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 Number:	021446 Supplement 36 022488 Supplement 14
Drug Name:	Lyrica® (pregabalin)
Indication:	Adjunctive therapy for children 1 month through < 4 years of age with partial onset seizures
Applicant:	PF PRISM CV
Dates:	Receipt date: August 27, 2018 PDUFA Goal Date: May 27, 2019
Review Priority:	Priority
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Xiangmin Zhang, Ph.D.
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Medical Division:	Division of Neurology Products
Clinical Team:	Emily Freilich, M.D., Clinical Reviewer Philip Sheridan, M.D., Team Leader Eric Bastings, M.D., Deputy Director William Dunn, M.D., Director
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Keywords: clinical studies, NDA review

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1 EXECUTIVE SUMMARY

This review describes the statistical findings of Lyrica® (pregabalin) as an adjunctive therapy for children 1 month through < 4 years of age with partial onset seizures. The review confirmed that Study A0081042 - a randomized, double-blind, placebo-controlled, parallel-group study - in the new drug application provided statistical evidence that pregabalin is efficacious: pregabalin-placebo difference was statistically significant in terms of the logarithmic transformed 24-hour seizure rate.

2 INTRODUCTION

2.1 Overview

On August 27, 2018, Pfizer, Inc. (the Applicant) submitted a 505(b) new drug application (NDA) for Lyrica® (pregabalin) as an adjunctive therapy for children 1 month through < 4 years of age with partial onset seizures. The Applicant submitted one clinical study in the NDA to support the efficacy claim. This clinical study is summarized below and reviewed in Section 3.

Table 1. Clinical study in this review

Study Number	Phase and Design	Double-Blind Treatment Period (in day)	Study Arm (Number of randomized subjects per arm)	Study Population
A0081042	Phase3, randomized, double-blind, placebo-controlled, parallel-group	21	Placebo (70) 7 mg/kg/day (34) 14 mg/kg/day (71)	Male and female subjects 1 month through < 4 years of age with a diagnosis of epilepsy with seizures.

Source: statistical reviewer's summary

2.2 Data Sources

The electronic submission of this NDA is located at
\\cdsesub1\evsprod\NDA021446\0553\
\\cdsesub1\evsprod\NDA021446\0599\
\\cdsesub1\evsprod\NDA022488\0084\
\\cdsesub1\evsprod\NDA022488\0089\

The study report is located at
\\cdsesub1\evsprod\NDA021446\0553\m5\53-clin-stud-rep\535-rep-effic-safety-stud\partial-onset-seizures\5351-stud-rep-contr\a0081042\

The datasets are located at
\\cdsesub1\evsprod\NDA021446\0553\m5\datasets\a0081042\

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

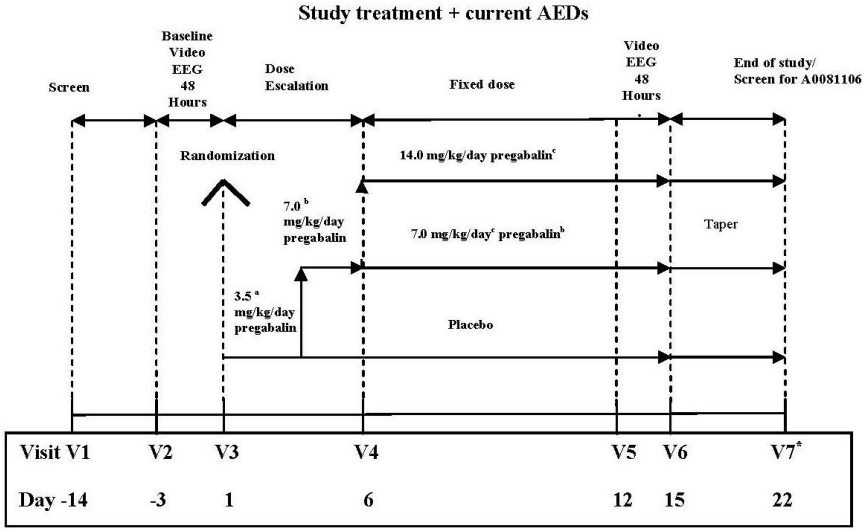
The data quality and analysis quality are adequate. The statistical reviewer was able to perform independent review using the Applicant's submitted datasets and confirm the Applicant's analysis results.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study A0081042 (hereafter referred to as Study 1042) was a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, multi-center clinical study to evaluate the efficacy, safety, and tolerability of pregabalin in subjects 1 month through < 4 years of age. Accounting for an approximately 10% discontinuation rate, approximately 123 subjects were planned to be randomized in a 2:2:1 ratio to placebo group, 7 mg/kg/day pregabalin group, or 14 mg/kg/day group.

Figure 1. Design diagram



* Eligible subjects may be assessed for screening into study A0081106 and complete end of study activities for A0081042 at Visit 7 (V7)
a [3 mg/kg/day for subjects 1 to 3 months of age];
b [6 mg/kg/day for subjects 1 to 3 months of age];
c [12 mg/kg/day for subjects 1 to 3 months of age]

Source: study design diagram in protocol amendment 1

Figure 1 depicts the study design of Study 1042. The study consisted of a five-day double-blind dose escalation period, a nine-day double-blind fixed dose treatment period, and a seven-day double-blind taper period. The total duration of the double-blind treatment phase is twenty-one days.

During the study, two 48-hour Video-Electroencephalogram (EEG) evaluations were performed: one at the baseline and the other at the end of the fixed dose treatment period. One of the inclusion criteria of Study 1042 was that subjects must have at least two partial onset seizures as determined by the investigator or designee during the 48-hour Video-EEG at baseline. Subjects that were randomized but subsequently determined by the central reader to have less than two partial-onset seizures were allowed to continue the study. However, a central reader evaluated the Video-EEG data to determine the number of seizures for efficacy evaluation.

The primary efficacy endpoint was the change from baseline to Visit 6 in the 24-hour EEG seizure rate as determined by the central reader. The 24-hour EEG seizure rate is defined as the number of seizures during the 48-hour EEG divided by the number of hours of Video-EEG monitoring then multiplied by 24 hours.

3.2.2 Statistical Methodologies

The efficacy analysis population was the modified intent-to-treat (mITT) population, defined as all randomized subjects who took at least one dose of study drug during the double-blind treatment period, have a baseline with at least one partial onset seizure identified by Video-EEG and a follow-up Video-EEG.

The primary endpoint of 24-hour EEG seizure rate was transformed on a logarithmic scale after adding a value of 1. log(24-hour EEG seizure rate + 1) was analyzed using a linear model that included log(24-hour EEG seizure rate + 1) at baseline as the covariate and treatment, age at randomization (< 1 years, 1-2 years of age, > 2 years of age), and geographic region (North America + Europe + Middle East, Asia Pacific, Rest of the World) as effects.

In order to control the overall type I error, tests of the two doses were planned in the following order, each step at the two-sided significance level of 0.05:

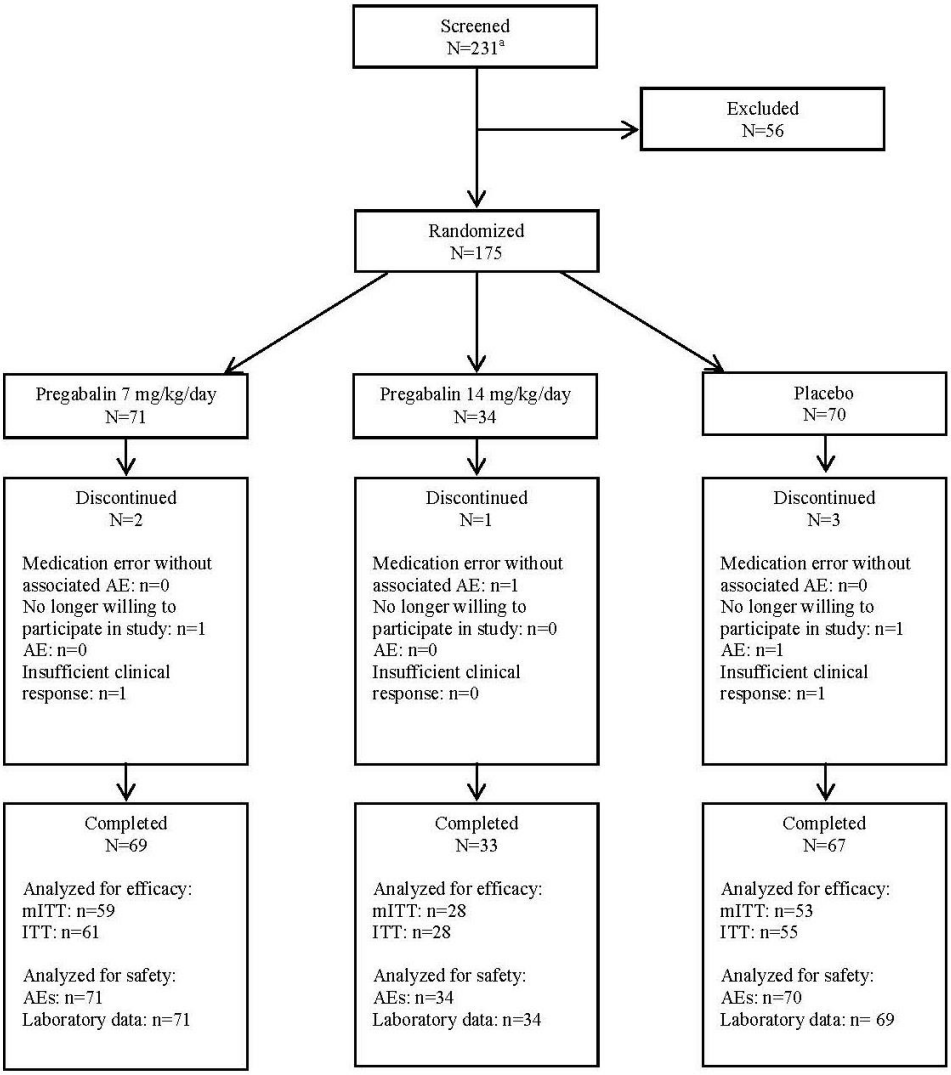
Step 1. Test equal treatment of pregabalin 14 mg/kg/day vs placebo for the primary endpoint.
Step 2. Test equal treatment of pregabalin 7 mg/kg/day vs placebo for the primary endpoint.

The initial planned sample size was a total of 123 subjects for randomization. A blinded sample size re-estimation using the method described in Keiser and Friede (2011)[1] was planned to be conducted when approximately two thirds of the subjects have completed the study. The maximal sample size after the sample size re-estimation was 150.

[1] Friede, T., & Kieser, M. (2011). Blinded sample size recalculation for clinical trials with normal data and baseline adjusted analysis. *Pharmaceutical Statistics*, 10(1), 8-13.

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

Figure 2. Subject disposition



Source: Section 14.1, Table 14.1.1.1, Table 14.1.1.2
Randomization for this study was 2:1:2.
N is the number of subjects from the safety population for a given group, n is the number of subjects analyzed meeting this reporting criterion.
The mITT population was the primary efficacy population and consisted of randomized subjects who took at least 1 dose of study drug during the double-blind treatment phase, had a baseline with at least 1 POS seizure identified by V-EEG, and a treatment phase V-EEG.
The ITT population consisted of randomized subjects who took at least 1 dose of study drug during the double-blind treatment phase and had a baseline with at least 1 POS identified by V-EEG.
Abbreviations: AE = adverse event; ITT = intent-to-treat; mITT = modified intent-to-treat; POS = partial onset seizures; V-EEG = video-electroencephalogram.
a. Six of these subjects had been re-screened.

Source: Figure 2 in the clinical study report body

Figure 2 presents the subject disposition of Study 1042. A total of 231 subjects were screened in 64 study centers in 23 countries; a total of 175 subjects were randomized in 52 study centers in 22 countries. Among the randomized subjects, 70 subjects (40.0%) were randomized to the placebo group, 71 (40.6%) to the 7 mg/kg/day group, and 34 (19.4%) to the 14 mg/kg/day group.

A total of 169 out of 175 (96.6%) randomized subjects completed the study: 67 out of 70 (95.7%) in the placebo group, 69 out of 71 (97.2%) in the 7 mg/kg/day group, and 33 out of 34 (97.1%) in the 14 mg/kg/day group.

A total of 140 out of 175 (80.0%) randomized subjects are included in the mITT population for efficacy evaluation: 53 out of 70 (75.7%) in the placebo group, 59 out of 71 (83.1%) in the 7 mg/kg/day group, and 28 out of 34 (82.4%) in the 14 mg/kg/day group. Many randomized subjects were excluded from the efficacy evaluation because their 24-hour EEG seizure rates were zero, as determined by the central reader.

Table 2. Subject demographics, mITT population

	Pregabalin 7 mg/kg/day (N=71)	Pregabalin 14 mg/kg/day (N=34)	Placebo (N=70)	Total (N=175)
Number (%) of Subjects				
Age (months):				
<12	9 (12.7)	2 (5.9)	7 (10.0)	18 (10.3)
12-24	19 (26.8)	10 (29.4)	20 (28.6)	49 (28.0)
>24	43 (60.6)	22 (64.7)	43 (61.4)	108 (61.7)
Mean	27.5	28.5	28.8	28.2
SD	12.7	12.5	12.6	12.6
Range	4-48	4-47	3-47	3-48
Sex:				
Male	45	20	38	103
Female	26	14	32	72
Race:				
White	47 (66.2)	24 (70.6)	49 (70.0)	120 (68.6)
Asian	23 (32.4)	10 (29.4)	19 (27.1)	52 (29.7)
Other	1 (1.4)	0 (0.0)	2 (2.9)	3 (1.7)

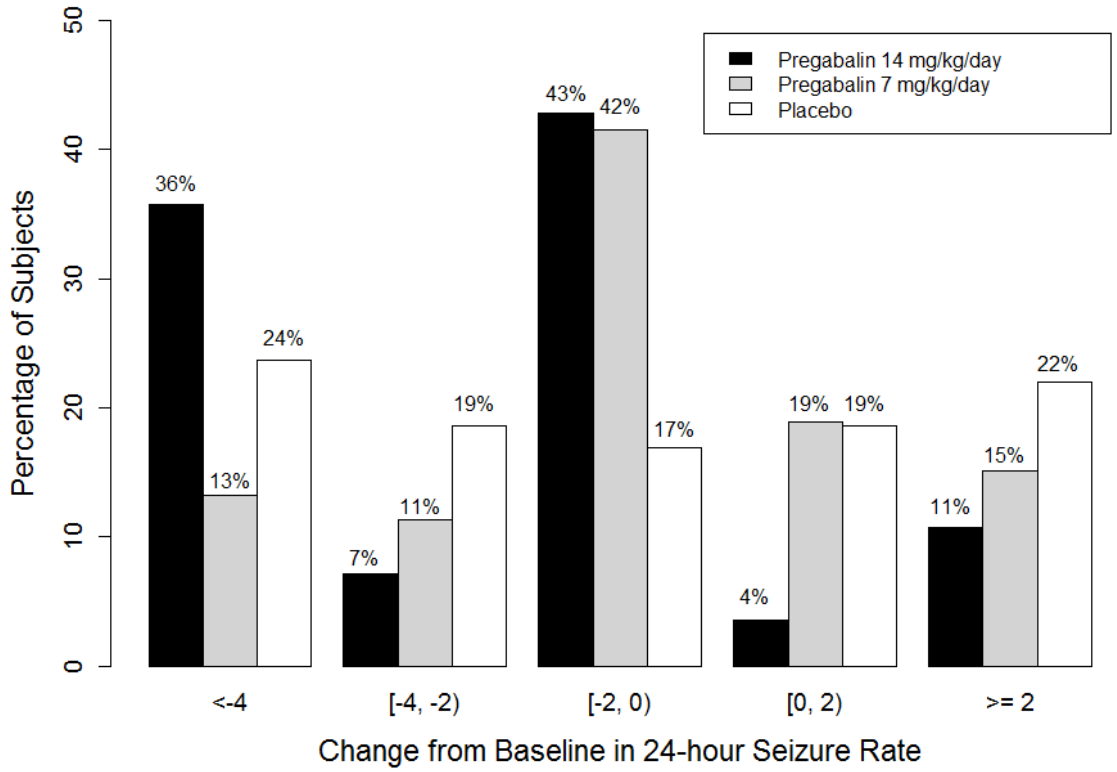
Source: selected from Table 10 in the clinical study report body

Table 2 summarizes the demographic characteristics of the enrolled subjects. The treatment groups appeared similar in terms of age, sex, and race. The average age of the enrolled subjects was approximately 28.2 months (standard deviation (SD) = 12.6). Overall, there were more male subjects than female ones in the study. The majority of the enrolled subjects were white.

3.2.4 Results and Conclusions

The blinded sample size was conducted on the first 95 randomized and treated subjects. The re-estimated sample size exceeded the sample size limit of 150 total subjects. Therefore, the sample size was adjusted to 150 subjects. The total number of subjects randomized were 175 and the total number of subjects in the efficacy analysis was 140.

Figure 3. Distributions of changes from baseline in 24-hour seizure rate, mITT population



Source: statistical reviewer

Figure 3 depicts the empirical distributions of change from baseline in 24-hour seizure rate of the three groups. Because Study 1042 had only two video-EEG assessments - one at the baseline and the other at the end of the fixed dose treatment period - data from all subjects in the mITT population were used in this figure; there were no missing data. The numbers of subjects were 53, 59, and 28 for the placebo, pregabalin 7 mg/kg/day group, and pregabalin 14 mg/kg/day group, respectively. The categorizations in the x-axis do not reflect clinically important cut-offs but are only used to facilitate the demonstration of the general distributions of the changes from baseline in 24-hour seizure rate. Negative changes from baseline indicate improvements. The percentages of subjects that had improvement were 59.3%, 66.0%, and 85.7% for the placebo group, pregabalin 7 mg/kg/day group, and pregabalin 14 mg/kg/day group, respectively. The distributions were skewed. While 24% of the placebo subjects had an improvement greater than 4 seizures per 24 hours, 22% of the placebo group subjects had an increase of more than 2 seizure rates per 24 hours. Each of the three groups had several subjects with changes from baseline in large magnitudes, e.g. more than 10 (i.e. 10 more or 10 less seizures compared to baseline).

Table 3. Study A0081042 primary analysis, mITT population

Visit		Pregabalin 7 mg/kg/day (N=59)	Pregabalin 14 mg/kg/day (N=28)	Placebo (N=53)
Baseline	n	59	28	53
	Min	0.5	0.3	0.3
	Median	1.73	1.86	1.37
	Max	5.5	3.8	4.0
	Mean	2.03	1.86	1.66
	95% CI of Mean	(1.73, 2.33)	(1.49, 2.23)	(1.40, 1.91)
	SD	1.157	0.945	0.920
DB Phase	n	59	28	53
	Min	0.0	0.0	0.0
	Median	1.57	0.87	1.19
	Max	5.7	3.5	4.5
	Mean	1.81	1.10	1.36
	95% CI of Mean	(1.49, 2.12)	(0.69, 1.51)	(1.03, 1.69)
	SD	1.219	1.065	1.193
	LS Mean	1.69	1.15	1.58
	95% CI of LS Mean	(1.46, 1.92)	(0.83, 1.47)	(1.32, 1.83)
	Standard error	0.115	0.163	0.129
	Versus Placebo (log)			
	LS Mean Difference	0.11	-0.43	
	95% CI of LS Mean Difference	(-0.19, 0.42)	(-0.80, -0.06)	
	Standard error	0.153	0.185	
	p-value	0.4606	0.0223	

Source: Table 13 in the clinical study report body

Table 3 presents the primary analysis results of Study 1042. The descriptive statistics are based on logarithm transformed 24-hour seizure rate. Pregabalin 14 mg/kg/day was significantly (p-value = 0.0223) better than placebo in reducing 24-hour seizure rate. The comparison between the pregabalin 7 mg/kg/day and placebo in the primary endpoint was not significant (p-value = 0.4606). The treatment difference between the pregabalin 7 mg/kg/day group and placebo was not in the direction favoring pregabalin, however, the 95% confidence interval of this treatment difference contains 0, not indicating that this difference favored placebo.

The efficacy appeared to be driven by three foreign study centers. After removing data from either Center 1069 (the center is in Ukraine, with 21 subjects randomized), Center 1084 (the center is in Philippines, with 13 subjects randomized), or Center 1209 (the center is in Russian Federation, with 3 subjects randomized), respectively, the pregabalin-placebo comparison turned out not significant for either dose.

Four sensitivity analyses were conducted by the Applicant for the primary endpoint. The numerical results of a post-hoc ranked analysis of covariance and a post-hoc Wilcoxon-Mann Whitney test, both performed on the 24-hour seizure rate, provided similar p-values to the ones under the primary analysis. Numerical results of a pre-specified ranked analysis of covariance

and a pre-specified Wilcoxon-Mann Whitney test, both performed on the logarithmic transformed 24-hour seizure rate, showed that none of the pregabalin-placebo comparisons were statistically significant.

Based on the least squares means from the primary analysis results, percentage reduction relative to placebo was derived from the following formula:

$$\frac{[\exp(LSMean(pregabalin))-1]-[\exp(LSMean(placebo))-1]}{\exp(LSMean(placebo))-1} \times 100\%.$$

The percentages of reduction relative to placebo were 44% and -15% (i.e. 15% increase) for the pregabalin 14 mg/kg/day group and pregabalin 7 mg/kg/day group, respectively.

3.3 Evaluation of Safety

Please refer to Dr. Emily Freilich's clinical review for a detailed evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Sex, Race, Age, and Geographic Region

Table 4. Study A0081042 analyses by age, sex, and race, mITT population

	Pregabalin		Placebo
	7 mg/kg/day	14 mg/kg/day	
AGE (<12 months, 12-24 months, and >24 months)			
<12 months (n)	9	2	3
Baseline	12.19 (1.4, 37.5)	6.47 (2.0, 11.0)	3.03 (2.0, 7.9)
% Change from Baseline	-28.68 (-76.1, 163.1)	-44.90 (-63.6, -26.2)	-44.13 (-58.0, 35.7)
12 to 24 months (n)	16	7	14
Baseline	4.83 (0.7, 206.2)	5.28 (0.3, 19.5)	6.07 (0.3, 56.2)
% Change from Baseline	-39.62 (-100.0, 371.4)	-37.49 (-100.0, 2099.7)	26.62 (-100.0, 291.7)
>24 months (n)	34	19	36
Baseline	3.94 (0.7, 254.9)	8.66 (0.7, 42.7)	2.75 (0.4, 34.9)
% Change from Baseline	-0.49 (-100.0, 1111.6)	-91.68 (-100.0, 94.1)	-33.90 (-100.0, 186.0)
SEX			
Male (n)	40	15	28
Baseline	4.81 (0.7, 254.9)	8.98 (0.3, 27.4)	3.79 (0.3, 56.2)
% Change from Baseline	-23.15 (-100.0, 1111.6)	-85.98 (-100.0, 2099.7)	-33.15 (-100.0, 291.7)
Female (n)	19	13	25
Baseline	4.34 (0.7, 39.6)	4.40 (1.0, 42.7)	2.75 (0.7, 28.3)
% Change from Baseline	13.47 (-100.0, 371.4)	-42.41 (-100.0, 94.1)	-13.53 (-100.0, 186.0)
RACE			
White (n)	38	18	34
Baseline	4.09 (0.7, 86.6)	5.10 (0.7, 42.7)	2.55 (0.4, 56.2)
% Change from Baseline	-18.47 (-100.0, 371.4)	-54.75 (-100.0, 84.8)	-32.76 (-100.0, 291.7)
Asian (n)	20	10	18
Baseline	7.54 (0.7, 254.9)	7.16 (0.3, 19.5)	5.47 (0.3, 34.9)
% Change from Baseline	-6.36 (-100.0, 1111.6)	-82.66 (-100.0, 2099.7)	-17.36 (-100.0, 186.0)

Actual seizure rates, not log-transformed, are reflected in this table.
Data are presented are median (min, max)

Source: selected from Table 9 in the integrated summary of effectiveness

Table 4 presents the medians of 24-hour seizure rates at baseline and medians of changes from baseline in the 24-hour seizure rate (without logarithmic transformation) by sex, age, and race. Only three subjects (one subject for each dose group) were from the United States (US), therefore, subgroup analysis by region (US vs non-US) was not conducted. Overall, there is no compelling evidence from the subgroup analyses that a specific age sub-group, sex, or race benefits differently from pregabalin.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The efficacy appeared to be driven by three foreign study centers. After removing data from any one of the three centers, the pregabalin-placebo comparisons were not significant. On the other hand, removing data from any one of the three centers would still provide pregabalin-placebo difference in the direction favoring pregabalin 14 mg/kg/day group. For example, for the pregabalin 14 mg/dg/day group, the percentage of reduction relative to placebo was 44%. This percentage of reduction would change to 41%, 40%, or 36.5% if Center 1069, Center 1084, or Center 1209 was removed.

5.2 Collective Evidence

One clinical study, Study A0081042, in the NDA submission provided efficacy evidence of pregabalin. For the 14 mg/kg/day group in this study, pregabalin-placebo difference was statistically significant (p-value = 0.0223) in terms of logarithmic transformed 24-hour seizure rate; the percentage of reduction relative to placebo was 44%.

5.3 Conclusions and Recommendations

Based on the statistical evidence from Study A0081042, pregabalin appears effective as adjunctive therapy for children 1 month through < 4 years of age with partial onset seizures.

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/s/

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I concur with the review.

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