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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Supplement #: 209-501

Drug Name: Pregabalin extended release tablets (Lyrica CR)

Indication(s): Management of neuropathic pain associated with DPN, PHN and FM

Applicant: Pfizer, Inc.

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1. EXECUTIVE SUMMARY

Pregabalin as an immediate release (IR) formulation has been approved since 2004 for neuropathic pain associated with diabetic peripheral neuropathy (DPN), post-herpetic neuralgia (PHN), adjunctive therapy for adult patients with partial onset seizures, fibromyalgia (FM) and neuropathic pain associated with spinal cord injury. The applicant has developed an extended release (ER) formulation and is seeking indications for management neuropathic pain associated with DPN, PHN and FM. To support efficacy, 2 phase 3 studies were reviewed. Study A0081224 (PHN) and Study A0081245 (FM) had a similar study design with multicenter, randomized, double-blind (DB), placebo-controlled, randomized withdrawal design.

In my review, the efficacy of pregabalin ER was evaluated by using the change from baseline to final week of treatment in the weekly mean pain scores. Missing pain scores were imputed by a multiple imputation (MI) method. For patients discontinued from the study due to AEs or lack of efficacy, the Week 19 mean pain scores were assigned based on the distribution of single blind (SB) baseline mean pain scores. For patients discontinued from the study due to other reasons, the Week 19 mean pain scores were assigned based on the distribution of post randomization weekly mean pain scores. Each imputed dataset was analyzed by using an analysis of covariance (ANCOVA) model and the results of each imputed dataset were then combined by using the Rubin's rule (1976).

To further explore pain response profile, I also conducted a cumulative responder analysis of the change in mean pain scores from the SB baseline to Week 19. Two rank-based non-parametric tests were conducted: Wilcoxon Rank Sum and Van der Waerden test. Both tests are more sensitive to the differences in the left tails of the distributions of pain improvements, in which we have more interests.

In Study A0081224 (PHN), my analyses of the change in baseline pain at the end of the study indicated that there was a statistically significant improvement for pregabalin ER compared to placebo. However, in Study A0081245 (FM), statistical evidence of efficacy was not demonstrated.

Based on my review, there are adequate efficacy data to support approval of pregabalin ER for management of neuropathic pain associated with PHN and DPN. As study results failed to demonstrate the efficacy of pregabalin ER in patients with FM, it should be clearly stated in Section 14 that the efficacy of pregabalin ER in management of neuropathic pain associated with FM has not been established.

2. INTRODUCTION

2.1 Overview

Pregabalin has been approved since 2004 for neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, adjunctive therapy for adult patients with partial onset seizures, fibromyalgia and neuropathic pain associated with spinal cord injury. The approved formulations are IR oral capsule and oral solution, with a dose range of 150 mg to 600 mg per day given in equally divided doses twice or three times a day depending upon the specific indication. Pregabalin ER tablets have been developed to support once daily administration following the evening meal. The applicant claimed that the pregabalin ER formulation may provide convenience and ease of clinical use thus may enhance patients' compliance and potentially improve their adherence.

The clinical development program of pregabalin ER has been discussed between the agency and the applicant (b) (4)

In the information/advice request (IR) letter (IND 53,763) dated March 30, 2009, the agency stated that at least one efficacy trial in one patient population (DPN and PHN) was required for proposed neuropathic pain indications and one efficacy trial was required for proposed FM indication. In the type B meeting (IND 107,333) dated April 19, 2016, the agency stated (b) (4)

For the PHN study, the agency made the following comments in the IR letter dated August 2, 2010:

- a. We recommend that you also conduct an analysis comparing the differences in pain between baseline and end-of-therapy. The results should support the findings from the primary analysis.
- b. Your plan to treat those subjects who do not experience a Loss of Therapeutic Response (LTR) event as having censored observations is not an acceptable imputation method, because subjects who withdraw due to a poor clinical outcome that is not coded as loss of efficacy would be inappropriately assigned the neutral status of censored. In particular, subjects who withdraw due to an adverse event would be censored. We recommend that you treat all patients who withdraw as experiencing treatment failure at the time of withdrawal.
- c. On page 41 of the protocol, you state, "The number of events (time to LTR) in the double-blind phase will be followed throughout the study, with the number of patients entering the dose optimization phase adjusted to allow the required number of events to occur in the double-blind phase." If you plan to adjust the sample size during the trial, then you must establish standard operating procedures. These should specify when the interim analyses will take place, whether the analyst will be blinded to treatment, procedures for keeping unblinded results (if applicable) from other study personnel, and what algorithm will be used to determine the new sample size. You must also show that the planned method does not increase the type I error rate.
- d. For the purpose of determining the primary endpoint, it is not clear whether pain will be averaged by (non-overlapping) week or over floating (overlapping) windows that include the previous 7 days. For example, a patient could respond poorly on double-blind days 5 through 11, but still show at least a 30% improvement from baseline for each of the first two weeks. Clarify how the primary endpoint will be ascertained in such a situation. Also clarify whether the time resolution of the primary endpoint will be days or weeks.
- e. Clarify how the primary endpoint will be ascertained when there are intermittent missing diary data, i.e., the subject misses one or more entries while still enrolled in the study.

- f. If you intend to put any secondary endpoints in the label, then you must control for multiple endpoints. Also, the imputation method for these endpoints should assign poor outcomes to patients who withdraw early.
- a. Be advised that the sleep outcomes secondary endpoint data being gathered in the Phase 3 protocol will not be able to support a claim in labeling.

The current submission contains 12 phase 1 clinical pharmacology studies and 3 phase 3 clinical studies. My review focuses on the 2 phase 3 studies in patients with PHN and FM. The phase 3 study in patients diagnosed with epilepsy failed to demonstrate the efficacy and is not discussed in my review.

Table 1: Summary of trials to be assessed in the statistical review

Trial ID	Design*	Treatment/ Sample Size	Endpoint**
A0081224	DB, PC, RWD in patients with PHN	SB: 801 DB: 413 Pregabalin ER: 208 Placebo: 205	Primary: time to LTR
A0081245	DB, PC, RWD in patients with FM	SB: 441 DB: 121 Pregabalin ER: 63 Placebo: 58	Primary: time to LTR

*: DB: double-blind; PC: placebo-controlled; RWD: randomized withdraw design

** : LTR: loss of therapeutic response

Source: Reviewer

2.2 Data Sources

The clinical study report is located at the following location in the CDER electronic document room (EDR):

<\\Cdsub1\EVSPROD\NDA209501\0001>

The original submission did not contain SDTM datasets. The request for datasets was made in the 74-day letter. We further clarified our requirements of datasets in a teleconference dated March 9, 2017. The applicant subsequently submitted the datasets and SAS code on March 23, 2017. These datasets, define files, and programs are located in EDR at:

<\\Cdsub1\EVSPROD\NDA209501\0006>

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The electronic datasets and define files submitted by the applicant were of acceptable quality, and were sufficient for validating study results.

3.2 Evaluation of Efficacy

3.2.1 Study A0081224: Post-herpetic neuralgia

Study Design and Endpoints

Study A0081224 was a phase 3, multicenter, randomized, DB, placebo-controlled, randomized withdrawal study in patients with PHN. The study was conducted at 129 centers in 17 countries from April 2011 until September 2014. The study consisted of 4 phases: baseline (1 week), SB (6 weeks), DB treatment (13 weeks) and taper phase (1 week). After the baseline period, eligible patients entered the SB phase and received daily administration of pregabalin ER. The optimized pregabalin ER dose was determined during the first 4 weeks of the SB phase. This optimized dose was utilized for the remainder of the study. Patients with at least 50% improvement in pain from baseline at the end of the SB phase were considered as responders and were randomized equally to receive either pregabalin ER (at the optimized dose) or matching placebo once daily for 13 weeks. Patients unable to tolerate the optimized dose of study medication were discontinued from the study.

The primary objective of the study was to evaluate the efficacy of pregabalin ER compared with placebo for the treatment of pain associated with post-herpetic neuralgia in patients who initially respond to pregabalin ER. The primary efficacy endpoint was the time to loss of therapeutic response (LTR), where LTR was defined as <30% pain response relative to the SB baseline or patient discontinuation due to lack of efficacy or AEs in the DB phase of the study. The assessment of LTR was based on the pain diary in which pain scores were measured daily using an 11-point numeric rating scale (NRS) with a 24-hour recall period. To calculate <30% pain response relative to the SB baseline, the baseline pain score was defined as the mean of the last 7 observations prior to the start of the SB treatment, and the mean pain score was calculated as the 7-day rolling average of pain in the DB phase. Secondary efficacy endpoints included a secondary LTR endpoint where 5-day rolling average pain scores during the DB phase were compared to the 5-day randomization baseline pain score. Additional secondary efficacy endpoints were rate of 30% and 50% pain responders, NRS score for pain; weekly NRS pain (1 week recall period), medical outcome study sleep scale, patient global impression of change, short form 36 health survey, daily sleep interference diary, hospital anxiety and depression scale, brief pain inventory short form, and benefit, satisfaction and willingness to continue measure.

Statistical Methodologies

The primary efficacy analysis set consisted of all randomized patients who received at least 1 dose of study medication in the DB phase.

Historically, the division has stated that a drug intended to treat chronic pain is efficacious if it can demonstrate the efficacy in a long term period (usually 3 months). The applicant's defined primary efficacy endpoint (time to LTR) does not assess the long term efficacy effect as it may occur early during the DB period. Based on clinical input, I evaluated efficacy by using the change from baseline to the final week of treatment in the weekly mean pain scores. To impute missing pain scores, a MI method was utilized according to the following criteria:

- For patients who completed the study through Week 19, the observed value of Week 19 mean pain score was used for analysis.
- For patients who discontinued for reasons other than tolerability or lack of efficacy, the Week 19 mean pain score was imputed based on the distribution of post randomization weekly mean pain scores. Using a Markov Chain Monte Carlo method, missing data in the post-baseline weekly mean pain score from Week 7 to 19 were imputed with treatment and SB baseline weekly mean pain score in the model. The imputed score at Week 19 for each patient was used for analysis.
- For patients who withdrew due to an AE or lack of efficacy, their Week 19 mean pain scores were imputed according to the distribution of SB baseline mean pain scores.

For each imputed dataset, the change from baseline to final week of treatment in the mean pain scores was analyzed by using an ANCOVA model with terms for SB baseline mean pain scores, pooled center decided before unblinding and treatment. Then, the results of each imputed dataset were combined by using the Rubin's rule (1976).

The current approach favored by the division is that a drug intended to treat chronic pain is not efficacious if patients cannot stay on the treatment for the trial duration. Thus, strategies to handle missing data should not attribute any treatment benefit to patients discontinuing from the study. In the analyses of the change in mean daily pain from baseline to Week 19, the applicant used the last observation carried forward (LOCF) imputation method for patients with missing Week 19 mean pain scores. This method is not acceptable as a good outcome may be assigned to patients that dropped out due to AEs. The MI method I utilized ensured that a bad outcome was attributed to patients that discontinued the study due to AEs. Additionally, single imputation methods such as LOCF or BOCF are discouraged as they underestimate variability, the MI method I utilized adjusted this unknown variability.

To further explore the impact of missing data on the primary analysis, I conducted a cumulative responder analysis of the change in mean pain scores from the SB baseline to Week 19. In this analysis, the percentage improvement from SB baseline was calculated for each patient and dropouts were classified as non-responders. This methodology defines an outcome that can be ascertained in a high proportion of participants by incorporating dropouts as part of the outcome. I conducted two rank-based non-parametric tests: Wilcoxon Rank Sum and Van der Waerden test. Both tests are more sensitive to the differences in the left tails of the distributions of pain improvements, in which we have more interests.

For completeness, I also replicated applicant's primary efficacy analysis of the time to LTR. Kaplan-Meier estimates of the survival curve were calculated and the log-rank test was used to compare the treatment groups. Patients who did not experience an LTR event were analyzed as censored observations.

Patient Disposition, Demographic and Baseline Characteristics

The disposition of patients is shown in Table 2. A total of 1117 patients were screened for inclusion in the SB phase of the study, of which 801 patients received at least 1 dose of SB pregabalin ER. Among them, 141 patients (18%) discontinued from the study during the SB phase. The primary reason for discontinuation during the SB phase was due to related AEs (46 [6%] patients).

There were 660 patients who completed the SB treatment phase and were evaluated for inclusion in the DB phase of the study. Of these, 242 (30%) patients were not randomized with the primary reason indicated as they didn't have at least 50% improvement in pain at the end of the SB phase compared to the SB baseline.

A total of 418 patients were randomized and 413 patients received at least 1 dose of DB treatment, of which 208 patients received pregabalin ER and 205 patients received placebo. Five patients were randomized but discontinued before receiving study treatment.

There were 182 (88%) patients in the pregabalin ER treatment group and 160 (78%) patients in the placebo group who completed the study. The primary reasons for discontinuation of pregabalin ER treatment during the DB phase were other (7 [3%]) and no longer willing to participate (6 [3%]). The primary reasons for discontinuation of placebo treatment during the DB phase were no longer willing to participate (15 [7%]) and insufficient clinical response (11 [5%]).

Table 2: Patient disposition in Study A0081224 – Number (%) of Patients

SB Phase	Pregabalin ER (N=801) n (%)	
Completed SB Period	660 (82)	
Discontinued SB Period	141 (18)	
Related AE	46 (6)	
Insufficient clinical response	32 (4)	
No longer willing to participate	29 (4)	
Lost to follow-up	10 (1)	
Unrelated AE	8 (1)	
Protocol violation	8 (1)	
Other	8 (1)	
Entire 13-week DB Randomized Withdrawal Phase		
	Pregabalin ER (n=208) n (%)	Placebo (n=205) n (%)
Completed DB Period	182 (88)	160 (78)
Discontinued DB Period	26 (12)	45 (22)
Insufficient clinical response	2 (1)	11 (5)
No longer willing to participate	6 (3)	15 (7)
Lost to follow-up	1 (0)	2 (1)
Other	7 (3)	4 (2)
Protocol + GCP non-compliance	4 (2)	3 (1)
Protocol violation	0 (0)	1 (0)

Patient died	0 (0)	1 (0)
Related AE	5 (2)	7 (3)
Unrelated AE	1 (0)	1 (0)

Source: Clinical Study Report Section 10.1, Figure 2. GCP: good clinical practice

The demographic and other background characteristics for all patients in the primary efficacy analysis set are presented in the appendix. The majority of patients (77%) were white. The mean age was 61.9 years in the pregabalin ER group and 62.2 years in the placebo group. About 62% of patients were female. The demographic and other background characteristics were comparable between two treatment groups.

Results and Conclusions

There were 208 patients from the pregabalin ER treatment group and 205 patients from the placebo group included in the primary efficacy analysis set. My results using a MI method are shown in Table 3. Weekly mean pain scores were calculated as the mean of all available pain scores in that week. When calculating the SB and DB baseline mean pain scores, if less than 4 entries were present in the last 7 days then entries from previous days would be included until there were 4 non-missing pain entries. At the end of the DB phase, from the SB baseline to the DB endpoint, the pregabalin ER group showed a statistically significant greater improvement in the mean daily pain scores compared to the placebo group, with the least square (LS) mean difference -1.0 compared to placebo ($p < 0.0001$). From the DB baseline to the DB endpoint, the same statistically significance between two groups that favored pregabalin ER was demonstrated.

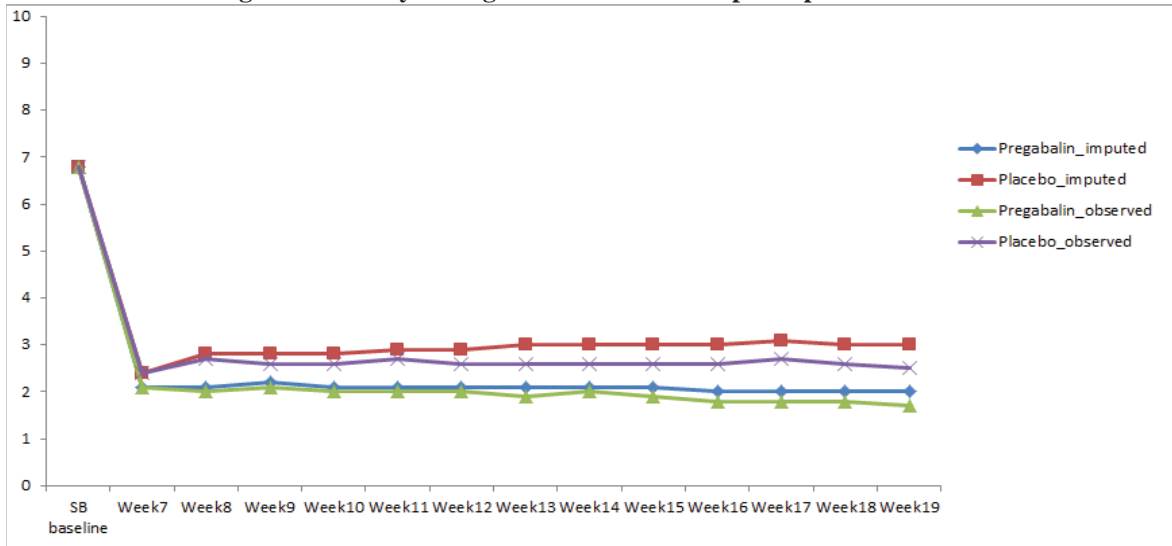
**Table 3: Change in mean daily pain scores at DB endpoint (Week 19)
(MI)**

	Treatment			Pregabalin ER vs. Placebo		
	n	LS mean	SE	LSMD	95% CI	p-value
SB baseline to DB endpoint						
Pregabalin ER	208	-4.7	0.1	-1.0	(-1.4, -0.6)	< 0.0001
Placebo	205	-3.7	0.2			
DB baseline to DB endpoint						
Pregabalin ER	208	0.2	0.1	-1.0	(-1.3, -0.6)	< 0.0001
Placebo	205	1.1	0.1			

Source: Reviewer's analyses. LSMD: least square mean difference.

The weekly average of the observed and imputed pain scores over time for each treatment group is displayed in Figure 1. The overall trend of the observed and imputed weekly mean pain scores for the placebo group were plateau after randomization and the pain curves of two treatment groups separated well.

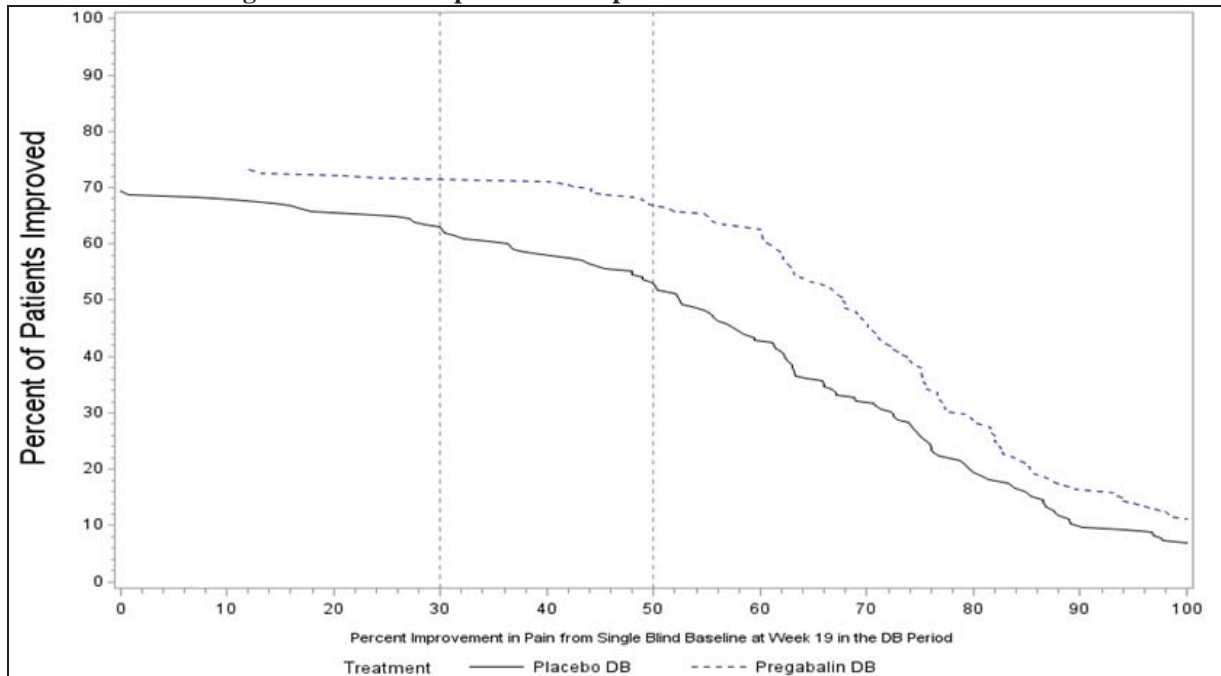
Figure 1: Weekly average of observed and imputed pain scores over time



Source: Reviewer’s analyses

To further explore the pain response profile, I generated continuous responder curves where non-completers are classified as non-responders. As shown in Figure 2, at all levels of response there were more pregabalin ER treated patients than placebo treated patients. The two curves were statistically significantly different when applying the non-parametric tests (Wilcoxon rank sums test: p-value = 0.005; Van der Waerden test: p-value = 0.009).

Figure 2: Percent improvement in pain from SB baseline at Week 19

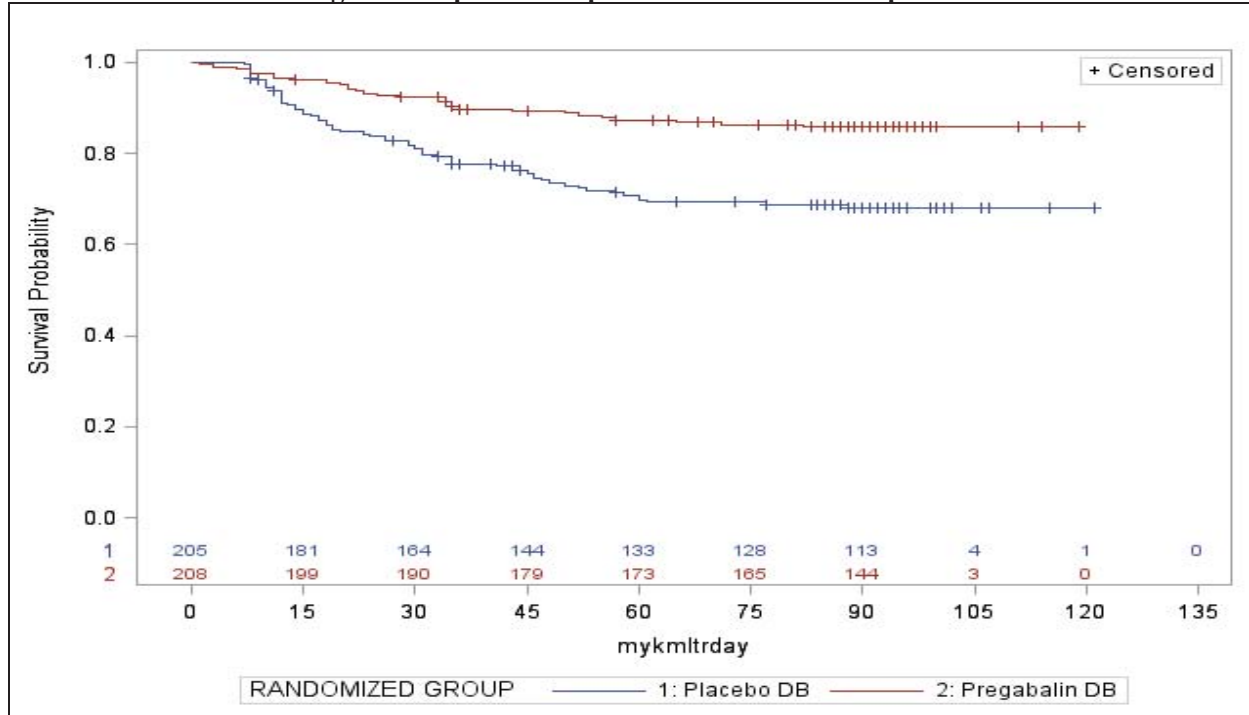


Source: Reviewer’s analyses

For completeness, I replicated the applicant’s primary efficacy analysis of the time to LTR. My results were similar to the applicant’s results. There were 29 of 208 patients (14%) in the

pregabalin ER group who experienced LTR. While in the placebo group, there were 63 of 205 (31%) patients who experienced LTR. The Kaplan-meier analysis result of the time to LTR was statistically significant in favor of pregabalin ER ($p < 0.0001$). The median time from randomization to LTR during the DB phase was not estimable because less than half of the patients in both treatment groups experienced LTR during the DB treatment phase. The first quartile time to LTR was Day 46 in the placebo group, whereas for the pregabalin ER group, the first quartile LTR was not estimable because fewer than 25% of patients experienced LTR during the DB phase.

Figure 3: Kaplan-Meier plot of time to LTR in DB phase



Source: Reviewer's analyses

Table 4: Kaplan-Meier estimates of time to LTR in DB phase

Treatment	N	Time to LTR (days)			p-value (log-rank test)	Failed n	Censored n	Percent censored
		1 st quartile (days)	95% CI	Median				
Placebo	205	46	31-77	-	-	63	142	69
Pregabalin ER	208	-	-	-	< 0.0001	29	179	86

Source: Reviewer's analyses

I also replicated the applicant's analyses of change in mean daily pain at Week 19, where missing pain scores were imputed using the last observation carried forward (LOCF) method. My results are similar to the applicant's results. As good outcomes were assigned to the patients that discontinued from the study due to AEs, the LOCF method is not acceptable.

**Table 5: Change in mean daily pain scores at DB endpoint (Week 19)
(LOCF)**

	n	Treatment		Pregabalin ER vs. Placebo		
		LS mean	SE	LSMD	95% CI	p-value
SB baseline to DB endpoint						
Pregabalin ER	208	-4.9	0.1	-0.9	(-1.3, -0.6)	< 0.0001
Placebo	205	-3.9	0.1			
DB baseline to DB endpoint						
Pregabalin ER	208	0.0	0.1	-0.9	(-1.2, -0.6)	< 0.0001
Placebo	205	0.9	0.1			

Source: Reviewer's analyses. LSMD: least square mean difference.

3.2.2 Study A0081245: Fibromyalgia

Study Design and Endpoints

Study A0081245 was a phase 3, multicenter, randomized, DB, placebo-controlled, randomized withdrawal study in patients diagnosed with FM. The study was conducted at 50 centers in 4 countries from March 2011 until July 2012 and consisted of 4 phases: baseline (1 week), single-blind (SB) (6 weeks), DB treatment (13 weeks) and taper phase (1 week). Study A0081245 had a similar design to Study A0081224, except that the optimized pregabalin ER dose was determined in the first 3 weeks of the SB phase and was then used in a fixed manner for the remainder of the study.

The primary objective of the study was to evaluate the efficacy of pregabalin ER compared with placebo for the treatment of FM among patients who initially respond to pregabalin ER. The primary and secondary efficacy endpoints were identical to the PHN study.

Statistical Methodologies

The statistical methods utilized to analyze Study A0081245 are similar to the methods used in Study A0081224 except that an ANCOVA model with terms for SB baseline mean pain scores and treatment was used to analyze each imputed dataset.

Patient Disposition, Demographic and Baseline Characteristics

The disposition of patients is shown in Table 6. A total of 770 patients were screened for inclusion in the SB phase of the study, of which 441 patients received at least 1 dose of SB pregabalin ER. Among them, 121 patients (18%) discontinued from the study during the SB phase. The primary reason for discontinuation during the SB phase was due to related AEs (48 [11%] patients).

There were 320 patients who completed the SB treatment phase and were evaluated for inclusion in the DB phase of the study. (b) (4)

A total of 122 patients were randomized and 121 patients received at least 1 dose of DB treatment, of which 63 patients received pregabalin ER and 58 patients received placebo. One patient was randomized but discontinued before receiving study treatment.

There were 46 (73%) patients in the pregabalin ER treatment group and 47 (81%) patients in the placebo group who completed the study. The primary reasons for discontinuation of pregabalin ER treatment during the DB phase were insufficient clinical response (6 [10%]) and no longer willing to participate (6 [10%]). The primary reason for discontinuation of placebo treatment during the DB phase was insufficient clinical response (9 [16%]).

Table 6: Patient disposition in Study A0081245 – Number (%) of Patients

SB Phase	Pregabalin ER (N=441) n (%)	
Completed SB Period	320 (73)	
Discontinued SB Period	121 (27)	
Related AE	48 (11)	
Insufficient clinical response	37 (8)	
No longer willing to participate	15 (3)	
Lost to follow-up	10 (2)	
Unrelated AE	4 (1)	
Protocol violation	3 (1)	
Other	4 (1)	
 Entire 13-week DB Randomized Withdrawal Phase		
	Pregabalin ER (n=63) n (%)	Placebo (n=58) n (%)
Completed DB Period	46 (73)	47 (81)
Discontinued DB Period	17 (27)	11 (19)
Insufficient clinical response	6 (10)	9 (16)
No longer willing to participate	6 (10)	1 (2)
Lost to follow-up	1 (2)	1 (2)
Other	1 (2)	
Related AE	2 (3)	
Unrelated AE	1 (2)	

Source: Clinical Study Report Section 10.1, Figure 2.

The demographic and other background characteristics for all patients in the primary efficacy analysis set are presented in the appendix. The majority of patients (90%) were white. The mean age was 50.3 years in the pregabalin ER group and 49.3 years in the placebo group. Most of patients were female (91%). The demographic and other background characteristics were comparable between two treatment groups.

Results and Conclusions

There were 63 patients from the pregabalin ER treatment group and 58 patients from the placebo group included in the primary efficacy analysis set. My results using a MI approach are shown in Table 7. At the end of the DB phase, the pregabalin ER group did not show a statistically significant greater improvement in the mean daily pain score compared to the placebo group.

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Table 10: Reviewer's subgroup analyses

Pregabalin ER					Placebo				difference
n (%)	SB Baseline pain score (SD)	Week 19 mean pain score (SD)	Change from SB baseline to Week 19 in weekly mean pain score (SD)	n (%)	SB Baseline pain score (SD)	Week 19 mean pain score (SD)	Change from SB baseline to Week 19 in weekly mean pain score(SD)		
Sex									
female	134 (64%)	7.0 (1.6)	1.9 (1.7)	-5.1 (2.2)	122 (60%)	7.0 (1.4)	2.9 (2.1)	-4.1 (2.2)	-1.0
male	74 (36%)	6.6 (1.4)	2.0 (1.4)	-4.6 (2.0)	83 (40%)	6.6 (1.3)	3.1 (2.4)	-3.5 (2.4)	-1.1
Race									
white	158 (76%)	6.7 (1.5)	2.0 (1.6)	-4.7 (2.0)	158 (77%)	6.7 (1.4)	3.2 (2.2)	-3.5 (2.1)	-1.2
non-white	50 (24%)	7.4 (1.4)	1.8 (1.6)	-5.6 (2.2)	47 (23%)	7.5 (1.3)	2.4 (2.3)	-5.1 (2.4)	-0.5
Age									
< 65	112 (54%)	6.9 (1.5)	1.8 (1.3)	-5.2 (1.9)	102 (50%)	6.9 (1.3)	2.3 (1.9)	-4.6 (2.1)	-0.6
≥ 65	96 (46%)	6.7 (1.5)	2.1 (1.9)	-4.6 (2.3)	103 (50%)	6.8 (1.4)	3.6 (2.4)	-3.1 (2.2)	-1.5

Source: Reviewer's analyses

4.2 Other Special/Subgroup Populations

No other subgroup analyses were performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were two main statistical issues identified in the review of the two studies submitted to support the efficacy of pregabalin ER for management of neuropathic pain associated with PHN, DPN and FM. First, the primary efficacy endpoint of both studies was not clinically relevant as the time to LTR does not assess the long term efficacy effect of the study drug. Second, the LOCF method that the applicant used to impute missing pain scores is not acceptable since it

may attribute good outcomes to patients that discontinued due to AEs. I was able to adequately address these concerns. First, based on clinical input, I evaluated the change in baseline pain at the end of the DB phase of the study. Second, I utilized a MI procedure to assess the impact of missing data.

5.2 Collective Evidence

The efficacy of pregabalin ER was evaluated by the change from baseline to final week of treatment in the weekly mean pain scores. In Study A0081224, patients diagnosed with PHN, the pregabalin ER group had a statistically significant greater improvement in the mean daily pain scores compared to the placebo group. In addition, at all levels of response (percent change from baseline), there were more pregabalin ER treated patients than placebo treated patients. However, in Study A0081245, patients diagnosed with FM, statistical evidence of efficacy was not demonstrated for pregabalin ER when compared to placebo.

5.3 Conclusions and Recommendations

Based on the information submitted and my analyses of a clinically relevant endpoint, change in baseline pain at the end of the study, there are adequate efficacy data to support approval of pregabalin ER for management of neuropathic pain associated with PHN and DPN. However, my analyses of the same endpoint in Study A0081245 failed to demonstrate the efficacy of pregabalin ER for the treatment of pain associated with FM. It should be clearly stated in Section 14 that the efficacy of pregabalin ER in management of neuropathic pain associated with FM has not been established.

5.4 Labeling Recommendations

As the efficacy of pregabalin ER was evaluated by the change from baseline to the final week of treatment in the weekly mean pain scores, this information should be reported on the label instead of the results for the applicant's defined primary efficacy endpoint. Continuous responder curves should also be reported. Furthermore, it should be clearly stated that Study A0081245 failed to demonstrate the efficacy of pregabalin ER in management of neuropathic pain associated with FM.

Appendix

Demographics of Study A0081224

Source: Clinical Study Report Section 11.2.1

	Pregabalin CR DB			Placebo DB		
	Number (%) of Subjects					
	Male	Female	Total	Male	Female	Total
	74 (35.6)	134 (64.4)	208 (100.0)	83 (40.5)	122 (59.5)	205 (100.0)
Hormonal Status						
Premenopausal	-	28 (20.9)		-	20 (16.4)	
Postmenopausal	-	106 (79.1)		-	102 (83.6)	
Age (Years)						
<18	0	0	0	0	0	0
18 - 44	8 (10.8)	18 (13.4)	26 (12.5)	9 (10.8)	15 (12.3)	24 (11.7)
45 - 64	29 (39.2)	57 (42.5)	86 (41.3)	27 (32.5)	51 (41.8)	78 (38.0)
≥65	37 (50.0)	59 (44.0)	96 (46.2)	47 (56.6)	56 (45.9)	103 (50.2)
Mean	62.7	61.4	61.9	64.2	60.9	62.2
SD	14.5	12.9	13.5	13.3	14.1	13.9
Range	22 - 86	25 - 86	22 - 86	27 - 85	21 - 83	21 - 85
Race						
White	56 (75.7)	102 (76.1)	158 (76.0)	63 (75.9)	95 (77.9)	158 (77.1)
Black	10 (13.5)	21 (15.7)	31 (14.9)	13 (15.7)	23 (18.9)	36 (17.6)
Asian	5 (6.8)	5 (3.7)	10 (4.8)	6 (7.2)	2 (1.6)	8 (3.9)
Other	3 (4.1)	6 (4.5)	9 (4.3)	1 (1.2)	2 (1.6)	3 (1.5)
Weight (kg)						
Mean	84.3	74.1	77.8	80.7	74.1	76.8
SD	19.1	18.4	19.3	16.9	17.5	17.5
Range	52.4 - 179.2	43.4 - 153.3	43.4 - 179.2	40.0 - 135.6	42.0 - 120.0	40.0 - 135.6
Height (cm)						
Mean	173.7	161.4	165.8	173.8	161.3	166.3
SD	7.8	6.4	9.1	6.4	7.2	9.2
Range	152.0 - 193.0	147.3 - 179.0	147.3 - 193.0	158.0 - 190.0	132.3 - 180.3	132.3 - 190.0

Demographics of Study A0081245

Source: Clinical Study Report Section 11.2.1

Demographic Characteristics	Number (%) of Subjects		
	Pregabalin CR SB 165 - 495 mg/day (N=441)	Pregabalin CR DB 330 - 495 mg/day (N=63)	Placebo DB (N=58)
Age (years)			
< 18	0	0	0
18 - 44	178 (40.4)	21 (33.3)	21 (36.2)
45 - 64	227 (51.5)	37 (58.7)	30 (51.7)
≥ 65	36 (8.2)	5 (7.9)	7 (12.1)
Mean (SD)	47.6 (12.9)	50.3 (12.1)	49.3 (12.7)
Range	18-79	24-79	20-74
Sex			
Male	49 (11.1)	5 (7.9)	6 (10.3)
Female	392 (88.9)	58 (92.1)	52 (89.7)
Weight (kg)			
Mean (SD)	81.1 (20.5)	78.4 (14.4)	85.8 (23.6)
Range	44.1-176.0	44.1-110.7	50.5-176.0
Height (cm)			
Mean (SD)	163.9 (7.9)	162.6 (6.9)	163.3 (8.3)
Range	146.0-198.1	146.6-179.0	148.7-183.0
Race			
White	355 (80.5)	57 (90.5)	52 (89.7)
Black	32 (7.3)	3 (4.8)	3(5.2)
Asian	49 (11.1)	3 (4.8)	3 (5.2)
Other	5 (1.1)	NA	NA

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/s/

YAN ZHOU
09/08/2017

DAVID M PETULLO
09/09/2017
I concur.