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/Supplement #:	21-446/S-032 22-488/S-011
Drug Name:	Lyrica (Pregabalin)
Indication(s):	Management of fibromyalgia
Applicant:	Pfizer Inc.
Date(s):	Letter date: February 29, 2016 PDUFA date: December 29, 2016
Review Priority:	Standard
Biometrics Division:	II
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Keywords:	NDA review, clinical studies

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1. EXECUTIVE SUMMARY

Lyrica (pregabalin) capsules and Lyrica oral solution were approved in 2007 and 2010 for the management of Fibromyalgia (FM) in adults. The capsule formulation was approved under NDA 21-446 and the oral formulation was approved under NDA 22-488. Both approvals included the requirement of conducting a study to evaluate the safety and efficacy of pregabalin for pediatric patients with FM. This submission contains the results from that required post-marketing pediatric study. It was submitted to FDA as supplement 32 under NDA 21-446 and supplement 11 under NDA 22-488.

The primary efficacy variable evaluated in this study was the change from baseline to Week 15 in mean pain score which was derived from daily pain numeric rating scale. The analysis result showed greater numerical improvement for pregabalin compared to placebo. However, statistical evidence of efficacy was not demonstrated for the pre-specified primary efficacy variable.

Based on my review, the study was not adequately powered to demonstrate superiority of pregabalin over placebo, (b) (4) The results from this study should be described in section 8.4 (Pediatric subpopulation) of the product and it should be clearly stated that the efficacy of this product in children 12 to 17 years old 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. In the approval of Lyrica for FM, a pediatric study in children under 12 years was waived due to the low incidence of this condition. However, a pediatric study, originally specifying 13 to 16 years of age, was required for post-marketing assessment under the Pediatric Research Equity Act (PREA). Subsequently, the agency modified the age requirement to 13 to 17 years, and finally accepted the age range for the study as 12 to 17 years.

This submission contains the results from a phase 4 clinical study that was submitted to fulfill the PREA requirement. Study A0081180 was a 15-week, multicenter, randomized, double-blind, parallel group, placebo-controlled study to evaluate the safety and efficacy of pregabalin in 107 adolescents aged 12 to 17 years of old. The final report submission date for the study was originally specified as January 31, 2012. On December 19, 2012, the applicant requested a revised date based on a sample size of 162. In April 2013, the agency revised the final report submission date to December 31, 2017 and stated:

"because the Division has determined that the limited patient population due to the low prevalence of pediatric fibromyalgia has made it very difficult to conduct a large randomized controlled treatment study in this population."

The study was originally designed to enroll 162 patients. In an IR letter dated January 18, 2013, the agency made the following recommendations:

2. Include formal hypothesis tests comparing the treatment groups in the protocol, as well as an appropriate sample size for that objective.

3. You propose to use last observation carried forward (LOCF) imputation for the efficacy pain measure for all patients who discontinue for any reason. It is important to ensure that positive pain values are not imputed for patients who have a negative outcome (i.e. adverse events or inability to tolerate minimum dose requirement). Single imputation methods such as LOCF are not currently preferred for efficacy analyses. Consult the National Academy of Sciences (NAS) report on missing data which was commissioned by the FDA. The report can be found online at http://www.nap.edu/catalog.php?record_id=12955. We strongly recommend that you take the NAS report into consideration and propose an approach to handle treatment and/or study discontinuations that is consistent with the NAS recommendations. We favor approaches that attribute poor outcomes to those patients that discontinue prior to the end of the study. Also include appropriate sensitivity analyses to assess the impact of missing data and discontinuations on the primary analyses.

In a Type C written response letter dated March 04, 2014, the agency agreed the planned imputation method, hypothesis testing approach and sample size revision were acceptable:

Question 1: *In its January 18, 2013 letter, FDA recommended the following: "It is important to ensure that positive pain values are not imputed for patients who have a negative outcome (ie, adverse events or inability to tolerate minimum dose requirement). Single imputation methods such as LOCF are not currently preferred for efficacy analyses. We favor approaches that attribute poor outcomes to those patients that discontinue prior to the end of the study. Also include appropriate sensitivity analyses to assess the impact of missing data and discontinuations on the primary analyses."*

Pfizer proposes to use a multiple imputation method as described in Rubin[1]. This method is consistent with the NAS report. In this method, non-favorable outcomes will be assigned to subjects who do not complete the study as follows:

- *Discontinuation due to adverse event or due to lack of efficacy: subjects will have endpoint mean pain scores assigned according to the distribution of baseline mean pain scores, which will attribute poor outcomes to subjects who cannot tolerate treatment.*

- *Discontinuation for reasons other than tolerability or lack of efficacy: the endpoint mean pain score will be assigned based on the distribution of post randomization weekly mean pain scores, using a Markov chain Monte Carlo method.*

As recommended by FDA, sensitivity analyses will be performed to assess the robustness of the multiple imputation result. A mixed model repeated measures (MMRM) analysis will be used. Other imputation methods will also be carried out as sensitivity analyses: baseline observation carried forward (BOCF), last observation carried forward (LOCF), and modified baseline observation carried forward (mBOCF) which will apply the BOCF rule for subjects discontinued due to adverse events or lack of efficacy and the LOCF rule for subjects discontinued due to any other reasons. An mBOCF imputation analysis is reflected in product label for study F1.

Does FDA agree with the proposed imputation strategy and sensitivity analyses?

FDA Response to Question 1:
Yes. The planned imputation and analyses are acceptable.

Question 2: *In its January 18, 2013 letter, the Division requested that Pfizer "include formal hypothesis tests comparing the treatment groups in the protocol, as well as an appropriate sample size for that objective." Pfizer plans to include formal hypothesis testing.*

Pfizer proposes a sample size of 106 subjects (approximately 53 per treatment group), with 80% power to detect a treatment difference of □1.1. As of 09 Dec 2013, 103 subjects have been randomized. Pfizer will continue its efforts to randomize further subjects into the study until discussions with the Division on the sample size are concluded.

Detailed information regarding the proposed approach, including statistical assumptions, is provided in Section 9.1.

Does FDA agree with the proposed hypothesis testing approach and proposed sample size?

FDA Response to Question 2:
Yes, we agree. The information provided in Section 9.1 is sufficient to justify the planned sample size.

The study was completed in 2014 and enrolled 107 patients.

2.2 Data Sources

The original submission did not contain subject-level efficacy datasets. However, this information was requested and subsequently submitted by the Applicant. The clinical study report is located at the following location in the CDER electronic document room (EDR):

\\Cdsesub1\EVSPROD\NDA021446\0173

The datasets, define files, and programs are located in EDR at:

\\Cdsesub1\EVSPROD\NDA021446\0208

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 Design and Endpoints

Study A0081180 was a phase 4, 15-week, multicenter, randomized, double-blind, parallel group, placebo-controlled study in pediatric patients 12 to 17 years of age with FM. The study was conducted at 23 study centers in 4 countries from May 2010 until December 2014. The study was consisted of 4 phases: screening/baseline (1 week), dose optimization (3 weeks), fixed dose (12 weeks) and follow-up/taper (1 week). After the baseline period, eligible pediatric adolescents with FM were randomized equally to receive either placebo or pregabalin dosed twice daily. The initial dosing was 75 mg/day. Based on efficacy and tolerability, the doses were optimized over the following 3-week period to 75 mg/day, 150 mg/day, 300 mg/day or 450 mg/day. After this 3-week period, patients remained at the optimized doses for an additional 12 weeks without further dose adjustment followed by a 1-week dose tapering period. Patients unable to tolerate study medication were discontinued from the study.

The primary objective of the study was to evaluate the safety and efficacy of pregabalin (75-450 mg/day) compared with placebo in an adolescent FM population. The primary efficacy endpoint was the change from baseline to Week 15 in mean pain score. Pain scores were measured daily using an 11-point numeric rating scale (NRS) with a 24-hour recall period. Secondary efficacy endpoints included weekly mean pain score at each week, 30% and 50% pain responders, weekly pain NRS at Week 15 (1-week recall), patient global impression of change at Week 15, weekly mean sleep quality score at each week (from the daily sleep diary) and weekly mean sleep quality score at endpoint (from the daily sleep diary) which was defined as the mean of the last 7 diary entries prior to Week 15 while the patient was on study drug.

3.2.2 Statistical Methodologies

The statistical analysis of each efficacy endpoints was based on the full analysis set (FAS) which included all randomized patients who received at least one dose of study drug.

The applicant defined the causal estimand as the treatment difference in the change from baseline to final week of treatment using the mean pain scores for all randomized patients during the time

they tolerate treatment or complete the planned study duration. A multiple imputation (MI) method was utilized to impute the missing pain scores:

- For patients who completed the study through Week 15, the observed value of Week 15 mean pain score was used for analysis.

- For patients who discontinued for reasons other than tolerability or lack of efficacy, the Week 15 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 1 to 15 were imputed with treatment, center and baseline weekly mean pain score in the model. The imputed score at Week 15 for each patient was used for analysis.

- For patients who could not tolerate treatment (defined as those who withdrew due to an adverse event (AE) or abnormal laboratory test results) or discontinued due to lack of efficacy, their Week 15 mean pain scores were imputed according to the distribution of baseline mean pain scores.

For each imputed dataset, the primary efficacy endpoint was analyzed by using an analysis of covariance (ANCOVA) model with terms for baseline mean pain score, center 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. The primary analysis method had a desirable feature in that a bad outcome was attributed to patients that discontinued the study due to AEs. The method additionally account for sources of variability introduced by different imputations.

To assess the robustness of the MI analysis of the primary efficacy endpoint, the following sensitivity analyses were performed:

- ANCOVA model with the baseline observation carried forward (BOCF) imputation method for patients with missing Week 15 mean pain scores

- ANCOVA model with the last observation carried forward (LOCF) imputation method for patients with missing Week 15 mean pain scores

- ANCOVA model with the modified baseline observation carried forward (mBOCF) imputation method for patients with missing Week 15 mean pain scores, which applied the BOCF for patients discontinued due to AEs, and the LOCF for patients discontinued due to any other reasons.

In my review, I also conducted a cumulative responder analysis of the change in mean pain scores from the baseline to Week 15. In this analysis, the percentage improvement from 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 dropout 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.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The disposition of patients is shown in Table 1. A total of 107 adolescents were randomized and received study drug. Of the 54 adolescents randomized to the pregabalin group, 5 (9.3%) patients were no longer willing to participate in the study and 4 (7.4%) patients discontinued the study due to AEs. In contrast, of the 53 patients randomized to the placebo group, 7 (13.2%) patients were no longer willing to participate in the study, 3 (5.7%) patients discontinued the study due to AEs, and 3 (5.7%) patients discontinued the study due to insufficient clinical response.

Table 1: Patient disposition in Study A0081180 – Number (%) of Patients

Discontinuations	Pregabalin (N=54) n (%)	Placebo (N=53) n (%)
Discontinuations	10 (18.5)	17 (32.1)
Relation to Study Drug Not Defined	6 (11.1)	13 (24.5)
Insufficient clinical response	0	3 (5.7)
No longer willing to participate	5 (9.3)	7 (13.2)
Other	1 (1.9)	1 (1.9)
Protocol violation*	0	2 (3.8)
Related to Study Drug	4 (7.4)	3 (5.7)
Adverse event	4 (7.4)	3 (5.7)
Not Related to Study Drug	0	1 (1.9)
Adverse event	0	1 (1.9)

Source: Clinical Study Report Section 10.1

The demographic and other background characteristics for all patients are presented in the appendix. The majority of patients (86.0%) were female. The mean age was 14.7 years. Most patients were 14 years (21.5%), 15 years (36.4%) and 16 years old (23.4%). Few patients (1.9%) were 17 years old, which is likely due to this age group being added to the study 2 years after its initiation with amendment 2. The majority of patients were white (57.0%) or Asian (33.6%). The demographic and other background characteristics were comparable between two treatment groups.

3.2.4 Results and Conclusions

There were 54 patients from the pregabalin treatment group and 53 patients from the placebo group included in the full analysis set. The applicant's results and my results are shown in Tables 2 and 3 respectively. The weekly mean pain scores were calculated as the mean of the available pain scores in that week. At least four entries within a week were required to calculate a mean score otherwise the weekly mean pain score was considered missing. Of 53 patients

randomized to the placebo group, 2 patients (10191001 and 10271004) did not have more than four entries within the baseline week and therefore their baselines were set as missing. The applicant did not use these 2 patients in the analysis of the primary efficacy endpoint. However, I used them in my analyses as their missing baseline scores could be imputed using the proposed MI method.

Table 2: Applicant's results of primary efficacy endpoint

(b) (4)

Source: Clinical Study Report Section 11.4.1.1.1

Table 3: Reviewer's results of primary efficacy endpoint

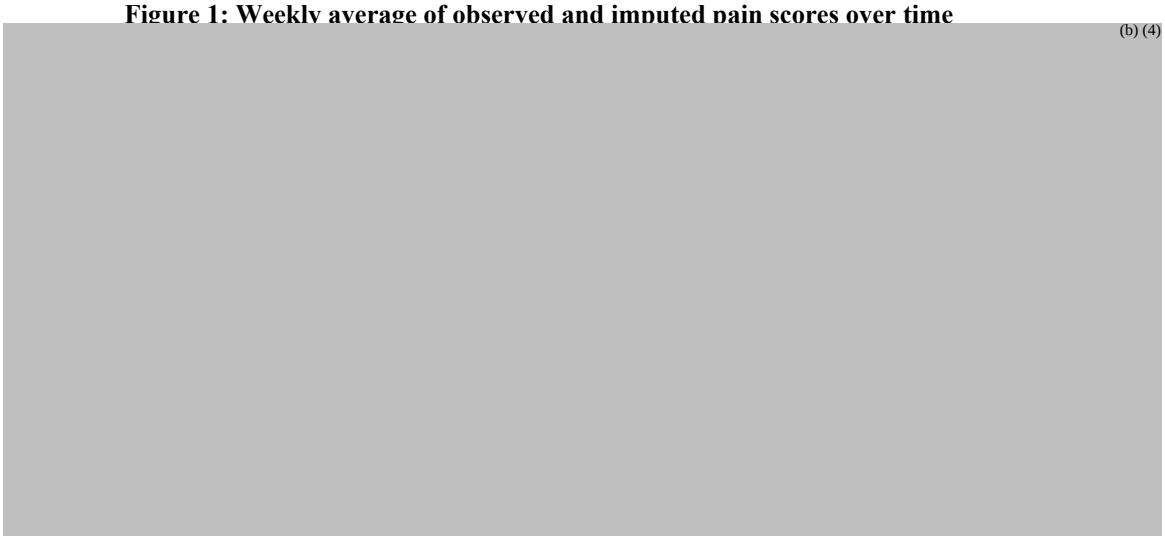
(b) (4)

Source: Reviewer's analyses

My analysis of the primary efficacy endpoint (mean change from baseline to Week 15 in pain intensity) agreed with the applicant's analysis. Numerically there was a greater improvement for the pregabalin treated patients when compared to placebo treated patients, but did not reach statistical significance. The weekly average of observed and imputed pain scores over time for each treatment group is displayed in Figure 1.

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

(b) (4)

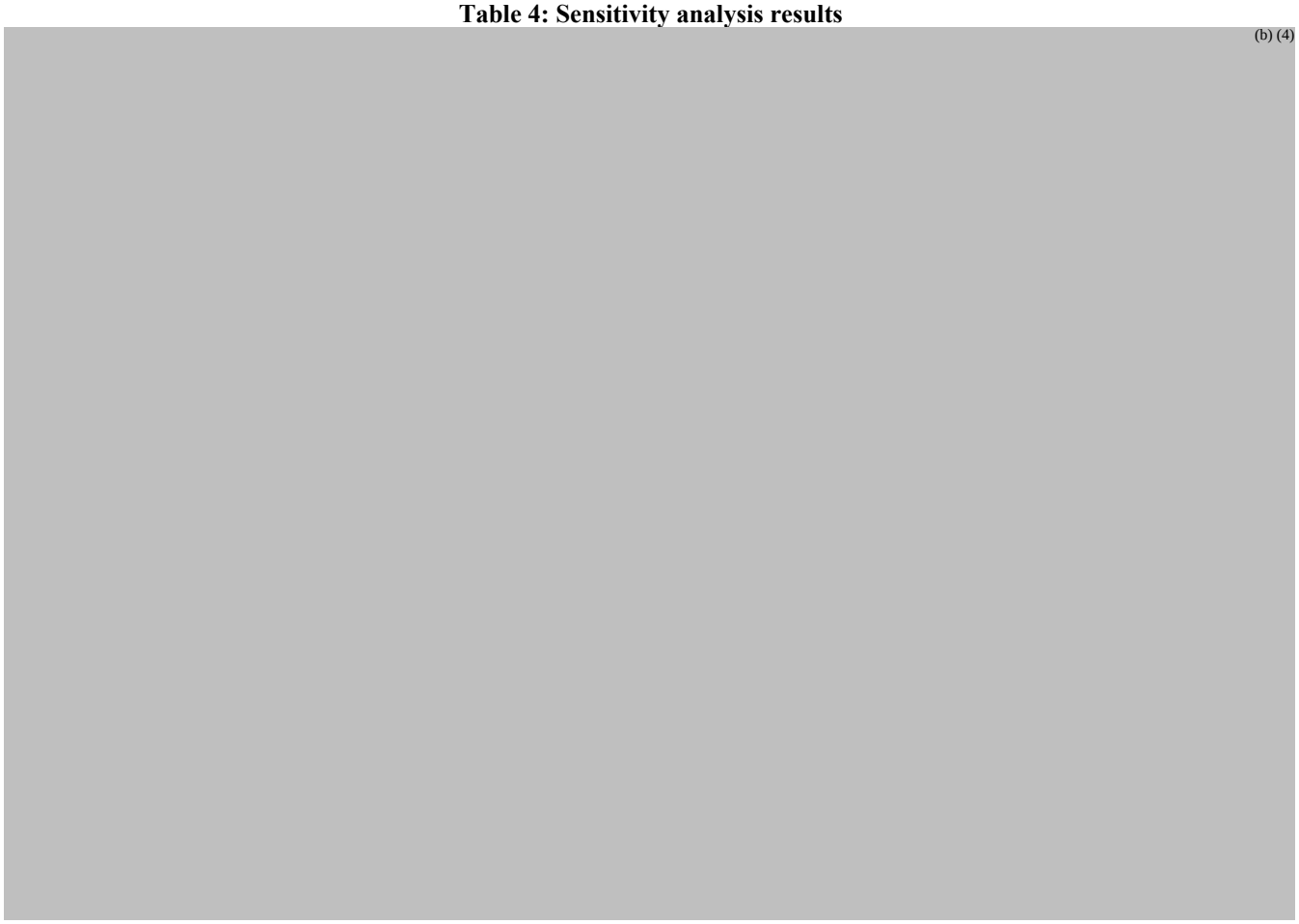


Source: Reviewer's analyses

Results of sensitivity analyses using alternate imputation approaches are in agreement with the primary efficacy analysis, there was a numerical trend favoring pregabalin that was not statistically significant. Results are shown in Table 4.

Table 4: Sensitivity analysis results

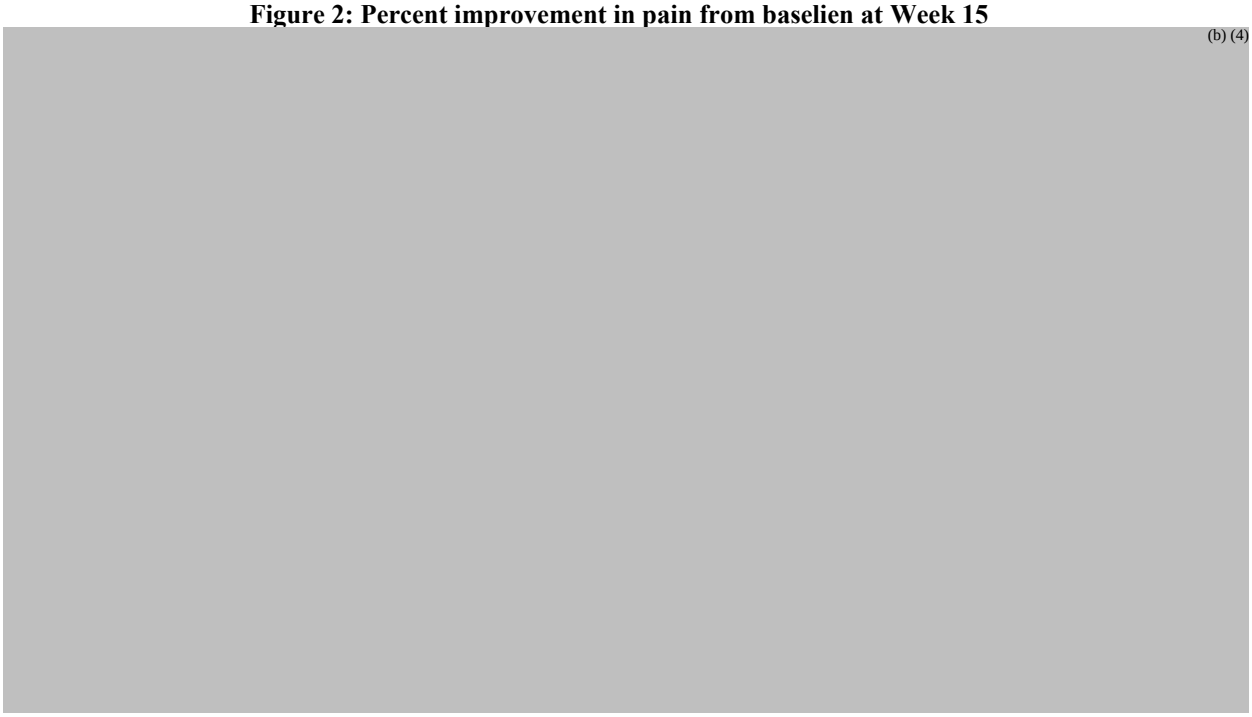
(b) (4)



Source: Reviewer's analyses

To further explore the pain response profile, I also 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 treated patients than placebo treated patients. However, the two curves were not significantly different when applying the non-parametric tests (Wilcoxon rank sums test: p-value = (b) (4); Van der Waerden test: p-value = (b) (4)).

Figure 2: Percent improvement in pain from baselien at Week 15



Source: Reviewer's analyses

Per the request of the clinical team, the primary efficacy endpoint was also analyzed for the following two situations:

- Excluding patients who did not meet the American College of Rheumatology criteria;
- Excluding patients from sites where there were financial disclosure problems.

The results (not shown) were similar to those that included all patients. The pregabalin treated patients had numerically greater improvement compared to the placebo treated patients, but it did not reach statistical significance.

3.2 Evaluation of Safety

The evaluation of the safety data was conducted by Dr. Robert Levin. The reader is referred to Dr. Levin's review for detailed information regarding the adverse event profile.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

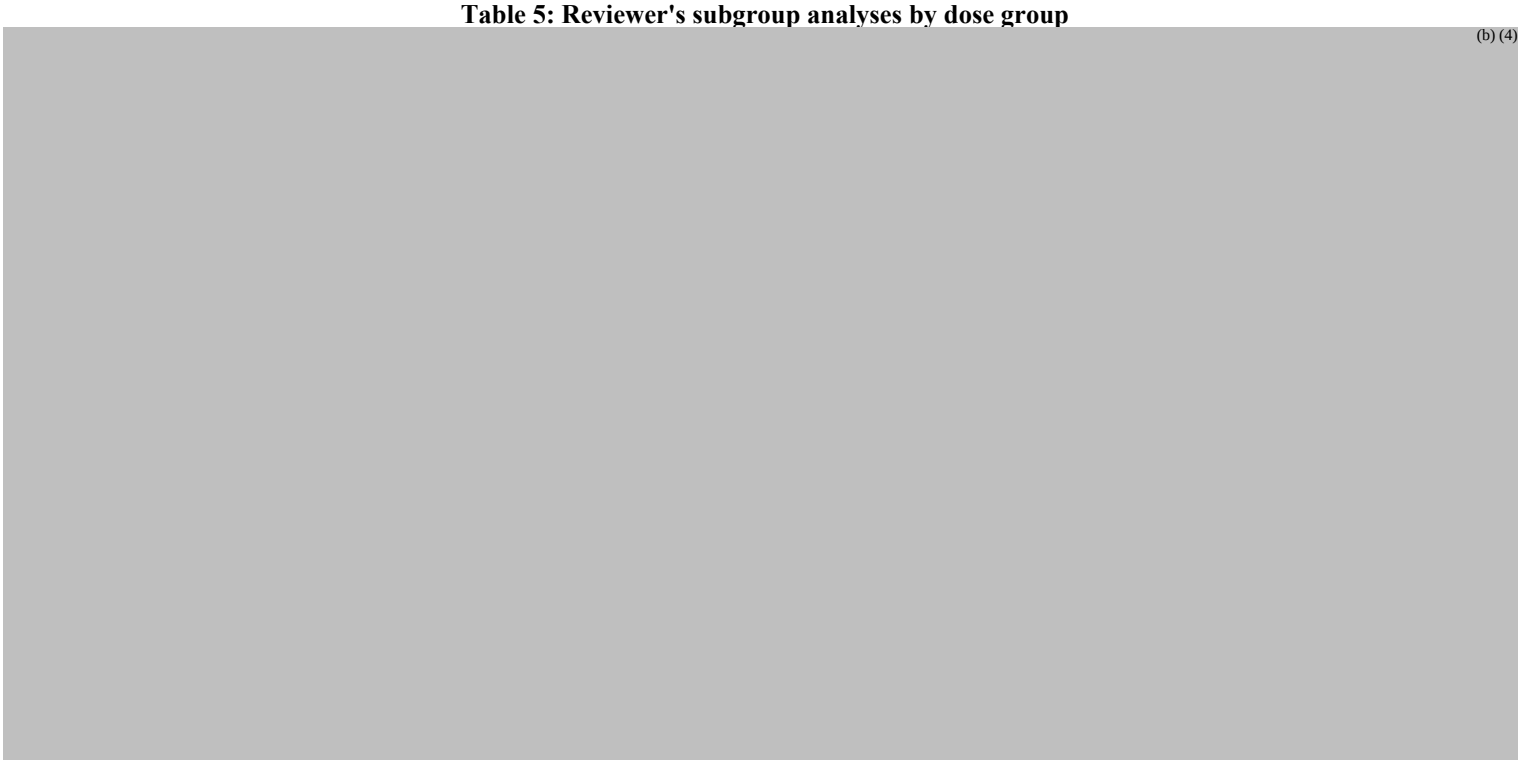
The applicant did not plan or conduct any formal subgroup analysis in the original submission. Per the request of the clinical team, I conducted subgroup analyses for the dose group and country. As the study was not adequately powered to detect statistically significant differences in treatment group comparisons, subgroup analyses of the primary efficacy endpoint were considered exploratory in nature.

4.1 Dose group and country

Table 5 presents subgroup analyses results by dose group. The results were only numerically in favor of the lowest and highest dose of pregabalin.

Table 5: Reviewer's subgroup analyses by dose group

(b) (4)



Source: Reviewer's analyses

Table 6 presents subgroup analyses results by country. The results were similar between U.S. and other three countries.

Table 6: Reviewer's subgroup analyses by country

(b) (4)

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 was one statistical issue identified in the efficacy analyses regarding the sample size.

The study was originally designed to enroll 162 patients. However, given the low incidence of FM in adolescents there was difficulty in recruiting patients. The applicant re-calculated the sample size of the study and reduced the enrollment to 107 patients. However, the estimated treatment effect of the study was only half of that assumed in the sample size re-calculation. Hence the study may not have been adequately powered to detect statistically significant differences in treatment group comparisons.

5.2 Collective Evidence

Study A0081180 was conducted to fulfill the pediatric requirement specified in the approval letter of pregabalin for FM. Efficacy was evaluated in pediatric patients 12 to 17 years of age diagnosed with FM. The pre-specified primary efficacy endpoint was change from baseline to Week 15 in mean pain score which was derived from daily pain numeric rating scale. The results of the primary efficacy variable were numerically in favor of pregabalin but statistical significance was not noted.

5.3 Conclusions and Recommendations

Based on the information submitted, Study A0081180 did not demonstrate superiority of pregabalin over placebo, and as such does not provide substantial evidence of efficacy for the treatment of FM in patients 12 to 17 years of age.

5.4 Labeling Recommendations

According to the draft guidance "Guidance for Industry and Review Staff: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling" dated February 2013, the information of this failed study should only be described in section 8.4 (Pediatric subpopulation) of the product and it should be clearly stated that the efficacy of this product in children 12 to 17 years of age has not been established.

Appendix

Demographics

Source: Clinical Study Report Section 11.2.1

Demographic Characteristics	Pregabalin (N=54)	Placebo (N=53)	Total (N=107)
Hormonal Status - Number (%) of Female Subjects	48	44	92
Premenarchal	1 (2.1)	1 (2.3)	2 (2.2)
Menarche	47 (97.9)	43 (97.7)	90 (97.8)
Age (years)			
Mean	14.6	14.7	14.7
SD	1.2	1.2	1.2
Range	12-17	12-16	12-17
Age (years) - Number (%) of Subjects			
12 years	4 (7.4)	3 (5.7)	7 (6.5)
13 years	5 (9.3)	6 (11.3)	11 (10.3)
14 years	15 (27.8)	8 (15.1)	23 (21.5)
15 years	18 (33.3)	21 (39.6)	39 (36.4)
16 years	10 (18.5)	15 (28.3)	25 (23.4)
17 years	2 (3.7)	0	2 (1.9)
Race - Number (%) of Subjects			
White	29 (53.7)	32 (60.4)	61 (57.0)
Black	2 (3.7)	3 (5.7)	5 (4.7)
Asian	21 (38.9)	15 (28.3)	36 (33.6)
Other	2 (3.7)	3 (5.7)	5 (4.7)
Weight (kg)			
Mean	60.4	59.7	60.1
SD	21.4	17.7	19.6
Range	28.5-154.7	39.0-127.6	28.5-154.7
Height (cm)			
Mean	160.1	162.3	161.2
SD	7.6	8.2	7.9
Range	141.0-177.8	147.0-183.0	141.0-183.0

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/s/

YAN ZHOU
11/21/2016

DAVID M PETULLO
11/21/2016
I concur.