Lyrica, n=111	34 (30)	<0.28

Source: Reviewer

While there was not a significant difference, numerically there were more patients receiving Lyrica that had a reduction in baseline pain from moderate to mild.

As done with Study 125, I further explored the pain response profile using a cumulative response approach. The cumulative responder curve for this study is shown in Figure 2.

Figure 2. Cumulative proportion of responders for Study 1107



Source: Reviewer

Two different statistical tests were used to assess the difference between the two curves, the Van der Waerden test and Wilcoxon Ranks Sum test. Results are shown in Table 15.

Table 15. Statistical comparison of cumulative responder curves for Study 1107

Test	p-value
Van der Waerden	0.001
Wilcoxon Ranks Sum	0.003

Source: Reviewer

Clearly, there is a difference between the two curves as evidenced by the statistical tests that I applied.

Since the mean change in PI was significant, the proportion of patients with at least a 30% response rate was evaluated according to the sequential testing strategy. The applicant used LOCF for patients missing Week 16 data. This was not acceptable. I considered patients that withdrew prior to Week 16 or had missing PI scores for Week 16 as non-responders. My results along with the applicants are shown in Table 16.

Table 16. Proportion of patients with at least a 30% reduction in baseline pain at Week 16 for Study 1107

Analysis	Proportion of responders (%)		p-value
	placebo	Lyrica	
Applicant	33/105 (31)	48/105 (46)	0.04
FDA	32/108 (30)	43/111 (39)	0.16

Source: Reviewer

As a significant treatment effect was not observed in my analysis, the sequential testing would stop. Again, the conclusion was not affected by analyses conducted on the mITT population. Based on the cumulative responder curve in Figure 2, there were more responders in the Lyrica arm than in the placebo arm. Thus, I continued the sequential testing with the idea that results might provide supportive evidence.

My results for analysis of PGIC scores are shown in Table 17. I used a responder approach where patients with a score of 1 or 2 were considered responders; all others were considered non-responders.

Table 17. Responder analysis based on PGIC for Study 1107

Treatment	Number of responders (%)	p-value
Placebo, n=108	28 (26)	-
Lyrica, n=111	43 (39)	0.04

Source: Reviewer

This analysis was supportive, there were more responders in the Lyrica group than in the placebo group.

The pain related sleep interference scores were compared between treatment groups. The applicant used the mITT population and LOCF for missing data; I used the ITT population and BOCF. Results are shown in Table 18.

Table 18. Comparison of mean sleep interference scores for Study 1107

Treatment	N	Mean Sleep Interference Scores (SE)			
		baseline	Wk16	Change	p-value
Placebo	107*	5.2 (0.2)	4.2 (0.2)	-1.0 (0.2)	-
Lyrica	111	4.9 (0.2)	3.1 (0.2)	-1.8 (0.2)	0.0002

* 1 patient was missing baseline score and was excluded from analysis

Source: Reviewer

My results agree with the applicants (not shown). The BOCF imputation did not change my conclusions, patients treated with Lyrica had more of a change from baseline to Week 16.

To further explore the impact of the eight patients that were randomized to a fixed dose of Lyrica, I conducted all of the above analyses excluding these patients. My conclusions did not change.

3.3 Evaluation of Safety

The evaluation of the safety data was conducted by Dr. Joshua Lloyd. There were no unexpected adverse effects and the safety profile was comparable to that seen in the SCI population. No additional review of safety endpoints was requested and the reader is referred to Dr. Lloyd's review for detailed information regarding the adverse event profile

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

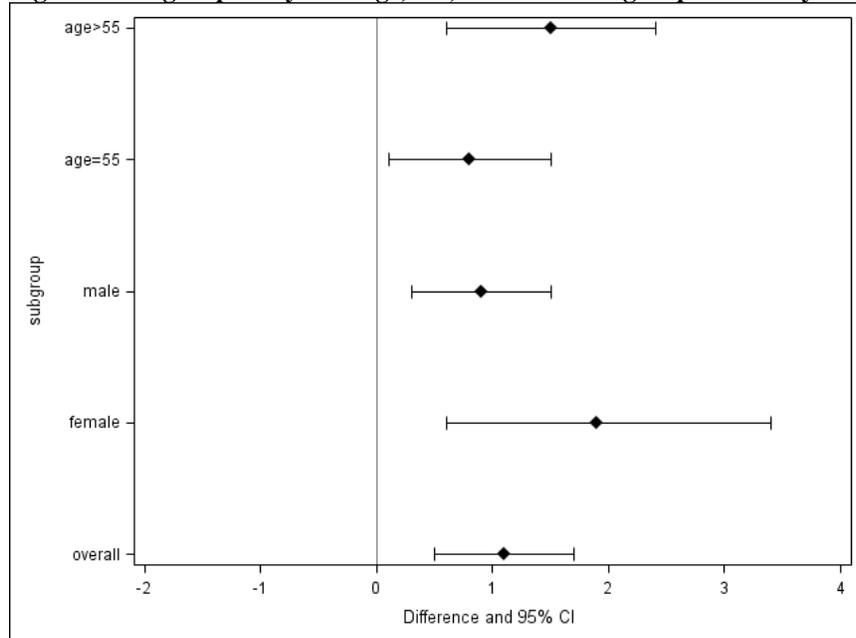
The applicant examined their primary efficacy endpoint in both studies for any differences due to age, gender, or racial subgroup. Age was categorized as less than or equal to 55 years old or greater than 55 years in age. For Study 125, site was examined for any treatment differences. Country was examined for any differences in the endpoint of interest for Study 1107. Results for each study will be discussed separately below.

Since I did not agree with the applicant's primary endpoints, I examined the change in pain from baseline to the end of the study for any differences due to age, gender, or racial subgroups. To explore the efficacy within subgroups, I utilized an ANCOVA model with treatment, age, gender, and country or site. I also included a treatment interaction for age, racial subgroup, sex, and country or site. The efficacy endpoint is summarized for each subgroup within each study.

Study 125

Since the majority of patients in this study were classified as Caucasian, racial subgroups were not summarized. The results for the other subgroups are shown in Figure 3. A positive difference favors Lyrica.

Figure 3. Subgroup analysis of age, sex, and racial subgroups for Study 125

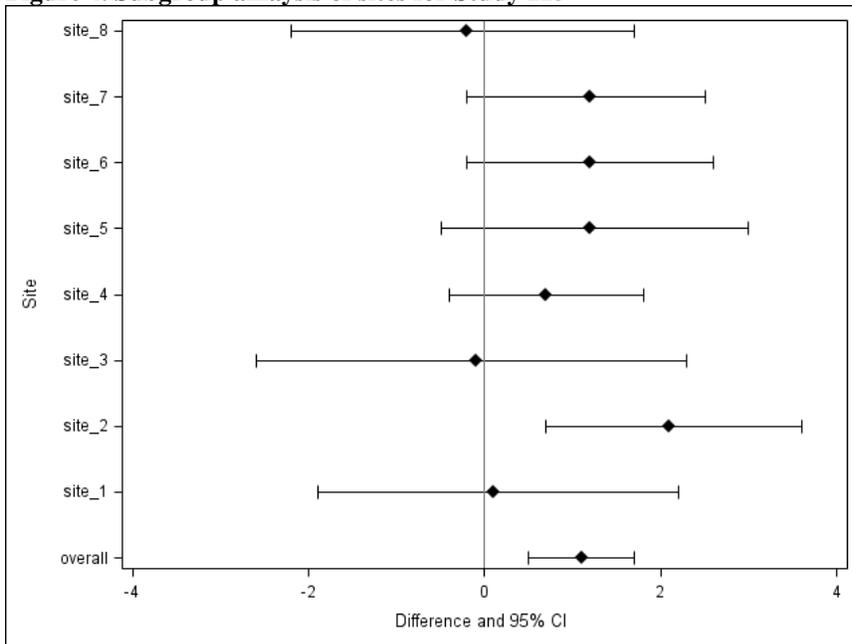


Source: Reviewer

When I included the interactions of sex and age in the ANCOVA model, there were no significant interactions.

Since this study was conducted at eight sites throughout Australia, I also examined the treatment effect by site. The difference between placebo and Lyrica is shown overall and for each site in Figure 4.

Figure 4. Subgroup analysis of sites for Study 125



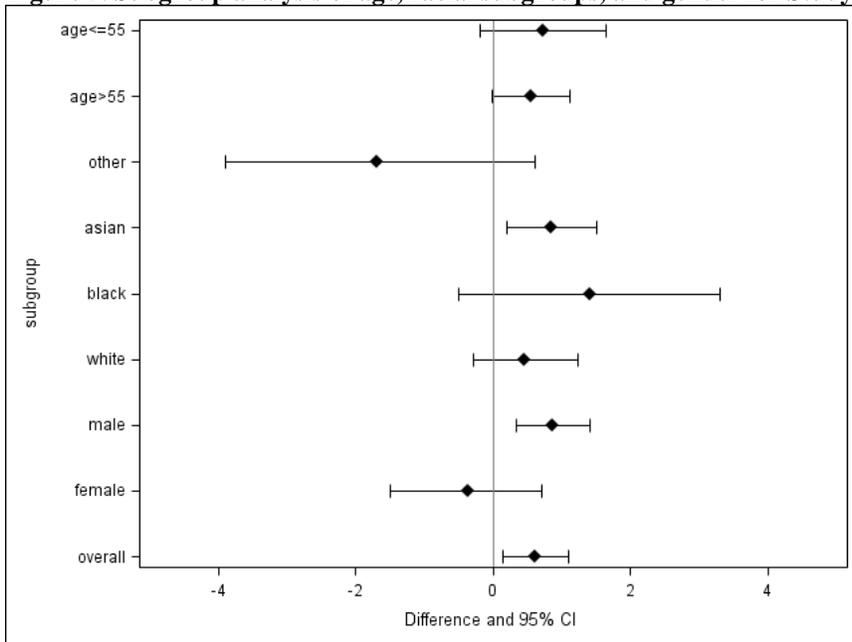
Source: Reviewer

Despite an overall significant treatment effect, the treatment effect for each site was not significant. This was not unexpected as the study was not powered to detect a treatment effect within each individual site. Further, when I included site and the interaction of treatment and site in the ANCOVA model, there was not a significant interaction.

Study 1107

The results of my efficacy analysis on the change in baseline PI at Week 16 were evaluated for any treatment interactions with gender, age, or racial subgroups using the ANCOVA model described above. The results are shown in Figure 5. Racial subgroups were evaluated as Caucasian, Asian, Black, and other.

Figure 5. Subgroup analysis of age, racial subgroups, and gender for Study 1107

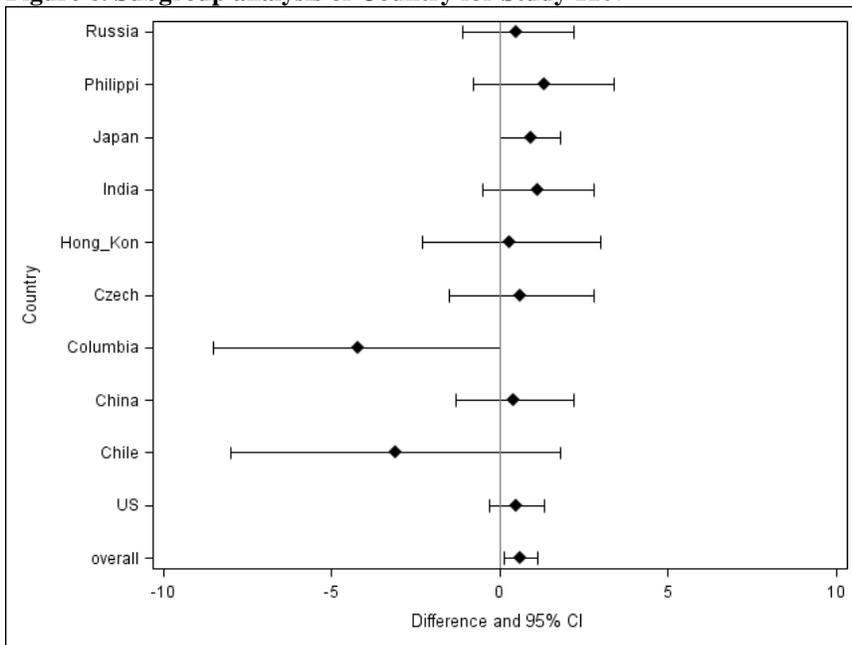


Source: Reviewer

There were no significant interactions of age, racial subgroups, and sex with treatment when included in ANCOVA model.

Since this study was conducted in 60 sites throughout the North and South America, Asia, and Europe, I also examined the treatment effect by country. The difference between placebo and Lyrica is shown overall and for each country in Figure 6.

Figure 6. Subgroup analysis of Country for Study 1107



Source: Reviewer

Although there was not a significant treatment effect observed in the United States, the effect was in the right direction. This was not unexpected as this trial was not powered to detect a treatment effect in individual countries.

4.2 Other Special/Subgroup Populations

For Study 125, no other subgroups of interest were identified or analyzed. However for Study 1107, the reviewing medical officer identified 59 patients, 33 randomized to placebo and 26 randomized to Lyrica that used rescue medication which may have influenced their PI scores. I explored the influence of these patients in my primary analyses by conducting two exploratory analyses. First, I excluded them from the analyses and second, I included them in the analysis but considered them as treatment failures, i.e. no change. Results of these analyses are shown in Table 19.

Table 19. Exploratory analyses to account for potential protocol violations

	Treatment	N	Change	Diff	p-value
Excluded	Placebo	75	0.9 (0.2)	-	-
	Lyrica	87	1.8 (0.2)	0.9	0.004
Considered as BOCF	Placebo	108	0.7 (0.2)	-	-
	Lyrica	111	1.5 (0.2)	0.8	< 0.001

Source: Reviewer

My conclusions did not change. There was still a significant treatment effect in favor of Lyrica.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

I reviewed two Phase 3 clinical trials to evaluate the efficacy of Lyrica in treating pain associated with SCI. The applicant's predefined primary efficacy endpoints were not the division's preferred efficacy endpoints; however, the analyses of the endpoints yielded statistically significant differences in favor of Lyrica. When I evaluated the studies using the division's recommended endpoints, a significant treatment effect was also noted. There were no concerns regarding the analysis populations, statistical analyses, or imputation of missing data that could not be addressed. Each study is discussed separately below.

For Study 125, the analysis of the applicant's primary efficacy endpoint, endpoint mean pain score, demonstrated a significant treatment effect in favor of Lyrica. Endpoint was defined as the mean pain score of the last seven post-randomization entries. My analyses of the mean change in pain at Week 12, using an imputation approach that was unlikely to assign a positive treatment effect to dropouts due to adverse events, was also significant in favor of Lyrica. These results were supported by the findings from analyses of various secondary endpoints such as PGIC and pain related sleep interference. Further when I examined the proportion of patients that demonstrated a reduction of moderate pain to mild pain, there were significantly more patients in the Lyrica arm than the placebo arm that experienced the reduction. This study was

conducted entirely outside of the United States; however, the standard of care is considered to be similar, and there were no concerns expressed by the clinical review team.

In Study 1107, there was a significant treatment effect for the applicant's primary efficacy endpoint, DAAC, and the change in baseline PI at Week 16. Regardless of the analysis population utilized, this finding was consistent. The efficacy of Lyrica was also supported by various secondary endpoints such as PGIC and pain related sleep interference scores. This study was multi-national but included patients from the United States. Evaluation of the subgroup of US patients did not yield a statistically significant difference; however, the difference numerically favored Lyrica.

5.2 Conclusions and Recommendations

My analyses of the applicant's primary efficacy endpoints and the endpoints of primary interest to the division yielded significant differences between Lyrica and placebo for both studies and were supported by various secondary endpoints. Further support of the efficacy of Lyrica for the proposed indication was provided by the examination of the cumulative responder curves for pain. Additional support was gained when I evaluated patients that had moderate pain reduced to mild pain.

In conclusion, the efficacy of Lyrica in treating pain associated with SCI was demonstrated. The safety profile of Lyrica in the SCI population is comparable to what is already known and no new safety concerns were identified. The overall risk-benefit profile of Lyrica appears favorable.

5.3 Label Review

Using the label provided in the submission, I have the following comments from Section 14.5. My comments and suggestions follow the applicant's proposed wording and are italicized.

14.5 Management of Neuropathic Pain after Spinal Cord Injury

The efficacy of LYRICA for the management of neuropathic pain associated with spinal cord injury was established in 2 double-blind, placebo-controlled, multicenter studies. Patients were enrolled with neuropathic pain associated with spinal cord injury that persisted continuously for at least 3 months or with relapses and remissions for at least 6 months. A total of 63% of patients completed study 1 and 84% completed study 2.

The above is accurate and consistent with the study report.

The patients had a minimum mean baseline pain score of ≥ 4 on an 11-point numerical pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). The baseline mean pain scores across the two studies ranged from 6.5 to 6.7.

There were six patients, two from Study 1 and 4 from Study 2 that did not have a mean baseline pain score > 4 . The mean baseline pain scores are reported correctly.

Patients were allowed to take [REDACTED] ^{(b) (4)} opioids, non-opioid analgesics, antiepileptic drugs, [REDACTED] ^{(b) (4)} if dose was stable for 30 days prior to screening. Patients were allowed to take acetaminophen during the studies; [REDACTED] ^{(b) (4)}

The above is consistent with the study report.

Study SCI 1: This 12 week, randomized, double-blind, parallel-group, multicenter, flexible dose (150-600 mg/day) study compared pregabalin with placebo.

The above statement does not reflect the fact that for Study 125, the 12 week study duration consisted of a 3 week dose titration period followed by a 9 week fixed dose period. I suggest wording such as 'The 12-week study consisted of a 3-week dose titration phase followed by a 9-week double-blind fixed dose phase.'

Treatment with LYRICA 150-600mg/day statistically significantly improved the endpoint weekly mean pain score and increased the proportion of patients with at least 30% and 50% reduction in pain score from baseline.

This statement is accurate and supported by the data. However, the proportion of patients with at least a 30% and 50% improvement in baseline pain at study end are secondary endpoints. Generally we recommend secondary endpoints that do not provide additional clinical information be excluded from the label. In addition, this information is ascertainable from the cumulative responder curve shown in Figure 10. However, there is precedent within the Lyrica label for allowing such wording.

The cumulative responder analysis is presented in Figure 10.

The above figure appears appropriate. However, I recommend the title be changed to be more descriptive and to reflect that pain intensity was assessed. Change to ‘Patients Achieving Various Levels of Improvement in Pain Intensity – Study SCII’. The applicant proposes the following statement for inclusion in the label, “Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study”. This outcome was not pre-specified; however, it is included in the approved label for other indications. I examined the mean change from baseline at Week 1 using the available pain scores regardless of a patient’s status at the end of the study. Results are shown in Table 20.

Table 20. Mean pains scores at baseline, Week 1, and the change from baseline at Week 1

	Mean (stder)		
	Baseline	Week 1	Change
Placebo (n=67)	6.7 (0.2)	6.5 (0.2)	0.2 (0.1)
Lyrica (n=70)	6.5 (0.2)	5.3 (0.2)	1.2 (0.2)

Source: Reviewer

I compared the mean change for the placebo group to the mean change for Lyrica using an ANCOVA model with treatment and baseline pain score. There was a significant difference noted, p -value < 0.001. If the review team deems this to be valuable supportive information, I am not concerned with the inclusion as it was highly significant.

Study SCI 2: This 16 week, randomized, double-blind, placebo-controlled, parallel-group, multi-center flexible dose (150-600 mg/day, in increments of 150 mg) study compared the efficacy, safety and tolerability of pregabalin with placebo.

The above statement does not take into account that Study 1107 consisted of a 4-week dose titration phase and a 12-Week fixed dose phase. Suggest wording such as 'The 12-week study consisted of a 3-week dose titration phase followed by a 9-week double-blind fixed dose phase.'

Treatment with LYRICA statistically significantly improved the primary efficacy endpoint

(b) (4)

DAAC is not acceptable as a primary endpoint; remove this statement from the label.

(b) (4)

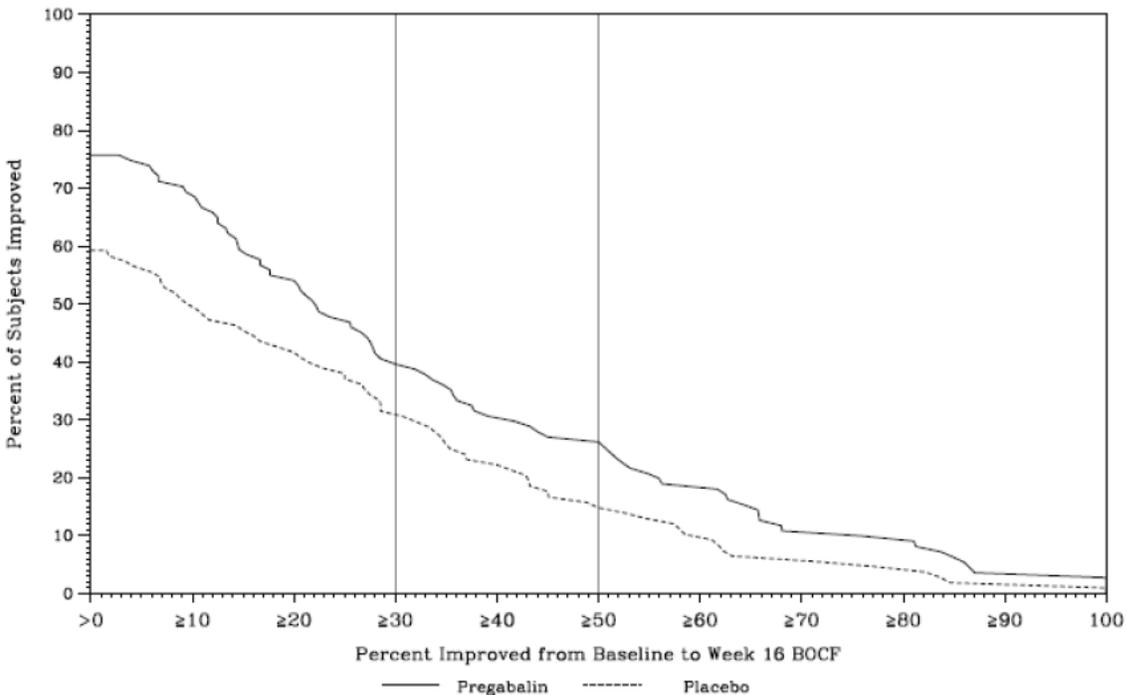
While the proportion of patients achieving a 30% improvement was a key secondary endpoint, it was not statistically significant in my analysis. In addition, the endpoint, at least a 50% improvement, was not pre-specified and would typically not be in the label. Further, the proportion of patients achieving at least a 30% and 50% improvement can be ascertained from the cumulative responder curve shown in Figure 11. However, there is precedent within the Lyrica label for allowing such wording. If these endpoints are included, it should be wording such as "Lyrica increased the proportion of patients with at least 30% and 50% reduction in pain score from baseline."

The cumulative responder analysis is presented in Figure 11. Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study.

Figure 11:

(b) (4) SCI 2

(b) (4)



The above figure is consistent with my review. The applicant proposes the following statement for inclusion in the label, “Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study”. This outcome was not pre-specified; however, it is included in the approved label for other indications. I examined the mean change from baseline at Week 1 using the available pain scores regardless of a patient’s status at the end of the study. Results are shown in Table 21.

Table 21. Mean pains scores at baseline, Week 1, and the change from baseline at Week 1

	Mean (stder)		
	Baseline	Week 1	Change
Placebo (n=108)	6.5 (0.1)	6.1 (0.1)	0.4 (0.1)
Lyrica (n=111)	6.4 (0.1)	5.6 (0.2)	0.9 (0.1)

There was a significant difference noted, p-value < 0.001. If the review team deems this to be valuable supportive information, I am not concerned with the inclusion as it was highly significant.

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/s/

DAVID M PETULLO
05/25/2012

DIONNE L PRICE
05/29/2012
concur