CENTER FOR DRUG EVALUATION AND RESEARCH

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-446
Drug Name:	Lyrica (pregabalin) capsules
Indication(s):	Diabetic Peripheral Neuropathy, Post-herpetic Neuralgia,
Applicant:	Pfizer
Date(s):	Original submission: 10/30/2003
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Keywords: Crossover design; Drug abuse potential study; Self-reported endpoint; Multiple endpoints

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1. EXCUTIVE SUMMARY

1.1 Conclusion and Recommendation

The applicant conducted study 098 for assessing the potential abuse liability of pregabalin. Although the subjects per sequence in the crossover design were unbalanced, which may due to the dropouts, the sequence effects in the study model were not statistically significant for 8 out of 10 variables considered in the reviewer's analyses. Because of at least 5 days washout period, and screening tests for alcohol and prohibited drug use before administrating next treatment, the first-order carryover effect in the study model is also not statistically significant in all the cases. Overall, the study was conducted well. It is also evident that 75% of study subjects identified placebo as placebo in the end of session drug identification.

Based on Controlled Substance Staff (CSS) suggestion, End of Session Drug Liking, Emax of Visual Analog Scales (VAS) – Liking, Good Drug Effect, High were considered as primary variables, and Emaxs of VAS – Sedated, Simulated, Addiction Research Center Inventory (ARCI) – MBG, BG, LSD, PCAG, and End of Session Drug Identification were considered as secondary variables in the reviewer's statistical analyses. For all primary variables and most of secondary variables, diazepam served as an acceptable positive control for evaluating the subjective effects of pregabalin. The study results show that for all primary variables and secondary variables pregabalin failed to demonstrate the absence of potential for drug abuse. The data from study 098 does not support the sponsor's claim that pregabalin should not be a schedule 4 drug.

1.2 Brief Overview of Clinical Studies

1.2.1 Study objectives

Evaluate the abuse potential of pregabalin versus diazepam and placebo in recreational sedative users.

1.2.2 Study design

This study is a randomized, double-blind, placebo-controlled single center study of the abuse potential of pregabalin in 15 subjects who are recreational sedative users or moderate alcohol users. The study consists of 9 sessions:

- Screening session
- Practice session
- 5 drug treatment sessions
- Lottery session
- Follow-up session

The study used a crossover design with 5 sequences and 5 periods based on the following Latin square:

Sequence	Period	# of replications
1.	E B D C A	2
2.	C E B A D	3
3.	B C A D E	4
4.	D A E B C	3
5.	A D C E B	3

where the letters A, B, C, D, and E denote placebo, 15 mg diazepam, 30 mg diazepam, 200 mg pregabalin and 450 mg pregabalin respectively.

The applicant was intended to use three repeated Latin squares and randomly assigned the study subjects to one square with one of five sequences. However, the subjects per sequence are unbalanced in this study. It may be due to the dropouts. The data were recorded for 15 study subjects, who completed the study.

1.2.3 Participant population

Fifteen male or female volunteers aged 18 to 40 years who are recreational sedative users, defined as those reporting using a sedative (eg, barbiturates, benzodiazepines) for its intoxicating effects on at least 6 occasions but who have no signs of dependence. Volunteers who are moderate to heavy drinkers, defined as more than 12 drinks per week, will also be eligible.

1.2.4 Participant disposition

In the applicant's report, thirty-nine volunteers were interviewed, yielding a total of 21 eligible candidates, two of whom withdrew consent prior to the first session. Of the 19 remaining, 15 volunteers completed the study. However, this is inconsistent with the information for incompletes and ineligible volunteers from Appendix 2 in the applicant's report, in which 5 eligible candidates did not complete the study. The information about eligible volunteer disposition is listed in Table 2 on page 10.

1.2.5 Primary and secondary endpoints

In applicant's protocol, the primary measures of abuse potential are defined as follows:

- the cross-over point at which the subject's preference changes from receiving drug again to giving or receiving money, on the multiple-choice procedure (MCP) which will be performed after at least 5 day washout period for a lottery session following completion of all 5 drug sessions.
- the hourly changes from predrug on POMS, VAS and ACRI
- drug liking using the End of Session Questionnaire.

There is no secondary variable proposed in the protocol 1008-098.

1.3 Statistical Issue and Findings

1.3.1 Choice of the Primary Endpoints

It can be seen that there are a large number (see page 9) of primary endpoints defined in protocol 1008-098. The evaluation for the drug abuse potential is not clearly defined with multiple primary endpoints in the protocol.

The first primary endpoint from a multiple choice procedure after completion of 5 drug sessions showed no difference between diazepam and placebo. The applicant stated that this study is limited in its ability to evaluate any potentially reinforcing value of pregabalin.

The other primary variables were based on hourly changes from predrug except the drug liking using the End of session questionnaire. The CSS believe that the peak response of a treatment from predrug baseline is a more proper measure for evaluation of potential for drug abuse than the hourly changes in response of a treatment. The CSS decided to use the following primary and secondary endpoints in evaluation of potential for abuse liability of pregabalin.

Primary variables:

VAS – Emax of Good Drug Effect
VAS – Emax of High
VAS – Emax of Drug Liking
End of Session Drug Liking

Secondary

ARCI – Emax of MBG
ARCI – Emax of BG
ARCI – Emax of PCAG
ARCI – Emax of LSD
VAS – Emax of Sedated
VAS – Emax of Stimulated
End of Session Drug Identification

where Emax is computed from change from predrug baseline.

1.3.2 Evaluation criteria

In Inferential Analysis Plan (see Appendix 3 in protocol of study 1008-098), the applicant stated its interpretation of study results as follows:

The profile of effects on the POMS, ARCI, and VAS scale scores and on physiologic parameters following pregabalin administration will be compared to the profile produced by diazepam, all relative to placebo. If pregabalin has a similar profile and scores are changed to the same degree

as either dose of diazepam, the abuse liability of pregabalin would be presumed to the similar to diazepam. If the change scores were greater, the abuse liability of pregabalin might be considered greater. If the profile was divergent or the change score smaller, it could be presumed to have less abuse liability. Similar comparisons will be made among treatments to compare the effects of pregabalin on the MCP crossover point scores and the EOSQ drug liking scores to the effects produced by diazepam, all relative to placebo.

Since too many primary variables were proposed by the applicant. It is difficult to define "a similar profile" either for diazepam and pregabalin or for placebo and pregabalin.

In fact, to claim there is no potential for abuse liability of pregabalin, for each primary variable the applicant needs to show that

- diazepam has statistically larger mean response than placebo (to insure the validation of the positive control of diazepam)
- pregabalin has statistically lower mean response than double the mean response of placebo
- pregabalin has statistically lower mean response than diazepam

The given significance level of each test is 5%. Since to show no drug abuse potential of pregabalin, the applicant needs to reject all three null hypotheses for each primary endpoint, Type I error rate adjustment is not needed for this case.

1.3.3 Sample size and power of statistical tests

Sample size was determined by reviewing the diazepam literature by the applicant. With 20 eligible volunteers 25% of them dropped the study for various reasons (See Table 2 on page 10). The data submitted for this study are for 15 completed subjects. Impact on the results by these dropouts is unknown. With 15 observations for each treatment, the power of statistical tests in the analysis is low.

For controlling the rate of error decision on conservative side, instead of a two-tailed test for testing difference in mean response between pregabalin and placebo, the FDA requests the applicant to show statistically lower mean response of pregabalin than twice the mean response of placebo in a drug abuse potential study.

1.3.4 Study results from reviewer's statistical analyses

For all primary variables and secondary variables defined by the CSS pregabalin failed to demonstrate that its mean response is less than double the mean response of placebo and has lower mean response than diazepam. That is, the data do not support the applicant's claim of no potential abuse liability of pregabalin.

2. INRODUCTION

2.1 Background of the Review

Pregabalin is a new chemical entity currently under review by the FDA for the treatments of diabetic peripheral neuropathy, post-herpetic neuralgia, [redacted] epilepsy, and generalized anxiety disorder. Because of the FDA's concern of potential for abuse liability of pregabalin, the applicant submitted this study to demonstrate that there is evidence that pregabalin lacks drug abuse potential.

Since a large number (see page 9) of primary endpoints were defined in protocol 1008-098, and not all of them are of interest for potential for abuse liability assessment, this review will be focussed on the variables recommended by the FDA's Controlled Substance Staff (CSS).

2.2 Data Source

2.2.1 Procedure of Data Collection

Volunteers participated in one practice session and five drug sessions, with the drug sessions separated by at least a 5-day washout period. During the practice session, the study subjects learned to enter responses to the subjective effects questionnaires directly on the computer and became familiar with the procedures to be used in the drug sessions. The participants received a different test medication at each drug session. It was reported that order of the treatments was counterbalanced which is inconsistent with what reported in Appendix 1 in the applicant's report. From Appendix 1, it can be seen that two out of five treatment sequences were repeated 2 or 4 times and the other sequences were repeated 3 times. This might not be the intention of the applicant, but the order of the treatment was not counterbalanced.

After the five drug sessions were completed, the study subjects participated in a lottery session, in which they received drug or money, and a final follow-up session where screening tests were repeated and participants were debriefed.

During each of the drug sessions, urine for drug use verification and a breath alcohol reading was obtained. A session was rescheduled if breathalyzer readings were over 0.002 BAC (2 mg alcohol/100 ml blood) or the participant's urine was positive for cocaine, stimulants, barbiturates, or opiates. Urines positive for benzodiazepines were allowed if the level was below 1000 ng/ml in order to distinguish recent use of a benzodiazepine from diazepam received in a study session. The study medication was administered after these tests were completed. The effects of the study medication were evaluated using subjective scales including the Profile of Mood States (POMS), Addiction Research Center Inventory (ARCI), and Visual Analog Scales (VAS) completed 0.5 hr before drug, and 0.5, 1, 2, 3, 4, 5, and 6 hours post-drug administration. At 6-hr post-drug administration, an End of Session Questionnaire (EOSQ) and Multiple Choice Form were completed.

Following completion of all 5 drug sessions, participants returned after a minimum 5- day washout period for the lottery session. During the lottery session, volunteers received one of the

study medications again or varying amounts of money, based on the decisions they had made on the Multiple Choice Form.

Due to the nearly sufficient washout period and predrug screening, the data were not subject to possible mixed carryover effect which often is seen in crossover designs used in drug abuse potential studies.

2.2.2 Data location

In original NDA 21-446 submission, data submitted with the NDA for Study 098 were summary data. Per CSS request the applicant resubmitted data which were recorded during the study for each subject on August 18, 2004. The following is the link of the data sets used in this review.

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3. STATISTICAL EVALUATION

3.1 Evaluation of Potential for Abuse Liability of pregabalin

3.1.1 Study design and endpoints

This study is a randomized, double-blind, placebo-controlled single center study of the abuse potential of pregabalin in 15 subjects who are recreational sedative users or moderate alcohol users. The study consists of 9 sessions:

- Screening session
- Practice session
- 5 drug treatment sessions
- Lottery session
- Follow-up session

The study used a crossover design with 5 sequences and 5 periods based on the following Latin square, and supposed to have three replicates of the Latin square:

Sequence	Period	# of replications
1.	E B D C A	2
2.	C E B A D	3
3.	B C A D E	4
4.	D A E B C	3
5.	A D C E B	3

where the letters A, B, C, D, and E denote placebo, 15 mg diazepam, 30 mg diazepam, 200 mg pregabalin and 450 mg pregabalin respectively.

The applicant was intended to use three repeated Latin squares and randomly assigned the study subjects to one square with one of five sequences. However, the subjects per sequence are unbalanced in this study. It may be due to the dropouts. The data were recorded for 15 study subjects, who completed the study.

The primary endpoints defined in the applicant's protocol are

- the cross-over point at which the subject's preference changes from receiving drug again to giving or receiving money, on the MCP
- the hourly changes, from predrug on Profile of Mood States (POMS)
- the hourly changes, from predrug on Visual Analog Scales (VAS)
- the hourly changes, from predrug on Addiction Research Center Inventory (ARCI)
- Drug liking in End of Session Questionnaire (EOSQ)

The variables under the applicant consideration for POMS, VAS and ARCI are

POMS: anxiety, depression, anger, vigor, fatigue, confusion, friendliness, elation arousal and positive mood.

VAS: good drug effect, bad drug effect, drug liking, stimulated, high, anxious, sedated, down, hungry, friendly, miserable, on edge, alert, tired, talkative, self-confident, social, irritable, and confused.

ARCI: Stimulant-like effects (A, BG scales), Euphoria (MBG scale), Dysphoria and somatic complaints (LSD scale) and Sedation (PCAG).

There are a large number of primary endpoints used in the applicant's analysis, and some of them conflict with each other. Therefore, it is difficult to see a clear picture of potential for abuse liability of pregabalin based on all the primary endpoints defined by the applicant. For evaluating the potential abuse liability, the CSS suggested to use the following primary variables: VAS – Good Drug Effect, High and Liking, and End of Session Drug Liking. The secondary variables are VAS – stimulated and sedated, ARCI – BG, MBG, LSD and PCAG, and End of Session Drug Identification.

Since the CSS believe that the peak response of a treatment from predrug baseline is a more proper measure for evaluation of potential for drug abuse than the hourly changes in response of a treatment, the endpoints of these variables are defined as Emax of those variables computed from change from predrug baseline except the variables End of Session Drug Liking and End of session Drug Identification since there were no repeat measurements for these variables.

3.1.2 Participants

3.1.2.1 Participant characteristics

Thirty-nine volunteers were interviewed, yielding a total of 22 eligible candidates, two of whom withdrew consent prior to the first session. Of the 20 remaining, 15 volunteers completed the

study. Thirteen of the 15 completers met the alcohol consumption criterion and 5 met the sedative use criterion in subject selection. The participant demographics and previous drug use are shown in Table 1 (This is Table 2 from the applicant's report.)

Table 1. Participant demographics and drug Use

Characteristic	
Sex (male)	73%
Race	66.6% White
	20% African-American
	6.7% Hispanic
	6.7% Asian
Age	20-29, mean=22.7
Education	20% High School
	73.3% Some College
	6.7% College Graduate
Drinks/week* (n=13)	22 (13-50)
Tobacco use (yes)	27%
Drugs Used Recreationally	
Cocaine	20%
Benzodiazepines	33%
Marijuana	100%
Opiates	33%
Stimulants	20%
Hallucinogens	40%
Inhalants	33%

3.1.2.2 Participant disposition

In the applicant's report, thirty-nine volunteers were interviewed, yielding a total of 21 eligible candidates, two of whom withdrew consent prior to the first session. Of the 19 remaining, 15 volunteers completed the study. However, this is inconsistent with the information for incompletes and ineligible volunteers from Appendix 2 in the applicant's report, in which 5 eligible candidates did not complete the study. Table 2 gives the information about eligible volunteer disposition.

Table 2. Eligible Volunteer Disposition

Participant Code	Sex	Reason of Dropout
GAB 006	M	Quit due to new job after third drug
GAB007	M	Quit after third drug session. Subject contracted bacterial infection
GAB030	M	Left NRU unit AMA during first drug session
GAB032	F	Never made it to practice session
GAB034	M	Did not return phone calls. Never started practice session

3.1.3 Statistical methodologies

3.1.3.1 Statistical analyses (protocol-Defined)

Data from each of the scales of the POMS, VAS, and ARCI and the physiological measures were evaluated with repeated measures analysis of variance (ANOVA). The basic unit of analysis was the individuals' scores for each drug condition at each time point. ANOVAs with two within-subjects factors (drug condition[1], time) were used to evaluate changes, Huynh-Feldt corrected significance levels were used for repeated measures factors in which the assumption of sphericity was violated. On other measures (drug liking on the EOSQ, crossover points on MCP) ANOVAs with one within-subjects factor (drug condition[1] or session number[2]) were used to evaluate changes. When significant main drug effects were found, previously determined contrasts were evaluated. When a significant between drug and hour interaction was found these same contrasts were evaluated separately for each time point. Effects were considered significant if p-value of the test is less than or equal to 0.05. Exploratory analyses were performed for some key factors for p-value < 0.10.

The analyses specified above assume that the session during which drug treatment occurred had no impact on the results. ANOVAs with session number rather than drug were conducted to verify this assumption and showed statistically significantly interpretable results for session[2].

3.1.3.2 Statistical analyses by the reviewer

3.1.3.2.1 Study model

A mixed linear model with period, sequence, treatment and first-order carryover as fixed effects and subject nested with sequence as a random effect was used in the analyses. If the first-order carryover effect was not statistically significant, this fixed effect would be dropped from the model. If the responses as modeled did not appear to be normally distributed, then ranks of responses within subjects were used in the statistical analysis. Response "End of Session Drug Identification" was analyzed by descriptive statistics.

3.1.3.2.2 Evaluation Procedure

In order to claim there is no potential for abuse liability of pregabalin, for each primary variable the applicant needs to show that

- diazepam has statistically larger mean response than placebo (to insure the validation of the positive control of diazepam)
- pregabalin has statistically lower mean response than double the mean response of placebo
- pregabalin has statistically lower mean response than diazepam

The given significance level of each test is 5%.

1 In this reviewer's definition Drug condition is defined as Treatment.
2 In this reviewer's definition Session number is defined as Period.

More specifically, for each primary variable, tests of the following hypotheses were performed by the reviewer:

- the mean response of 15 mg diazepam is larger than that of placebo
- the mean response of 30 mg diazepam is larger than that of placebo
- double the mean response of placebo is larger than the mean response of 200 mg pregabalin
- double the mean response of placebo is larger than the mean response of 450 mg pregabalin
- the mean response of 15 mg diazepam is larger than that of 200 mg pregabalin
- the mean response of 30 mg diazepam is larger than that of 200 mg pregabalin
- the mean response of 15 mg diazepam is larger than that of 450 mg pregabalin
- the mean response of 30 mg diazepam is larger than that of 450 mg pregabalin

If both doses of diazepam fail to show greater mean response of an endpoint than placebo, the study results for this endpoint are considered invalid. If one of the doses of diazepam has significantly greater mean response than placebo, only results from the comparison between pregabalin and this dose level of diazepam are valid.

3.1.4 Results and conclusions

3.1.4.1 Applicant's results and conclusions from Study 098

After more than 8 pages of detailed explanation of the results obtained from the applicant's analyses for lots of protocol defined primary variables with 6 pages of tables and 14 graphics, the applicant summarized the results as follows:

In summary, diazepam decreased in a dose-dependent manner Arousal (POMS), BG (ARCI) and Alert (VAS) and increased Confusion (POMS), fatigue (POMS), PCAG (ARCI), good drug Effect (VAS), Sedated (VAS) and Tired (VAS) with peak effects between 1 and 3 hrs depending on the scale. Its identification as a sedative increased with dose. For 200 mg pregabalin the effects were similar with peak effects occurring at the same time as diazepam (Sedated and Tired) or 1 to 2 hours later (Arousal, Confusion, Fatigue, Good drug Effect, High, and PCAG). However on Alert, Arousal, BG, Confusion, Fatigue, PCAG, Sedated and Tired scales, 200 mg pregabalin had significantly greater effects than 450 mg pregabalin. This was especially pronounced for the Fatigue and Tired where 450 mg pregabalin had no significant effects compared to placebo. On the other hand, the high dose of pregabalin produced significantly greater effects compared to the low dose on the Good Drug Effect and High with scores similar to those for 30 mg diazepam. While the low dose was identified as a sedative by most individuals, the high dose of pregabalin was largely identified as a stimulant or placebo.

The applicant reported that the Multiple Choice Procedure yielded no significant drug effects. Individuals tended to always choose drug when the alternative was the loss of money but they chose money even at the lowest level. Although the cross-over value was lower for placebo ($0.10) than the drug conditions[1] (all averaged around $1) these differences were not significant.

In addition, the applicant reported that

The low dose of pregabalin had a profile of effects similar to the lower dose of diazepam. These data are not consistent with drug discrimination studies that have been done with pregabalin in comparison to another benzodiazepine, midazolam. The high dose of pregabalin had an entirely different profile of effects. In general, sedative-like effects were less than the 200 mg dose and there were indications of stimulant-like effects. Nevertheless on measures that are clearly related to drug-taking behavior, such as Good Drug Effect, the high dose of pregabablin produced effects comparable to 30 mg diazepam. The subjective effects of pregabalin were generally delayed relative to those of diazepam.

Based on the results, the applicant concluded that

- The profile of subjective effects of diazepam in recreational sedative/alcohol using participants was consistent with prior findings for diazepam and related anxiolytics. Thus, diazepam served as an acceptable positive control for evaluating the subjective effects of pregabalin.

- The 200 mg dose of pregabalin produced statistically significant effects compared to placebo on several subjective effects measures, and showed trends toward significance on several others. Arousal (POMS) was decreased, whereas Confusion (POMS), Fatigue (POMS), Good drug Effect (VAS), High (VAS), Sedated (VAS), and Tired (VAS) were increased. The profile was similar to the profile for the 15 mg dose of diazepam in that the majority of participants identified it as sedative.

- The 450 mg dose of pregabalin produced statistically significant effects compared to placebo on several subjective effects measures, and showed trends toward significance on several others. Except for Sedated (VAS), there were no sedative-like effects. Confusion (POMS), Good Drug Effect (VAS), Good Drug Effect (VAS), and High (VAS) were also increased. This dose differed from 30 mg diazepam on many scales, indicating more stimulant-like effects. Relative to diazepam, 450 pregabalin increases Arousal (POMS), BG (ARCI), and Alert (VAS). The profile of 450 mg pregabalin was similar to 30 mg diazepam in some respects (eg, Good Drug Effects) but there were substantial differences on many measures of sedation. Unlike 30 mg diazepam, pregabalin 450 mg was not consistently identified as a sedative. Thus, there are similarities and differences between 450 mg pregabalin and 30 mg diazepam.

- The time to reach peak subjective effects was generally shorter for diazepam than for pregabalin.

- Pregabalin was not different from placebo on physiologic measures. The high dose of diazepam produced increases in heart rate, most likely because participants were started awake from a sleep state.

- The multiple choice procedure showed no difference between diazepam and placebo. Thus, this study is limited in its ability to evaluate any potentially reinforcing value of pregabalin.

3.1.4.2 The reviewer's results and conclusions from Study 098

3.1.4.2.1 Results from primary analyses and conclusions

The first-order carryover effects were not statistically significant for all primary variables. Therefore, this term was dropped from the study model. The final model used by this reviewer was

response = period sequence treatment
random subject (sequence),

which was regardless of the significance of each of fixed effects in the model. There were 15 subjects, 5 periods, 5 sequences and 5 treatment arms in this study.

The residual analyses showed that model assumptions are satisfied for all primary endpoints.

From the SAS outputs attached in the Appendix I it can be seen that the overall treatment effects of the primary variables, End of Session Drug Liking and VAS-High, are statistically significant at 5%, and VAS-Good Drug Effect and Drug liking are not statistically significant with p-values of 0.0741 and 0.0735 respectively. For all primary variables, there is insufficient evidence to indicate that pregabalin has statistically lower mean response than diazepam. In most cases the observed mean response of pregabalin is greater than that of diazepam, and from those tests 63% of the p-values exceed 0.5 and 31% of them exceed 0.7. For all primary variables, there is insufficient evidence to indicate that pregabalin has a lower mean response than double the mean response of placebo. The range of p-values for those tests is from 0.2633 to 0.9399. In fact, there is strong evidence to indicate that mean response of pregabalin is greater than that of placebo for all primary variables (see those tests with *). Since diazepam has a statistically significant difference in mean response from placebo at 5% level, the study results are valid.

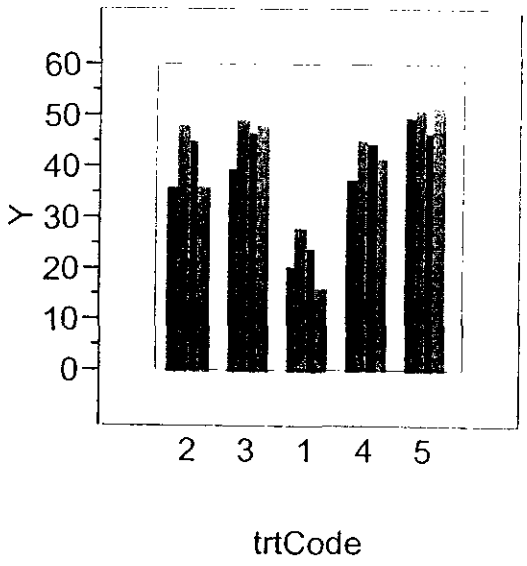
Figure 1 gives the overall view of the mean treatment effect of primary variables. Table 3 lists the mean and standard error of treatment effect of primary variables.

Table 3. Mean and Standard Error of treatment effect of the Primary Endpoints (Emax)

	Liking-ES		Drug Liking		Good Drug Effect		High	
Treatment	mean	std err	mean	std err	mean	std err	mean	std err
Placebo	20.73	5.37	29.13	7.45	28.07	7.54	16.87	7.86
15 mg DZP	36.20	9.93	48.40	8.62	45.67	7.48	36.80	7.68
30 mg DZP	39.87	6.48	53.13	7.56	51.13	6.76	48.53	8.38
200 mg PGB	37.73	8.31	48.87	9.05	47.67	8.69	42.27	8.86

450 mg PGB	49.53	8.37	52.33	9.71	49.93	8.61	52.07	9.63

Figure 1. Comparison of Treatment Effects



Mean (End of Session Drug Liking)
Mean (Emax of Drug Liking)
Mean (Emax of Good Drug Effect)
Mean (Emax of High)

1. Placebo
2. 15 mg diazepam
3. 30 mg diazepam
4. 200 mg diazepam
5. 450 mg diazepam

Note: The endpoints are based on Emax calculated from predrug baseline.

The SAS output for the primary variables are listed in Appendix I.

Conclusion

Based on the reviewer's statistical analyses, for all primary variables pregabalin has larger mean response than placebo. The analyses failed to demonstrate that pregabalin has less than 2 times the mean response of placebo. In addition, pregabalin does not have a statistically significant lower mean response than diazepam. Analyses of the study data failed to show that pregabalin has no potential for abuse liability in Study 098.

3.1.4.2.2 Results from secondary analyses and conclusions

Table 4 lists p-values of t tests for the first six secondary variables. The first column of Table 4 shows the direction of the inequality sign in the alternative hypothesis for each test. The

highlighted p-values are invalid for assessing potential for drug abuse due to failure to establish the drug abuse potential of the positive control in the study.

From Table 4 it can be seen that

(1) Due to the lack of significance of the tests for comparing both dose levels of diazepam with placebo for variables Stimulated and BG, this study on those variables does not show the absence of potential for drug abuse. However, for the variable Stimulated, Figure 2 shows that observed mean responses for both 200 mg and 450 mg pregabalin are much greater than those of 15 mg and 30 mg diazepam. In addition, 27% (4/15) of the subjects identified 200 mg pregabalin as a stimulant drug and 40% (6/15) of the subjects identified 450 mg pregabalin as a stimulant drug versus 7% in placebo and 7% and 13% in treatments 15 mg diazepam and 30 mg diazepam respectively in the end of session drug identification (See Table 5 - the applicant's report Table 8 on page 191 of 564). In this reviewer's opinion, pregabalin is more of a stimulant drug than diazepam. In fact, the test for greater mean response of 450 mg pregabalin than that of placebo is statistically significant with a p-value of 0.035.

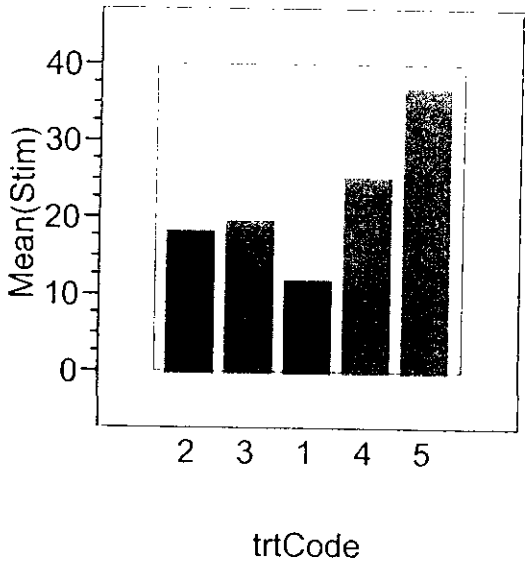
Table 4. Pairwise Comparisons of Treatments: p-values of t Tests with *df*=52 for Secondary Variables

	VAS		ARCI			
Alternative Hypothesis	Stimulated	Sedated	MBG	PCAG	LSD	BG
Placebo < 15 mg DZP	0.328	0.026	[illegible]	[illegible]	[illegible]	[illegible]
Placebo < 30 mg DZP	0.428	0.002	0.023	0.002	0.012	[illegible]
2Placebo > 200 mg PGB	0.004	0.742	0.006	0.235	0.822	0.005
2Placebo > 450 mg PGB	0.016	0.767	0.010	0.355	0.959	0.094
15 mg DZP > 200 mg PGB	0.679	0.636	[illegible]	[illegible]	[illegible]	[illegible]
15 mg DZP > 450 mg PGB	0.918	0.683	[illegible]	[illegible]	[illegible]	[illegible]
30 mg DZP > 200 mg PGB	0.767	0.231	0.235	0.015	0.513	[illegible]
30 mg DZP > 450 mg PGB	0.95	0.272	0.352	0.050	0.918	[illegible]

Table 5. Drug Identification (% of Participants)

Drug\Drug Identified	Placebo	Sedative	Stimulant
Placebo	73	20	7
15 mg diazepam	40	53	7
30 mg diazepam	0	87	13
200 mg pregabalin	0	73	27
450 mg pregabalin	20	40	40

Figure 2. VAS – Stimulated



trtCode 2 3 1 4 5

1. Placebo
2. 15 mg diazepam
3. 30 mg diazepam
4. 200 mg pregabalin
5. 450 mg pregabalin

(2) The statistical analysis for variable Sedated is valid. The study results do not support the applicant's claim of absence of potential abuse of pregabalin.

(3) For variable LSD, the valid positive control is 30 mg diazepam. Since both 200 mg and 450 mg pregabalin fail to show their mean responses are statistically significantly lower than that of 30 mg diazepam and double the placebo mean, the result for this variable does not support the claim of no potential for drug abuse of pregabalin.

(4) For variable PCAG, the valid positive control is 30 mg diazepam. Since both 200 mg and 450 mg pregabalin show that the mean response is not statistically significantly lower than double the placebo mean, the result for PCAG also does not support the claim of no potential for drug abuse of pregabalin.

(5) For variable MBG, the valid positive control is 30 mg diazepam. Although both 200 mg and 450 mg pregabalin show statistically significantly lower mean response than double the placebo mean, they fail to show statistically significant results when compared with 30 mg diazepam. Thus, the result for MBG still does not support the claim of no potential for drug abuse of pregabalin.

From Table 5 it can be seen that 40% of study subjects identified 15 mg diazepam as placebo. This explains why 15 mg diazepam failed significance tests for comparing with placebo in five out of 6 secondary variables (see Table 1). Three study subjects wrongly identified 450 mg pregabalin as placebo. Two of them took 200 mg pregabalin in the previous session. They identified 200 mg pregabalin as either a sedative drug or a stimulant drug. Although the inconsistent results from 20% of subjects may decrease the treatment effect of 450 mg pregabalin, 450 mg pregabalin still show there is not much difference or even higher mean response from scheduled 30 mg diazepam in all primary endpoints and most of secondary variables.

For reference the bar charts of treatment effects for individual variables, Sedated, MBG, PCAG, LSD and BG, are given in Appendix II. For the variables in ARCI scale, the range of the y-axis in the plot is based on the range of the variable, so that one can have a clear view about how the Emaxs of the treatments are related to the maximum possible value of the endpoint.

Conclusion

The results from the secondary analysis support this reviewer's findings from the primary analysis that the data failed to show that pregabalin has no potential for abuse liability in Study 098.

4. DISCUSSIONS AND CONCLUSIONS

4.1 Discussions

The statistical issues often seen in drug abuse potential studies were study design, mixed carryover effects due to insufficient washout period, selection of a proper study model and sample size determination. Comparing with such studies that the reviewer has seen before, study 098 was done relatively well. It was carefully designed so that there was no statistically significant carryover effect in the study, which made statistical analyses much easier. However, the study design could have been improved by using Williams' squares. The sample size of 15 used in the study is too small to detect the mean difference between two treatments with a reasonably large power.

The main differences between the applicant's statistical analyses and the reviewer's statistical analyses are the study model and primary endpoints. Since the applicant wanted to detect the time to reach peak subjective effects, thus, time was considered as a factor in the applicant's model and the protocol defined primary variables were based on hourly changes from predrug except the drug liking using the End of session questionnaire and End of Session Drug Identification. However, the CSS believe that the peak response of a treatment from predrug baseline is a more proper measure for evaluation of potential for drug abuse than the hourly changes in response of a treatment. Therefore, the primary variables and secondary variables are defined as Emax of the response from predrug baseline in the reviewer's analysis. Because the study had a crossover design, the reviewer considered period and sequence as fixed effects and subject nested with sequence as a random effect in the model.

Although the definition of the primary variables and the model used in the reviewer's analyses are different than those of the applicant's analyses, based on conclusions made by the applicant from its own statistical analyses, and using the evaluation criteria for assessing the potential of abuse liability of a drug by the agency (see page 11, section 3.3.3.2.2), the applicant would also fail to show the absence of the potential for abuse liability of pregabalin in study 098.

4.2 Conclusions

For all primary variables and most of secondary variables, diazepam served as an acceptable positive control for evaluating the subjective effects of pregabalin. The study results, for all primary variables and secondary variables, failed to demonstrate the absence of potential for drug abuse for pregabalin. Analyses of the data from study 098 do not support the sponsor's claim that pregabalin should not be a scheduled drug.

Appendix I: SAS Output for the Primary Analyses

End of Session Drug Liking

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
PERIOD	4	52	0.68	0.6063
SEQUENCE	4	10	0.71	0.6012
TRTCODE	4	52	2.64	0.0438

Label	Estimate	Standard Error	DF	t Value	p-value
placebo vs 15mg diazepam	-16.7723	9.4036	52	-1.78	0.0402
placebo vs 30mg diazepam	-20.0863	9.4036	52	-2.14	0.0187
2*placebo vs 200mg pregabalin	2.5692	15.6356	52	0.16	0.4351
2*placebo vs 450mg pregabalin	-9.1363	15.6356	52	-0.58	0.7193
placebo vs 200mg pregabalin	-18.3105	9.4248	52	-1.94	0.0288*
placebo vs 450mg pregabalin	-30.0159	9.4248	52	-3.18	0.0012*
15mg diazepam vs 200mg pregabalin	-1.5382	9.4036	52	-0.16	0.5647
15mg diazepam vs 450mg pregabalin	-13.2436	9.4248	52	-1.41	0.9171
30mg diazepam vs 200mg pregabalin	1.7758	9.4248	52	0.19	0.4257
30mg diazepam vs 450mg pregabalin	-9.9296	9.4036	52	-1.06	0.8527

VAS: Drug Liking

Effect	Num DF	Den DF	F Value	Pr > F
PERIOD	4	52	0.92	0.4615
SEQUENCE	4	10	0.74	0.5856
TRTCODE	4	52	2.28	0.0735

Label	Estimate	Standard Error	DF	t Value	p-value
placebo vs 15mg diazepam	-19.8778	8.9689	52	-2.22	0.0155
placebo vs 30mg diazepam	-21.1858	8.9689	52	-2.36	0.0110
2*placebo vs 200mg pregabalin	9.6625	15.1556	52	0.64	0.2633
2*placebo vs 450mg pregabalin	2.2844	15.1556	52	0.15	0.4404
placebo vs 200mg pregabalin	-16.9375	8.9891	52	-1.88	0.0326*
placebo vs 450mg pregabalin	-24.3156	8.9891	52	-2.71	0.0046*
15mg diazepam vs 200mg pregabalin	2.9403	8.9689	52	0.33	0.3722
15mg diazepam vs 450mg pregabalin	-4.4378	8.9891	52	-0.49	0.6882
30mg diazepam vs 200mg pregabalin	4.2483	8.9891	52	0.47	0.3193
30mg diazepam vs 450mg pregabalin	-3.1298	8.9689	52	-0.35	0.6368

VAS: Good Drug Effect

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
PERIOD	4	52	0.81	0.5226
SEQUENCE	4	10	0.61	0.6658
TRTCODE	4	52	2.27	0.0741

Label	Estimate	Standard Error	DF	t Value	p-value
placebo vs 15mg diazepam	-21.3869	9.4395	52	-2.27	0.0139
placebo vs 30mg diazepam	-22.7748	9.4395	52	-2.41	0.0097
2*placebo vs 200mg pregabalin	0.5798	16.1731	52	0.04	0.4858
2*placebo vs 450mg pregabalin	-2.5206	16.1731	52	-0.16	0.5616
placebo vs 200mg pregabalin	-21.0603	9.4608	52	-2.23	0.0152*
placebo vs 450mg pregabalin	-24.1607	9.4608	52	-2.55	0.0068*
15mg diazepam vs 200mg pregabalin	0.3266	9.4395	52	0.03	0.4863
15mg diazepam vs 450mg pregabalin	-2.7738	9.4608	52	-0.29	0.6148

30mg diazepam vs 200mg pregabalin	1.7145	9.4608	52	0.18	0.4286
30mg diazepam vs 450mg pregabalin	-1.3859	9.4395	52	-0.15	0.5581

VAS: High

Type 3 Tests of Fixed Effects

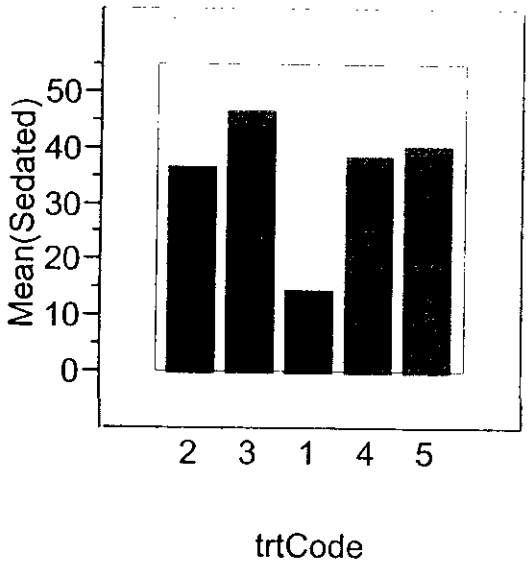
Effect	Num DF	Den DF	F Value	Pr > F
PERIOD	4	52	1.44	0.2351
SEQUENCE	4	10	3.87	0.0376
TRTCODE	4	52	4.76	0.0024

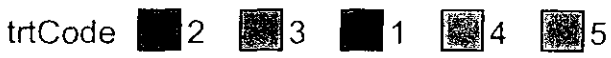
Label	Estimate	Standard Error	DF	t Value	p-value
placebo vs 15mg diazepam	-19.7088	9.2439	52	-2.13	0.0189
placebo vs 30mg diazepam	-31.4361	9.2439	52	-3.40	0.0007
2*placebo vs 200mg pregabalin	-13.3589	15.0715	52	-0.89	0.8103
2*placebo vs 450mg pregabalin	23.8106	15.0715	52	-1.58	0.9399
placebo vs 200mg pregabalin	26.5069	9.2647	52	-2.86	0.0031*
placebo vs 450mg pregabalin	-36.9585	9.2647	52	-3.99	0.0001*
15mg diazepam vs 200mg pregabalin	-6.7980	9.2439	52	-0.74	0.7673
15mg diazepam vs 450mg pregabalin	-17.2497	9.2647	52	-1.86	0.9659
30mg diazepam vs 200mg pregabalin	4.9292	9.2647	52	0.53	0.2985
30mg diazepam vs 450mg pregabalin	-5.5225	9.2439	52	-0.60	0.7236

Appendix II: Figures for the Secondary Analyses

Note: Each endpoint is based on Emax calculated from predrug baseline

Figure 3. VAS - Sedated





1. Placebo

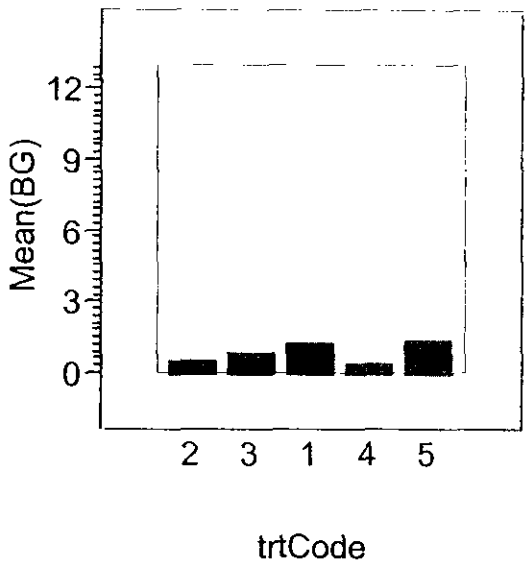
2. 15 mg diazepam

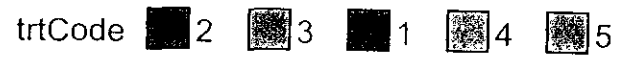
3. 30 mg diazepam

4. 200 mg pregabalin

5. 450 mg pregabalin

Figure 4. ARCI: BG





1. Placebo

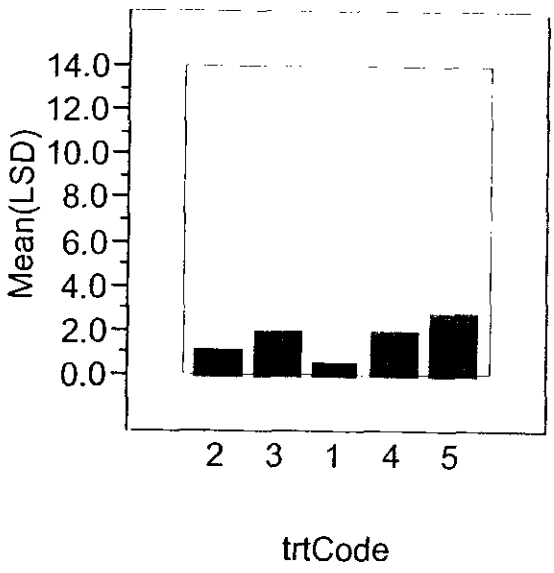
2. 15 mg diazepam

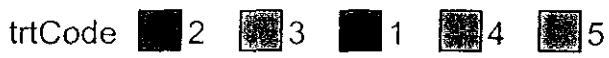
3. 30 mg diazepam

4. 200 mg pregabalin

5. 450 mg pregabalin

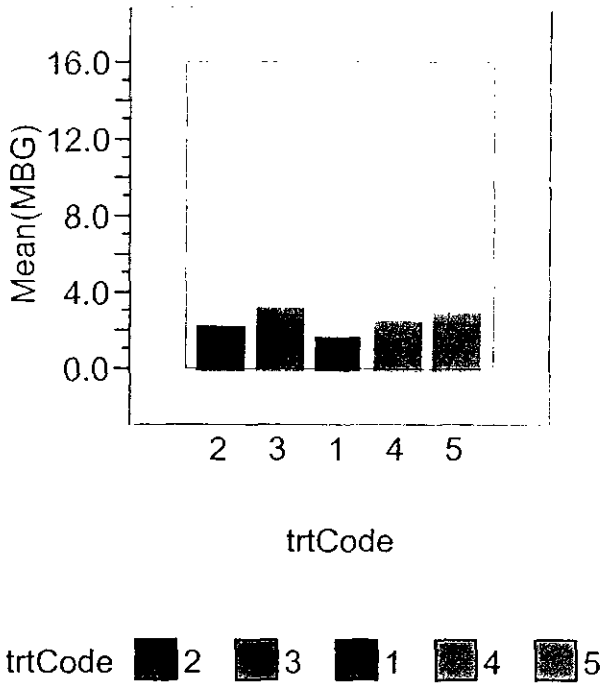
Figure 5. ARCI: LSD





1. Placebo
2. 15 mg diazepam
3. 30 mg diazepam
4. 200 mg pregabalin
5. 450 mg pregabalin

Figure 6. ARCI: MBG



1. Placebo

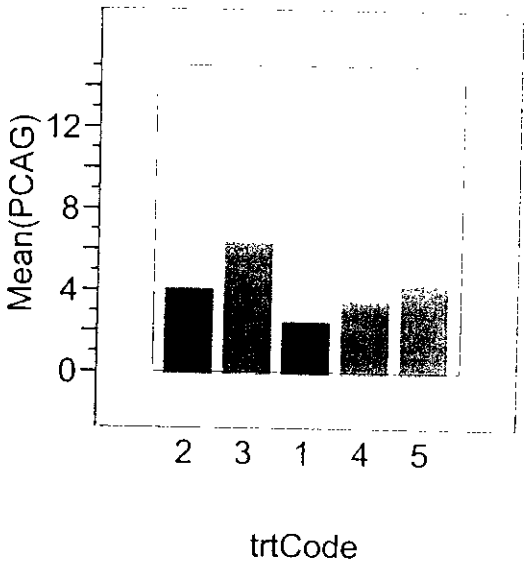
2. 15 mg diazepam

3. 30 mg diazepam

4. 200 mg pregabalin

5. 450 mg pregabalin

Figure 7. ARCI: PCAG



1. Placebo
2. 15 mg diazepam
3. 30 mg diazepam
4. 200 mg pregabalin
5. 450 mg pregabalin

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/s/

Ling Chen
10/13/04 02:44:35 PM
BIOMETRICS
Statistical review for drug abuse potential study 098
Please sign it. Thanks.

Yi Tsong
10/21/04 06:11:34 PM
BIOMETRICS

Please sign it off

Stella Machado
10/28/04 11:44:11 AM
BIOMETRICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-446
Name of drug:	Lyrica (pregabalin) capsules
Indication:	diabetic peripheral neuropathy
Applicant:	Pfizer
Dates:	Letter 10/30/2003; user fee (6 months) 4/30/2004
Review priority:	P
Biometrics division:	Division of Biometrics II
Statistical reviewer:	Thomas Permutt
Concurring reviewers:	S. Edward Nevius, Ph.D.
Medical division:	Anesthetic, Critical Care and Addiction (HFD-170)
Clinical team:	Mwango Kashoki, M.D.; Celia Winchell, M.D. (team leader)
Project manager:	Lisa Malandro

Keywords: NDA review, clinical studies, adverse events, survival analysis

The primary statistical review of this application is being conducted by Ling Chen, Ph.D. My review is meant to address a specific question about safety raised by Dr. Kashoki.

In animal testing pregabalin was associated with skin lesions that are not well understood. Dr. Kashoki examined the clinical data base for adverse events that might be related to these findings in animals. This examination was mainly confined to studies in diabetic neuropathy which is the subject of this application. (Other indications for pregabalin are covered in other, concurrent applications.) There is no reason to suppose that the toxic mechanism, whatever it might be, specially affects diabetics. However, the toxic effect might be both more harmful to and more easily detectible in diabetics because of their liability to abnormal healing of such lesions.

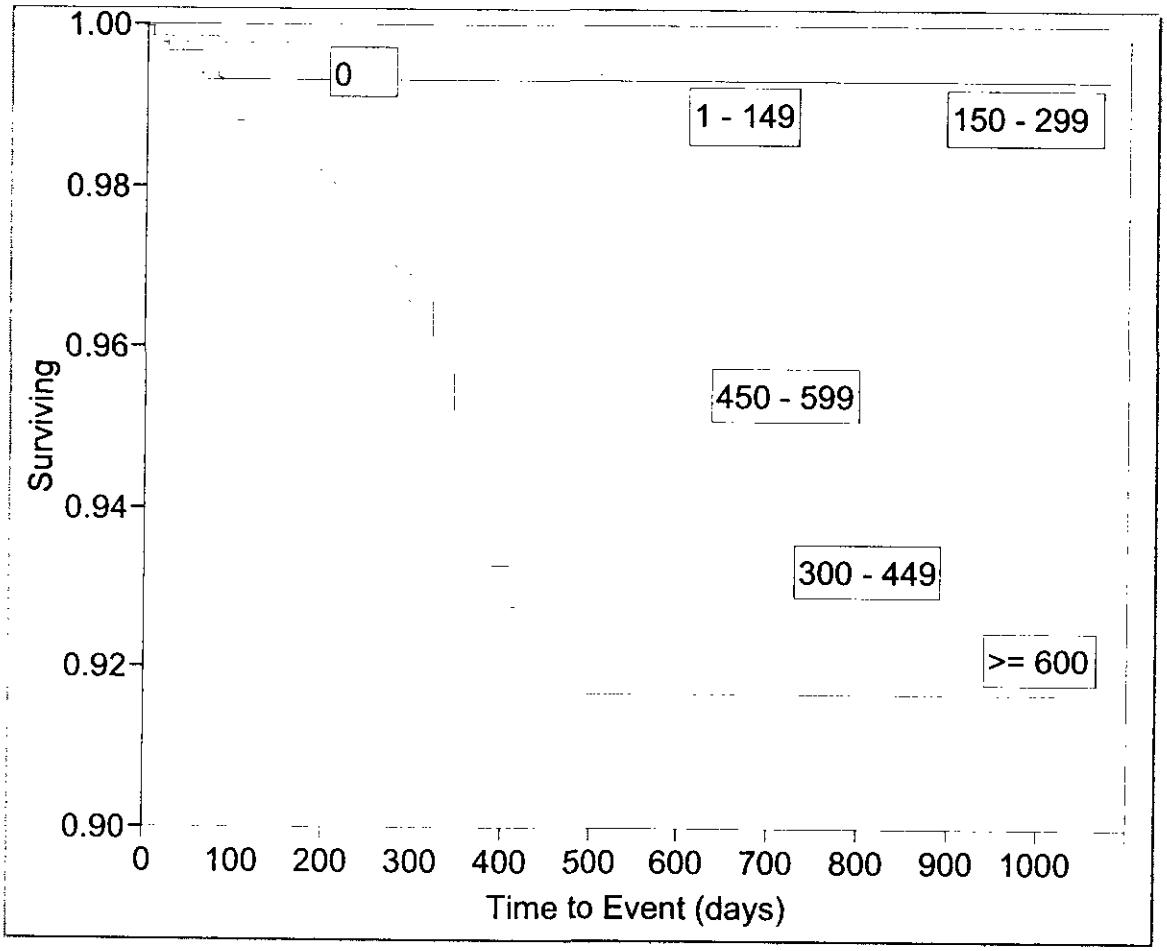
Dr. Kashoki identified 59 reports of skin ulcers in 45 diabetic patients in six studies (014, 029, 040, 131, 149, 173 as identified by the first three digits of the ISS patient identifier). She correlated these reports with the dose that the patients were taking when the ulcer came on, and she counted the number of other patients who took the same dose at some time. She noticed that the proportion of patients who had an ulcer was higher at higher doses (table). There are 49 cases of skin ulcers in this analysis. Four patients who reported ulcers at two doses are counted once with each dose. The other 10 duplicate reports were at the same doses, and each patient was counted only once at each dose.

dose	patients with ulcers	patients exposed
0	2 (0.3%)	709
<150	1 (0.1%)	1569
150–299	4 (0.2%)	1646
300–449	16 (0.7%)	2179
450–599	5 (0.7%)	722
≥ 600	21 (3.9%)	727

The studies involved escalating doses. Patients might be on a low dose for a short time on the way to a higher dose which they used for a longer time. If the exposure at higher doses were for longer times, then a bigger incidence per patient might not correspond to a bigger incidence per patient-day. What appears to be a dose effect might instead be an effect of longer exposure to higher doses. The total of exposure times at each dose is shown in the table below. In fact, the dose groups with more ulcers also had more exposure, approximately in proportion.

dose	patients exposed	total days exposed
0	709	26630
<150	1569	14080
150–299	1646	70479
300–449	2179	196262
450–599	722	57079
≥ 600	727	181940

The figure is a Kaplan-Meier plot of "survival" (free of skin ulcers) in the six studies, grouped by doses. The actual time of onset of adverse events was not readily available. What was available was the duration of exposure at the dose at which onset was reported. I adopted a very crude version of the midpoint convention, assigning the time to event as half the duration. Patients without an event were censored as of the duration of exposure.



The figure is a little misleading in that the right-hand tails of each curve are so prominent. In fact, the flat part of each curve is based on relatively little data and subject to great uncertainty. The events are in the steep parts of the curves. They appear to occur at quite similar rates for the various dose groups, and no dose effect is apparent.

As usual, the clinical database is too small confidently to rule out association between drug exposure and any but fairly common adverse events. The survival analysis cannot be said to exclude the possibility of a real, important effect. Neither can the analysis ignoring exposure times be said to show such an effect, however. The apparent effect in that analysis is an artifact of the study design.

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/s/

Thomas Permutt
4/28/04 09:36:53 AM
BIOMETRICS

S. Edward Nevius
4/29/04 04:04:14 PM
BIOMETRICS
Concur with review.

4-29-04

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-446
Drug Name:	Lyrica (pregabalin) capsules
Indication(s):	diabetic peripheral neuropathy
Applicant:	Pfizer
Date(s):	Letter 10/30/2003; user fee (6 months) 4/30/2004
Review Priority:	P
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Ling Chen, Ph.D. Mathematical Statistician
Concurring Reviewers:	J. Thomas Permutt, Ph.D. (team leader)
	S. Edward Nevius, Ph.D. (Director)
Medical Division:	Anesthetic, Critical Care and Addiction (HFD-170)
Clinical Team:	Mwango Kashoki, M.D.
	Celia Winchell, M.D. (team leader)
Project Manager:	Lisa Malandro

Keywords: Baseline control, Clinical studies, Drop-outs, Endpoint analysis/LOCF, NDA review, Nonparametric/dist. free tests.

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The efficacy of pregabalin TID 300 mg/d and 600 mg/d was demonstrated in Study 014, 029 and 131 using a baseline observation carried forward (BOCF) method of dealing with missing data due to dropouts, but only supported by one of two studies for either 300 mg/d dose or 600 mg/d dose in the study of percentage change from baseline if both baseline observation carried forward and maximum baseline pain score imputation for the use of rescue medication (BOCF & MBIR) methods were employed in calculating the primary endpoint.

Durations of the studies were 6 weeks, 5 weeks and 8 weeks for Studies 014, 029 and 131 respectively, which is less than 12 weeks suggested by the FDA. In fact, excluding titration period, Studies 014 and 029 were on the fixed study doses only for 4 weeks. One of two 12-week studies, Study 073, was terminated early due to a partial clinical hold placed by the FDA, in which the majority of patients only finished at most 3 weeks of the study. The other 12-week study, Study 149, failed using BOCF for the primary endpoint as reported by the applicant. In my responder analysis of Study 149, one can see that the failure of the efficacy study for Study 149 is attributable to the increase of the proportion of responders in the placebo group comparing the results from the other studies with shorter duration. A 6-week analysis was conducted for Study 149. The BID dose of 600mg/d based on creatinine clearance would have met the primary criterion of efficacy if the duration of the study had been 6 weeks instead of 12 weeks.

The averages of the responder rates of pregabalin 300 mg/d dose group in Studies 029 and 131 with BOCF and 600 mg/d dose group in Studies 014 and 029 with BOCF are 31% and 33% respectively. Corresponding averages of the responder rates of placebo group are 14% and 15% in comparing with 300 mg/d dose group and 600 mg/d dose group respectively. The responder rates from pregabalin groups are doubled comparing with the placebo group. The test for the difference in responder rates between pregabalin and placebo is very highly significant for both doses 300 mg/d and 600 mg/d with a p-value <0.0001.

Concurrent medications for pain were prohibited in the studies, with exception of up to 3 grams per day acetaminophen for Studies 014 and 029, and up to 325 mg/d aspirin and 4 g/d acetaminophen for Study 131. I took into the consideration both allowable rescue medication and prohibited medication for pain in the calculation of the primary endpoint by using MBIR. Comparing the results from BOCF with those from BOCF & MBIR, the responder rate would decrease by 6-9 % in pregabalin groups if the use of allowable or prohibited medication was taken into account in the study.

Approximately 61% of the patients in the placebo group experienced adverse events compared to 77% and 86% in pregabalin 300 mg/d dose group and the pregabalin 600 mg/d dose group respectively. The difference in AE rates between placebo group and pregabalin dose groups is also very highly statistically significant (p-value=0.0002 and

$\approx$ 0 for 300 mg/d dose and 600 mg/d dose respectively). It is evident that the AE rate increases when the dose level increases.

Overall, statistically the data support the applicant's claim that pregabalin is efficacious in pain relief in neuropathic pain associated with diabetic peripheral neuropathy, although the percentage of the patients who benefit from the pregabalin treatment is not very large. Approximately 6% more patients in pregabalin groups received at least 80% pain reduction compared with placebo group. Analyses of secondary variables, which are mostly alternate ways of measuring pain and pain reduction at the conclusion of the trials, also support the primary findings. However, the responder rates reported on labeling are not reliable since these results are from LOCF.

There is not enough evidence to support the efficacy and safety for the long term use of pregabalin due to the duration of the studies. Based on the medical officer's report, skin ulcers and visual abnormalities in a dose dependent manner were observed from pregabalin treatment groups. However, there is no statistical evidence to support that the relationship exits between dose and skin ulcers. The statistical analysis regarding this issue can be found in Dr. Thomas Permutt's report. I would like to suggest setting up a clinical margin for the efficacy testing in future studies for similar drug indications, which may help risk-benefit evaluations.

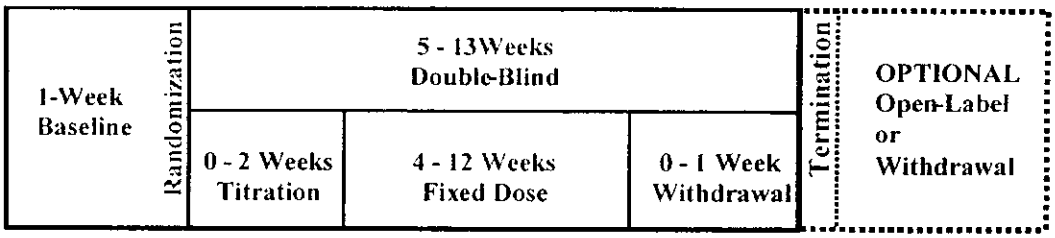
1.2 Brief Overview of Clinical Studies – Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

Pregabalin capsules are proposed by the applicant for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN). A total of six double-blind, placebo-controlled, multicenter studies of pregabalin were conducted in the United States (US), Europe, Australia, South Africa, and Canada. Based on the applicant's report DPN Studies 014, 029, 131 and 149 demonstrated statistically significantly greater improvement in pain relief with pregabalin treatment. In study 040, statistically significantly greater improvement was not achieved. US study 173 was terminated early due to a partial clinical hold placed by the FDA. A summary of the six studies is in Table 1 (see page 10).

1.2.1 Study Design

An overall study design is shown in applicant's Figure 1 on page 16 of 4749.

Figure 1. Overall Study Design for 11 Neuropathic Pain Studies



For all but Study 040, studies comprised two phases: Baseline Phase and Double-Blind Phase. Patients who completed or withdrew from the double-blind phase could elect to continue in open-label follow-on studies or discontinue treatment.

In Studies 029, 040, and 131, each pregabalin treatment group corresponded to a single pregabalin dose. In Studies 149 and 173, patients randomized to the 300/600 mg/d arm received a dose of 300 mg/d if their estimated creatinine clearance (CLcr) was 30 to 50 mL/min, or a dose of 600 mg/d if their CLcr was > 60 mL/min. Study 040 had an additional amitriptyline 75 mg/d treatment arm. Since the applicant does not claim pregabalin is better than amitriptyline, I will not discuss the comparison of amitriptyline with placebo in detail in this review.

1.2.2 Patient Population

Eligible patients were males or nonpreganant, nonlactating females of any race ≥18 years of age. To be randomized a patient must have completed at least 4 diary entries during baseline; have had a mean pain score≥ 4 over the 7-day baseline phase; and rated their pain at both screening and randomization as at least 40 mm on the 0 to 100 mm visual analog pain scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ).

In most studies, patients who had not responded to previous treatment with Neurontin ≥1200 mg/d were excluded. The protocol for Study 149 was amended to remove this exclusion criterion. In all 6 studies, patients were required to have pain present for at least one year. Additionally, in Studies 040, 029 and 131, pain was to have been present for no more than 5 years. Additional entry criteria for the DPN studies included screening hemoglobin A_{1c} levels ≤11%, and CLcr ≥60 mL/min (except for Studies 149 and 173, where the criterion was ≥30 mL/min). The patients in the DPN studies were required to discontinue all analgesic medications prior to baseline.

1.2.3 Efficacy Parameters

The primary criterion to establish efficacy in neuropathic pain studies was the endpoint mean pain score, derived from a daily pain diary recorded by the patient using an

11- point numerical rating. Upon awakening, the patient evaluated his/her pain for the previous 24 hours by circling the number on the scale that best described his/her pain.

The primary efficacy analysis included ITT patients who had at least one post-baseline pain score. In the applicant's report, the endpoints mean pain score is defined as follows:

Mean of the last 7 dairy entries while on study medication. Scores did not need to be recorded on consecutive days. If fewer than 7 scores were recorded by endpoint, available scores were used to determine the mean for all studies except Study 040. For Study 040, if fewer than 7 post-baseline scores (s) were available, the last 7-x scores from baseline were also used in the calculation of endpoint.

For patients who discontinued and did not complete the study, their endpoint mean score was based on the last set of pain scores that they recorded. Supplemental analyses of the primary parameter included proportion of responders (patients who had at least a 50% reduction from baseline in mean pain score at endpoint) and weekly analysis of pain scores.

1.2.4 Selection of the Review Studies

Based on the applicant's report Study 040 is a failed efficacy study at the dose level 600 mg/d. Study 173 was terminated early due to a partial clinical hold placed by the FDA, in which the majority of patients only finished at most 3 weeks study. Therefore, Studies 040 and 173 did not contribute meaningful information about efficacy.

Both 75 mg/d and 150 mg/d did not show efficacy in the studies. Considering LOCF endpoint mean pain scores, the dose 300 mg/d (TID) was supported by Studies 029 (5 week study) and 131 (8 week study) with a p-value 0.0001 for both studies; the dose 600 mg/d (TID) was supported by Studies 014 (6 week study) and 029 with p-values 0.0002 and 0.0001 respectively. These studies also showed statistical significance by using BOCF. The dose 300 mg/d or 600 mg/d (BID) based on creatinine clearance was supported by Study 149 with a p-value 0.0054 by using LOCF. This is the only study with regime BID and taking the creatinine clearance under consideration. However, the dose 300/600 mg/d in Study 149 failed by using BOCF. Therefore, the Studies 014, 029 and 131 were selected for review. Since Study 149 is the only study that considered creatinine clearance, used BID dose and had the FDA desired study duration of 12 weeks, I also did statistical analysis on Study 149. The study results will be presented in Appendix.

1.3 Statistical Issues and Findings

1.3.1 The Primary Endpoint and Study Durations

The primary endpoint is the mean of the last 7 diary entries while on study medication.

Table 3 (see page 16) summarized patient disposition for completed Studies 014, 029, 040, 131, and 149. Table 4 (see page20) lists the size of ITT population (N), the number of the complete patients (n_c), and the sample size (n) used in the study and the incomplete rate.

It can be seen from Tables 3 and 4 that although the dropout rate or incomplete rate is high, the actually used sample size in each study is close to the ITT population size. It is because the primary endpoint is defined as the mean of the last 7 dairy entries while on study medication. If a patient withdrew in the first day of the second week, the patient still could have a response to the primary variable. Since the duration of the study is a concern, the results from say, an 8 week study (Study 131) may not be reliable for interpretation of 8 week duration based on LOCF.

1.3.2 Rescue Medication and Efficacy of the Studies

Concurrent medications for pain were prohibited in DPN studies with the exception of acetaminophen which could be taken up to 3-4 g/d. It was reported by the applicant that for each of the studies supporting efficacy, the potential impact of rescue medication was assessed. The applicant claimed that since in each case, the proportion of patients who took acetaminophen (the only rescue medication that was allowed) was similar among the treatment groups; acetaminophen usage was unlikely to affect the results.

If pregabalin is efficacious, one will expect fewer patients in pregabalin group taking rescue medicine than those in placebo group. Since the primary endpoint is the mean of the last 7 dairy pain scores, even if the proportions of patients who took rescue medicine in treatment groups are similar, taking rescue medicine in early weeks will be different from taking rescue medicine during the baseline period or in last week in terms of affecting the efficacy assessment. A summary of the use of allowable or prohibited rescue medicine is provided in Table 5 (see page 21).

1.3.3 Efficacy Study Results

Although the primary endpoint is the mean pain score, in my opinion the analysis for the percentage change in endpoint mean pain score from baseline is more informative. Due to the concern of dropout rates and the issue of rescue medication, the responder analyses were performed using the following methods:

(1) Baseline observation carried forward (BOCF);
(2) Baseline observation carried forward and maximum baseline pain score imputation for the use of rescue medication (BOCF & MBIR).

The percentage change is defined as $P = \frac{T - B}{B} 100\%$. The responder defined by the Sponsor is the patient who had at least 50% reduction in pain.

The percentage changes in endpoint mean pain score from baseline by dose with BOCF or both BOCF & MBIR are listed in tables 6–11 (see page 22-25). The averages of the responder rates of 300 mg/d in Studies 029 and 131 and 600 mg/d in Studies 014 and 029 using BOCF are 31% and 33% respectively. Corresponding averages of the responder rates of placebo group are 14% and 15% in comparing with 300 mg/d dose group and 600 mg/d dose group respectively. The responder rates from pregabalin groups are doubled comparing with the placebo group. The test for the difference in responder rates between pregabalin and placebo is very highly significant for both dose 300 mg/d and 600 mg/d with p-value < 0.0001.

Considering the issue of rescue medication, I also did analysis based on BOCF & MBIR. The study results show that the responder rates of 300 mg/d dose group and 600 mg/d dose group dropped to 25% and 24% respectively. Although the responder rate does not change much in placebo group (14% vs. 14%, and 12 % vs. 15%), the test for the difference in responder rates is still statistically significant for both 300 mg/d dose and 600 mg/d dose.

The Wilcoxon rank sum test was performed to detect the improvement by using pregabalin for neuropathic pain associated with diabetic peripheral neuropathy in terms of median percentage change in endpoint mean pain score from baseline by dose with BOCF or BOCF & MBIR. The p-values of the tests are listed in Table 13 (see page 26). Bonferroni method was used in the multiple comparisons. Using BOCF, both doses 300 mg/d and 600 mg/d showed significant improvement in pain relief comparing with placebo. However, in the use of BOCF & MBIR, the dose 300 mg/d failed to demonstrate efficacy in Study 131 with a p-value of 0.0308 (α=0.025) and the dose 600 mg/d failed to demonstrate efficacy in Study 029 with a p-value of 0.0202 (α=0.0083), where α=0.025/ # of the comparisons in the study.

1.3.4 Other Issues

Approximately 61% of the patients in the placebo group experienced adverse events compared with 77% and 86% in pregabalin 300 mg/day dose group and the pregabalin 600 mg/day dose group respectively. The difference in AE rates between placebo group and pregabalin dose groups is also statistically significant.

No conclusion can be made on race, since other than white very few people from other race participated in these clinical trials.

There is no outstanding issue on either sex or age.

2. INTRODUCTION

2.1 Overview

Table 1. Summary of Six Studies for the Primary Endpoint -- ITT Population

Study ID	Phase	Center's Location	Duration /titration	Treatment	Dose/day	ITT/comp	n	p-value[1]	p-value[2]
014 [TID]	2/3	25 US & 3 Canada	6 week/2 week	Placebo		85/72	82		
				PGB 150	150mg/day	79/75	79	0.1763	0.0782
				PGB 600	600mg/day	82/72	82	0.0002	0.0002
029 [TID]	2/3	44 US	5 week/1 week	Placebo		97/89	97		
			For PGB 600mg	PGB 75	75mg/day	77/67	77	0.6267	0.4981
			/day group	PGB 300	300mg/day	81/76	81	0.0001	0.0002
				PGB 600	600mg/day	82/70	81	0.0001	0.0002
040 [TID]	3	49 Europe, Australia, South Africa	9 week/2 week	Placebo		81/62	80		
				PGB 600	600mg/day	86/62	86	0.0822	
				AMT	75mg/day	87/64	87	0.011	
131 [TID]	2/3	23 US	8 week	Placebo		70/62	69		
				PGB 300	300mg/day	76/65	75	0.0001	0.0014
149 [BID]	3	56 Europe, Australia, South Africa	12 week/1 week	Placebo		96/79	93		
				PGB 150	150mg/day	99/82	96	0.558	0.9156
				PGB 300	300mg/day	99/79	96	0.558	0.9156
				PGB 300/600	300mg/day or 600mg/day	101/78	98	0.0054	0.0912
173*[BID]	3	27 US	12 week/ 1 week	Placebo		30/1	29		
				PGB 150	150mg/day	34/2	34	0.4795	
				PGB 300	300mg/day	44/2	43	0.4795	
				PGB 300/600	300mg/day or 600mg/day	39/2	38	0.0375	

*: Study 173 was terminated early due to a partial clinical hold placed by the FDA.
1: Adjusted p-value for the test using LOCF based on Hochberg's procedure.
2: Adjusted p-value for the test using BOCF based on Hochberg's procedure, except Study 131.

Pregabalin capsules are proposed by the applicant for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN). A total of six double-blind, placebo-controlled, multicenter studies of pregabalin were conducted in the United States

(US), Europe, Australia, South Africa, and Canada. Based on the applicant's report DPN Studies 014, 029, 131 and 149 demonstrated statistically significantly greater improvement in pain relief with pregabalin 300 mg/d dose or 600 mg/d dose in using LOCF by the applicant. In study 040, statistically significantly greater improvement was not achieved. US study 173 was terminated early due to a partial clinical hold placed by the FDA. A summary of six studies are listed in Table 1.

Study 040 failed to demonstrate efficacy at the proposed dose level. Study 173 was terminated early due to a partial clinical hold placed by the FDA, in which the majority of patients only finished at most 3 weeks study. Therefore, Studies 040 and 173 did not contribute meaningful information about efficacy.

Both 75 mg/d and 150 mg/d did not show the efficacy in the studies. Considering LOCF endpoint mean pain scores, the dose 300 mg/d (TID) was supported by Studies 029 (5 week study) and 131 (8 week study) with a p-value 0.0001 for both studies; the dose 600 mg/d (TID) was supported by Studies 014 (6 week study) and 029 with p-values 0.0002 and 0.0001 respectively. These studies also showed statistical significance by using BOCF. The dose 300 mg/d or 600 mg/d (BID) based on creatinine clearance was supported by Study 149 with a p-value 0.0054 by using LOCF. This is the only study with regime BID and taking the creatinine clearance under consideration. However, the dose 300/600 mg/d in Study 149 failed to demonstrate efficacy by using BOCF. Therefore, the Studies 014, 029 and 131 were selected for review. Since Study 149 is the only study that considered creatinine clearance, used BID dose and had the FDA desired study duration of 12 weeks, per the medical officer's request, I also did statistical analyses on Study 149. The study results will be presented in Appendix.

2.2 Data Sources

The current NDA includes clinical efficacy studies 014, 029, 040, 131, 149 and 173 on neuropathic pain associated with diabetic peripheral neuropathy (DPN). Documents reviewed are located at \\Cdsesub1\n21446\N_000\2003-10-30\clinstat\neuro.

Studies 014, 029, 131 and 149 are described in detail below, and their efficacy findings are examined. The applicant provided electronic data for each study, and submitted the diary data for the information on the use of rescue medication, which includes the daily records for allowable rescue medicine and prohibited medicine for pain, after the NDA submission on January 8, 2004 per my request. The electronic paths of these data sets used in this review are listed as follows:

\\Cdsesub1\n21446\N_000\2003-10-30\crt\datasets\00014\diardiar.xpt
\\Cdsesub1\n21446\N_000\2003-10-30\crt\datasets\00029\diardiar.xpt
\\Cdsesub1\n21446\N_000\2003-10-30\crt\datasets\00131\diardiar.xpt
\\Cdsesub1\n21446\N_000\2003-10-30\crt\datasets\00149\derived\sta_diar.xpt
\\Cdsesub1\n21446\N_000\2004-01-08\crt\datasets\nda2003\diardiar.xpt
\\Cdsesub1\n21446\N_000\2004-01-08\crt\datasets\nda2003\rescmed.xpt

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

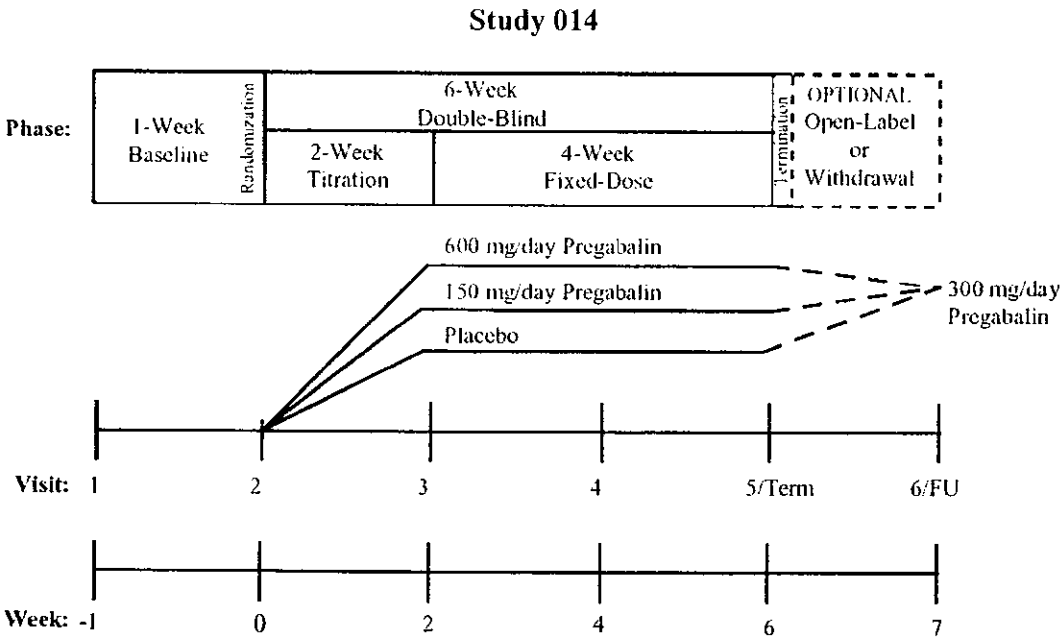
3.1.1 Study Design and Endpoints

The study design for Studies 014, 029, 131 is given in Figure 1. The studies comprised 2 phases:

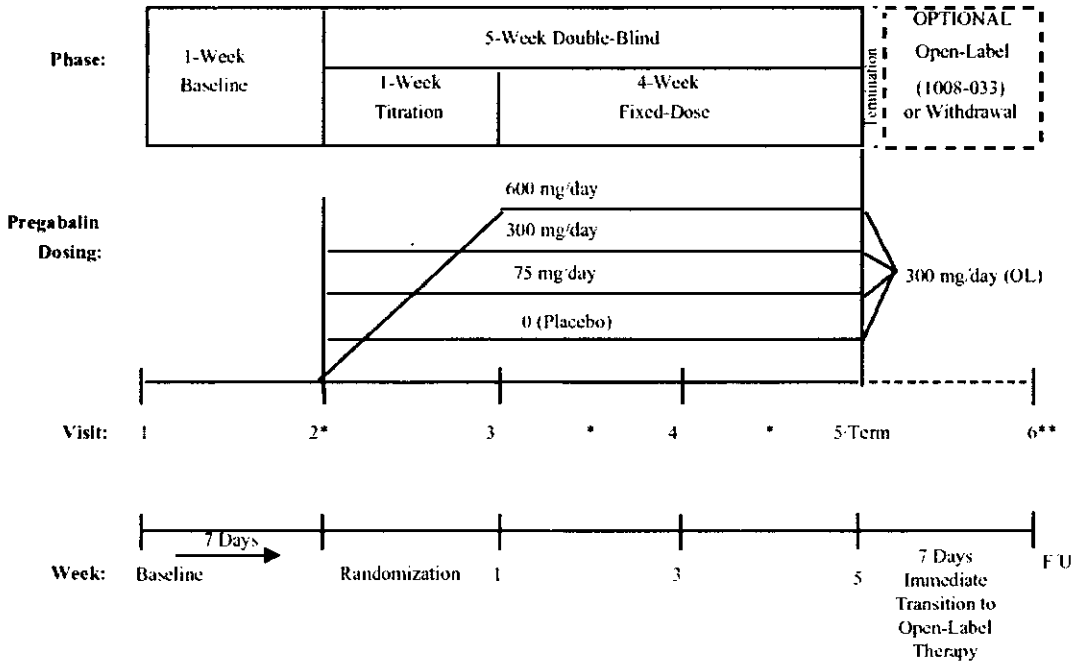
- Baseline: A 1-week phase during which patients were screened for eligibility to enter the double-blind phase; and
- Double-Blind: A 5- to 8 week phase at beginning of which DPN patients were randomly assigned to pregabalin or placebo treatment. Pregabalin doses were titrated over two weeks in Study 014; doses were not titrated in study 131; only the 600 mg/d in Study 029 was titrated. Patients remained at fixed-dose for the remainder of the double-blind phase (4 to 8 weeks).

Patients who completed or withdrew from the double-blind phase could elect to continue in open-label follow-on studies or discontinue treatment (represented by the dotted line portion of Figure 1).

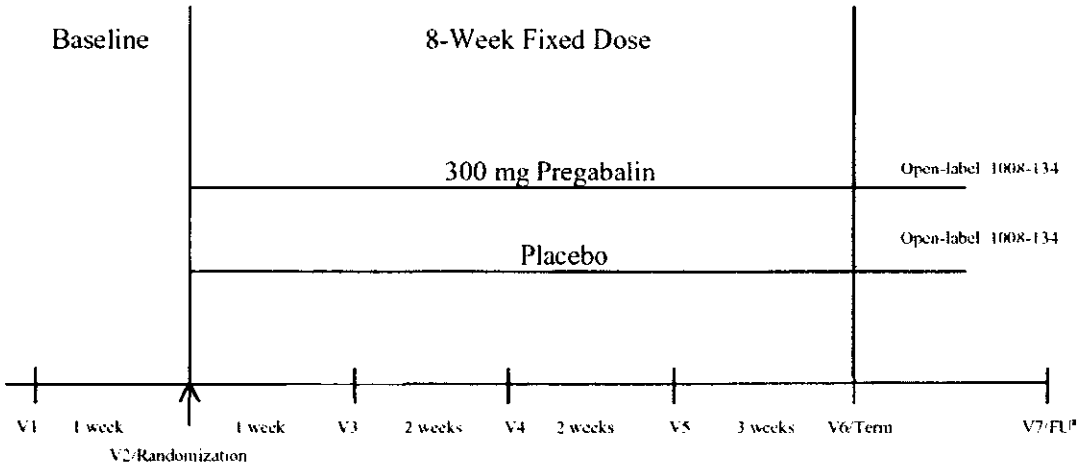
Figure1. Study Design for Studies 014, 029 and 131



Study 029



Study 131

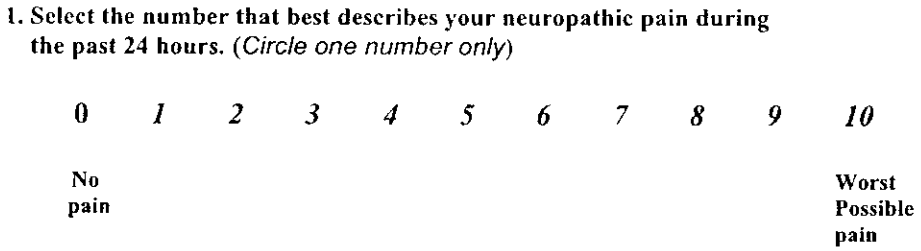


[a] Visit 7 follow-up only for those patients discontinuing study medication (ie, not entering open-label)

In Studies 014, 029, and 131, each pregabalin treatment group corresponded to a single pregabalin dose.

The primary criterion to establish efficacy in neuropathic pain studies was the endpoint mean pain score, derived from a daily pain diary recorded by the patient using an 11-point numerical rating (see Figure 2). Upon awakening, the patient evaluated his/her pain for the previous 24 hours by circling the number on the scale that best described his/her pain. The scale ranged from 0 (no pain) to 10 (worst possible pain).

Figure 2. Numerical Rating scale



The primary efficacy analysis included ITT patients who had at least one post-baseline pain scores. In the applicant's report the endpoints mean pain score is defined as follows:

Mean of the last 7 dairy entries while on study medication. Scores did not need to be recorded on consecutive days. If fewer than 7 scores were recorded by endpoint, available scores were used to determine the mean for all studies. except Study 040. For Study 040, if fewer than 7 post-baseline scores (s) were available, the last 7-x scores from baseline were also used in the calculation of endpoint.

For patients who discontinued or did not complete the study, their endpoint mean score was based on the last set of pain scores that they recorded. Supplemental analyses of the primary parameter included proportion of responders (patients who had at least a 50% reduction from baseline in mean pain score at endpoint) and weekly analysis of pain scores.

Although the primary endpoint is the mean pain score, in my opinion the analysis for the percentage change in endpoint mean pain score from baseline is more informative. Due to the concern of dropout rates and the issue of rescue medication, the primary endpoint was modified by using the following methods:

(1) Baseline observation carried forward (BOCF);
(2) Baseline observation carried forward and maximum baseline pain score imputation for the use of rescue medication (BOCF & MBIR).

The percentage change from baseline based on the modified endpoint mean pain score was considered as a primary variable in my statistical analysis.

Supplemental analyses of the primary parameter included the proportion of responders and weekly pain score by the applicant. Protocol-defined secondary parameters included:

- SF-MPQ;
- Sleep Interference;
- Clinical Global impression of Change (CGIC);
- Patient Global Impression of Change (PGIC); and
- Quality of Life (QOL)/Mood Assessments including SF-36 health Survey, Profile of Mood states (POMS), Zung self-Rating Depression Scale, Hospital anxiety and Depression Scale (HADS), Medical Outcomes Study (MOS) sleep scale and Euro QOL Health State Profile (EQ-5D).

The majority of secondary parameters were measured using patient self-assessment instruments. For the SF-MPQ, patients rated their pain intensity using VAS, present pain intensity (PPI) and pain descriptor scales. for all 3 scales, higher numbers indicate more intense pain. Sleep interference was evaluated using an 11-point numeric rating scale similar to that used for primary parameter. Impression of change was assessed by the patient and by the clinician on a 7-point scale (1=very much improved to 7=very much worse) and quality of life was measured using patient questionnaires.

3.1.2 Study Populations

3.1.2.1 Patient Characteristics

Table 2. Summary of Patient Characteristics: ITT Population, DPN Studies (Studies 014, 029, 040, 131, and 149)

Characteristics	PBO	PGB					AMT	All Patients
		75 mg/day	150 mg/day	300 mg/day[a]	600 mg/day[a]	Total	75 mg/day	
Sex, N (%)	N 426	N 77	N 176	N 266	N 335	N 854	N 87	N 1367
Male	239 (56.1)	43 (55.8)	110 (62.5)	144 (54.1)	198 (59.1)	495 (58.0)	55 (63.2)	789 (57.7)
Female	187 (43.9)	34 (44.2)	66 (37.5)	122 (45.9)	137 (40.9)	359 (42.0)	32 (36.8)	578 (42.3)
Premenopausal	28 (15.0)	6 (17.6)	8 (12.1)	19 (15.6)	20 (14.6)	53 (14.8)	9 (28.1)	90 (15.6)
Postmenopausal	159 (85.0)	28 (82.4)	58 (87.9)	103 (84.4)	117 (85.4)	306 (85.2)	23 (71.9)	488 (84.4)
Race, N (%)	N 426	N 77	N 176	N 266	N 335	N 854	N 87	N 1367
White	389 (91.3)	74 (96.1)	167 (94.9)	243 (91.4)	303 (90.4)	787 (92.2)	80 (92.0)	1256 (91.9)
Black	16 (3.8)	1 (1.3)	3 (1.7)	10 (3.8)	13 (3.9)	27 (3.2)	1 (1.1)	44 (3.2)
Hispanic	12 (2.8)	1 (1.3)	2 (1.1)	7 (2.6)	10 (3.0)	20 (2.3)	0 (0.0)	32 (2.3)
Other[b]	9 (2.1)	1 (1.3)	4 (2.3)	6 (2.3)	9 (2.7)	20 (2.3)	6 (6.9)	35 (2.6)
Age Categories, N(%)	N 426	N 77	N 176	N 266	N 335	N 854	N 87	N 1367
18-64 Years	282 (66.2)	48 (62.3)	127 (72.2)	182 (68.4)	224 (66.9)	581 (68.0)	61 (70.1)	924 (67.6)
65-74 Years	115 (27.0)	22 (28.6)	39 (22.2)	62 (23.3)	92 (27.5)	215 (25.2)	22 (25.3)	352 (25.7)
≥75 Years	29 (6.8)	7 (9.1)	10 (5.7)	22 (8.3)	19 (5.7)	58 (6.8)	4 (4.6)	91 (6.7)
Age (years)	N 426	N 77	N 176	N 266	N 335	N 854	N 87	N 1367
Mean (SD)	58.8 (11.2)	61.3 (10.5)	57.5 (11.3)	59.1 (10.9)	59.9 (10.1)	59.3 (10.7)	57.8 (12.0)	59.1 (10.9)
Median	60.0	61.0	58.0	60.0	61.0	60.0	59.0	60.0
Range	26 to 84	34 to 85	23 to 85	21 to 83	21 to 80	21 to 85	22 to 80	21 to 85
Weight (kg)	N 426	N 77	N 176	N 266	N 335	N 854	N 87	N 1367
Mean (SD)	91.21 (19.58)	96.12 (19.91)	91.09 (17.84)	93.56 (20.14)	91.64 (18.12)	92.53 (18.91)	86.34 (17.78)	91.72 (19.10)
Median	90.00	93.10	89.95	92.50	89.00	90.45	85.00	90.00
Range	44.5 to 187.4	52.3 to 173.8	54.0 to 139.3	54.5 to 160.8	46.0 to 165.9	46.0 to 173.8	50.0 to 141.0	44.5 to 187.4

ITT = Intent-to-treat; DPN = Diabetic peripheral neuropathy; PBO = Placebo; PGB = Pregabalin; AMT = Amitriptyline; SD = Standard deviation.

[a] In Study 149, patients randomized to the 300/600 pregabalin group received either 300 or 600 mg/day based on their CLcr, and are summarized here according to those doses.

[b] Other includes Asian or Pacific Islander, American Indian or Alaskan Native, or Other.

Note: This is Table 5 on 39 of 4749 in the applicant's report.

Patient characteristics for the five completed DPN studies are presented in Table 2. The majority of patients were white. Males comprised 58% of the DPN population. The median age was 60 year for the all-DPN population. Within the DPN population, treatment groups were well balanced in terms of duration of diabetes, hemoglobin A_{1c} levels, and baseline mean pain score. The majority of patients had type II diabetes for an average duration of 9 years.

3.1.2.2 Patient Disposition

Patient disposition for all completed studies 014, 029, 040, 131 and 149 is listed in Table 3. In Study 149, 11 patients withdrew following the MoH/EC decision. Disposition information for these 11 patients is tabulated but, as they were not included in the ITT population, no efficacy data is presented for these patients.

Table 3. Summary of Patient Disposition: Completed DPN Studies (Studies 014, 029, 040, 131, and 149)

Withdraw N, (%)	Pregabalin						AMT	
	Placebo	75mg/day	150 mg/day	300 mg/day[a]	600 mg/day[a]	Total	75 mg/day	All Patients
	N=429	N=77	N=178	N=269	N=338	N=862	N=87	
Entered Baseline Phase								2068
Completed Baseline Phase								1382(66.8)
Withdrawn During Baseline Phase								686 (33.2)
Did not Meet Criteria								565 (27.3)
Adverse Event								9 (0.4)
Other/Administrative								112 (5.4)
Randomized	430	77	178	270	339	864	88	1382
Intent-to-Treat[b]	329	77	178	269	338	862	87	1378
Completed Study	364(84.8)	67 (87.0)	157(88.2)	227 (84.4)	275 (81.4)	726(84.2)	64(73.6)	1154(83.7)
Withdrawn During Treatment Phase[c]	65 (15.2)	10 (13.0)	21 (11.8)	42 (15.6)	63 (18.6)	136(15.8)	23(26.4)	224 (16.3)
Lack of Compliance	4 (0.9)	1 (1.3)	0 (0.0)	2 (0.7)	5 (1.5)	8 (0.9)	2 (2.3)	14 (1.0)
Lack of Efficacy	26 (6.1)	4 (5.2)	8 (4.5)	7 (2.6)	10 (3.0)	29 (3.4)	3 (3.4)	58 (4.2)
Adverse Event	16 (3.7)	2 (2.6)	7 (3.9)	26 (9.7)	37 (10.9)	72 (8.4)	16(18.4)	104 (7.5)
Withdraw following EC/MoH decision[d]	3 (0.7)	0 (0.0)	2 (1.1)	3 (1.1)	3 (0.9)	8 (0.9)	0 (0.0)	11 (0.8)
Other/Administrative	16 (3.7)	3 (3.9)	4 (2.2)	4 (1.5)	8 (2.4)	19 (2.2)	2 (2.3)	37 (2.7)
Entered Open Label	367(85.5)	67 (87.0)	158(88.8)	218 (81.0)	285 (84.5)	728(84.5)	63(72.4)	1158(84.0)

a: In Study 149, patients randomized to the 300/600 mg/day pregabalin group received either 300 or 600 mg/day based on their CLcr, and are summarized here according to those doses.

b: Four patients were randomized but returned all study medications and are, therefore, not considered ITT.

c: For all studies, treatment refers to titration and fixed dose phases only.

d: for Study 149, 11 patients who withdrew as a result of the EC/MoH decision were not considered in the primary analysis.

Note: This is Table 8 on 43 of 4749 in the applicant's report

Eighty-four percent of patients in the DPN studies completed study. For pregabalin-and amitriptyline-treated patients, the most common reason for withdrawal was adverse events. Within the DPN population, 4% of placebo patients, 8% of pregabalin patients, and 18% of amitriptyline-treated patients withdrew due to adverse events.

3.1.3 Statistical Methodologies

3.1.3.1 Statistical Analyses (Protocol-Defined)

The ITT population was the analysis population for all primary and secondary analyses for each study, except for Study 149. In this study 11 patients were withdrawn from the study by requirement of ministries of Health/Ethics Committees (MoH/EC) in several countries, reducing the ITT population of 395 patients to an analyzed 384 patients.

The number of patients per treatment group was determined assuming 2-sided testing to give >90% power to detect a difference in endpoint mean pain scores $\geq$1.3 between at least 1 pregabalin group and placebo. The difference in endpoint mean pain score of 1.3 was based on published studies in DPN.

For outcome measures collected in daily diaries (pain and sleep interference), the following conventions were used:

- Baseline mean score: Mean of the last 7 diary entries before taking study medication. Scores did not need to be recorded on consecutive days. If fewer than 7 scores were recorded during baseline, the available scores were used to determine a mean.
- Endpoint mean score: Mean of the last 7 diary entries while on study medication. Scores did not need to be recorded on consecutive days. If fewer than 7 scores were recorded by endpoint, available scores were used to determine the mean for Studies 014, 029, 131 and 149.
- Weekly mean score: mean of the diary entries for each week in the study. Since each diary entry reflected the previous 24-hour period, the Week 1 mean was computed using all available entries from Days 2 through 8, Week 2 from Days 9 through 15, *etc.*
- Change from baseline: Compute as T-B, where T represents endpoint mean or weekly mean and B represents baseline mean.
- Responders: Patients with 50% or greater reduction from baseline to endpoint mean pain scores, defined as $[(T-B)/B]*100 \leq -50$, where T = endpoint mean pain score and B = baseline mean pain score.

In multiple comparisons, Hochberg's multiple comparison procedure was used to protect the type I error rate at the 0.05 level in studies with more than one primary comparison.

All statistical testing by the applicant was performed using SAS procedures. Patients with no data for a given efficacy measure at baseline or at the time point to be analyzed were treated as missing by the SAS procedure, rather than using imputed values.

For modeling purposes, small centers were combined (geographically if possible) to create one or more larger centers in the analyses. This grouping was done after the studies completed, but before the blind was broken.

Following upon the previous FDA reviewers request to examine the sensitivity of the primary analysis (endpoint mean pain score) in the pre-NDA meeting held on June 7, 2000, the applicant repeated the analyses using the baseline mean pain score, in place of endpoint, for any patient included in primary analysis who did not complete the study (BOCF analysis), resulting in a change from baseline of zero for these patients.

3.1.3.2 Statistical Analyses by the Reviewer

Although the primary endpoint is the mean pain score, in my opinion the analysis for the percentage change in endpoint mean pain score from baseline is more informative. Due to the concern of dropout rates and the issue of rescue medication, the responder analyses were performed using the following methods:

(1) Baseline observation carried forward (BOCF);
(2) Baseline observation carried forward and maximum baseline pain score imputation for the use of rescue medication (BOCF & MBIR).

The percentage change is defined as $P = \frac{T - B}{B} 100\%$.
Since the percentage change is not normally distributed, Wilcoxon rank sum test was performed to detect the improvement by using pregabalin for neuropathic pain associated with diabetic peripheral neuropathy in terms of median percentage change in endpoint mean pain score from baseline by dose with BOCF or BOCF & MBIR. Bonferroni method was used in multiple comparisons.

3.1.4 Results and Conclusions

3.1.4.1 Applicant's Results and Conclusions from Studies 014, 029 and 131

Study 014

This study evaluated the efficacy and safety of 2 doses of pregabalin in patients with neuropathic pain associated with diabetic peripheral neuropathy. Men and women at least 18 years of age with a diagnosis of diabetic, distal, symmetrical, sensorimotor polyneuropathy for 1 to 5 years were eligible to enroll in this 6-week double-blind, placebo-controlled, parallel-group, multicenter trial. Following a 1- week baseline phase, 246 patients were randomized to receive placebo, 150 mg/day pregabalin or 600 mg/day pregabalin. Study medication was given 3 times per day (TID) and pregabalin doses were titrated over 2 weeks. Patients were then maintained at their fixed dose for the remainder of the study (4 weeks).

The primary efficacy measure was the endpoint mean pain score. Based on LOCF, patients treated with 600 mg/d pregabalin had a significantly lower mean pain score than placebo patients (mean pain score 4.29 compared with 5.55; p-value=0.0002). Significant differences in favor of pregabalin 600 mg/d were seen for the following secondary parameters: daily sleep interference scores; short-Form-McGill pain questionnaire scores, visual analog and present pain intensity scores, patient and clinical global impression of change, and the bodily pain domain of the SF-36 quality of life (SF-36 QOL) questionnaire. The significant differences between the 600 mg/d group and the placebo group were apparent after 1 week for most parameters. Pregabalin treatment of 150 mg/d did not differ significantly from placebo in any measurement except the bodily pain domain of the SF-36 QOL questionnaire.

Study 029

This was a 5-week, double-blind, placebo-controlled, multicenter trial of 3 dosages of pregabalin for treatment of patients with painful diabetic neuropathy. The study was conducted in men and women at least 18 years of age with a diagnosis of type 1 or type 2 diabetes and painful, distal, symmetrical, sensorimotor polyneuropathy for 1 to 5 years. Following a 1-week baseline phase, 338 patients were randomized to receive placebo or pregabalin 75, 300 or 600 mg/d given 3 times a day (TID). Three hundred and thirty seven patients received treatment. Patients in the 75 and 300 mg/d treatment groups received their full dose on Day 1; patients in the 600 mg/d treatment group were titrated up to their final dose over 6 days.

The primary efficacy measure was the endpoint mean pain score. Based on LOCF, pregabalin at 300 and 600 mg/d, was significantly better than placebo in relieving pain as (mean scores = 3.80, 3.60 and 5.06 for pregabalin 300 mg/d, pregabalin 600 mg/d and placebo, respectively). Pregabalin doses $\geq$ 300 mg/d were statistically superior to placebo for each weekly mean pain score, proportion of responders, sleep interference, SF-MPQ sensory, affective and total scores, VAS and PPI scales, CGIC, and PGIC. The 300 mg/d dose was significantly better than placebo on the tension/anxiety mood scale of Profile of Mood States (POMS) and the 300 and 600 mg/d groups with significantly superior to placebo for the social functioning and bodily pain domains of the SF-36 QOL. The 75 mg/d was not statistically different from placebo.

Study 131

This study was an 8-week, double-blind, placebo-controlled, multicenter trail to evaluate the safety and efficacy of pregabalin 300 mg/d given three times a day (TID)compared with placebo for the symptomatic relief of painful diabetic peripheral neuropathy. The study was conducted in men and women at least 18 years of age with a diagnosis of painful, distal, symmetrical sensorimotor polyneuropay for 1 to 5 years. Following a 1-week baseline phase, 146 patients were randomized to pregabalin or placebo; all patients received at least 1 dose of study medication.

The primary efficacy parameter was the endpoint mean pain score. Based on LOCF, pregabalin was statistically superior to placebo in reducing pain (p-value=0.0001; mean score 2.99 for pregabalin group, 5.46 for placebo group). Weekly pain scores were statistically significantly different from placebo at every time point, beginning at Week 1. Forty percent of patients receiving pregabalin were responders compared with 14.5 % of patients receiving placebo. Pregabalin was effective for secondary efficacy measures of SF-MPQ mean sensory, affective, and total scores, sleep interference scores, PGIC, and CGIC as well as for the bodily pain domain of the SF-36 QOL questionnaire. The difference in POMS scores between treatment groups reached statistical significance for the mood states of tension/anxiety and total mood disturbance.

The primary studies were repeated using BOCF by the applicant. Pregabalin 300 mg/d dose was significantly better than placebo in both Study 029 and Study 131 with p-values 0.0002 and 0.0014 respectively. Pregabalin 600 mg/d dose was also significantly better than placebo. The p-value of the test in both Studies 014 and 029 was 0.0002.

3.1.4.2 The Reviewer's Results and Conclusions from Studies 014, 029 and 131

3.1.4.2.1 Issues related to the efficacy studies

The primary endpoint is the mean of the last 7 diary entries while on study medication. Table 4 lists the size of ITT population (N), the number of the complete patients (n_c), and the sample size (n) used in the study and the incomplete rate.

Table 4. Summary of the Sample Size Used and Incomplete Rate

Study	Arm	N	n_c	n	Incomplete Rate (%)
14	Placebo	85	72	82	15.3
	600 mg	82	72	82	12.2
29	Placebo	97	89	97	8.2
	300 mg	81	76	81	6.2
	600 mg	82	70	81	14.6
131	Placebo	70	62	69	12.9
	300mg	76	65	75	14.5

It can be seen from Tables 3 and 4 that although the dropout rates or incomplete rates are high, the actually used sample size in each study is close to the ITT population size. It is because the primary endpoint is defined as the mean of the last 7 dairy entries while on study medication. If a patient withdrew in the first day of the second week, the patient still could have a response to the primary variable. Since the duration of the study is a concern, the results from say, an 8 week study (Study 131) may not be reliable for interpretation of 8 week duration based on LOCF analysis.

Another issue that brought my attention was the use of rescue medication during trials.

Concurrent medications for pain were prohibited in DPN studies with the exception of acetaminophen which could be taken up to 3-4 g/d. It was reported by the applicant that for each of the studies supporting efficacy, the potential impact of rescue medication was assessed. The applicant claimed that since in each case, the proportion of patients who took acetaminophen (the only rescue medication that was allowed) was similar among the treatment groups; acetaminophen usage was unlikely to affect the results.

If pregabalin is efficacious, one will expect fewer patients in pregabalin group taking rescue medicine than those in placebo group. Since the primary endpoint is the mean of the last 7 dairy pain scores, even if the proportions of patients who took rescue medicine in treatment groups are similar, taking rescue medicine in early weeks will be different from taking rescue medicine during baseline period and/or in last week in terms of affecting the efficacy assessment.

A summary of the use of rescue medication, including both allowable and prohibited drug for pain, is provided in Table 5.

Table 5. Summary of the Use of Rescue Medication

Study 014				
Treatment	N	Allowed	Prohibited	Total
Placebo	85	13	3	16
150 mg/day PGB TID	79	12	1	13
600 mg/day PGB TID	82	13	2	15
Study 029				
Treatment	N	Allowed	Prohibited	Total
Placebo	97	14	7	21
75 mg/day PGB TID	77	12	6	17
300 mg/day PGB TID	81	11	3	14
600 mg/day PGB TID	82	10	8	18
Study 131				
Treatment	N	Allowed	Prohibited	Total
Placebo	70	7	7	13
300 mg/day PGB TID	76	9	5	13

It can be seen that there were around 17%-22% of the patients who took either allowable or prohibited medication for pain during the studies. Since ITT population included not only the patients who took allowable rescue medication but also those who took the prohibited medication for pain, the reported efficacy of pregabalin by the applicant using either LOCF or BOCF may not be reliable.

3.1.4.2.2 Statistical Evaluation of Evidence on Efficacy

The primary endpoint in my study is defined as follows:

- If a patient completed the study and finished last week diary, the endpoint is equal to the mean of the last week 7 diary pain scores.
- If a patient dropped the study before the last week, the endpoint is equal to his/her mean baseline score.
- If a patient had missing data within the last week, the missing data is replaced by his/her mean baseline score.
- If a patient took rescue medication (either allowable or prohibited), before the endpoint mean pain score is calculated, the pain score for that day is replaced by his/her maximum baseline score if the diary pain score is less than the maximum baseline score. (This modification is used only in BOCF & MBIR.)

Statistical Analyses were performed on the variable *percentage change from baseline* using BOCF and BOCF & MBIR for Studies 014, 029, 131and 149. The results from Study 149 are presented in Appendix.

The percentage changes in endpoint mean pain score by dose using BOCF or both BOCF & MBIR are given in Tables 6-11.

Table 6. Percentage Change From Baseline in Endpoint Mean Pain Score: With BOCF (Study 014)

TOTAL	85		79		82	
TREATMENT	Placebo		PGB 150 mg/d		PGB 600 mg/d	
Any Increase	21	24.7%	12	15.2%	7	8.5%
No Change	12	14.1%	7	8.9%	12	14.6%
>0% Decrease	52	61.2%	60	75.9%	63	76.8%
>=10% Decrease	39	45.9%	49	62.0%	52	63.4%
>=20% Decrease	25	29.4%	36	45.6%	41	50.0%
>=30% Decrease	18	21.2%	26	32.9%	40	48.8%
>=40% Decrease	15	17.6%	19	24.1%	33	40.2%
>=50% Decrease	11	12.9%	14	17.7%	24	29.3%
>=60% Decrease	6	7.1%	11	13.9%	16	19.5%
>=70% Decrease	5	5.9%	6	7.6%	11	13.4%
>=80% Decrease	4	4.7%	4	5.1%	9	11.0%
>=90% Decrease	1	1.2%	1	1.3%	4	4.9%
=100% Decrease	0	0.0%	1	1.3%	2	2.4%

Table 7. Percentage Change From Baseline in Endpoint Mean Pain Score: With BOCF & MBIR (Study 014)

TOTAL	85		79		82	
TREATMENT	Placebo		PGB 150 mg/d		PGB 600 mg/d	
Any Increase	17	20.0%	13	16.5%	6	7.3%
No Change	25	29.4%	18	22.8%	25	30.5%
>0% Decrease	43	50.6%	48	60.8%	51	62.2%
>=10% Decrease	31	36.5%	41	51.9%	41	50.0%
>=20% Decrease	18	21.2%	31	39.2%	34	41.5%
>=30% Decrease	12	14.1%	24	30.4%	34	41.5%
>=40% Decrease	11	12.9%	18	22.8%	28	34.1%
>=50% Decrease	7	8.2%	14	17.7%	19	23.2%
>=60% Decrease	3	3.5%	11	13.9%	12	14.6%
>=70% Decrease	2	2.4%	6	7.6%	8	9.8%
>=80% Decrease	1	1.2%	4	5.1%	7	8.5%
>=90% Decrease	0	0.0%	1	1.3%	2	2.4%
=100% Decrease	0	0.0%	1	1.3%	1	1.2%

Table 8. Percentage Change From Baseline in Endpoint Mean Pain Score: With BOCF (Study 029)

TOTAL	97		81		82		77	
Sum of FREQ								
SEG	Placebo		PGB 300 mg/d		PGB 600 mg/d		PGB 75 mg/d	
Any Increase	15	15.5%	8	9.9%	5	6.1%	12	15.6%
No Change	20	20.6%	12	14.8%	15	18.3%	18	23.4%
>%0 Decrease	62	63.9%	61	75.3%	62	75.6%	47	61.0%
>=%10 Decrease	49	50.5%	56	69.1%	59	72.0%	40	51.9%
>=%20 Decrease	36	37.1%	48	59.3%	50	61.0%	35	45.5%
>=%30 Decrease	28	28.9%	42	51.9%	41	50.0%	26	33.8%
>=%40 Decrease	20	20.6%	36	44.4%	35	42.7%	19	24.7%
>=%50 Decrease	16	16.5%	31	38.3%	30	36.6%	15	19.5%
>=%60 Decrease	13	13.4%	19	23.5%	24	29.3%	9	11.7%
>=%70 Decrease	8	8.2%	13	16.0%	14	17.1%	5	6.5%
>=%80 Decrease	4	4.1%	7	8.6%	10	12.2%	5	6.5%
>=%90 Decrease	1	1.0%	4	4.9%	4	4.9%	1	1.3%
=%100 Decrease	1	1.0%	1	1.2%	4	4.9%	0	0.0%

Table 9. Percentage Change From Baseline in Endpoint Mean Pain Score: With BOCF & MBIR (Study 029)

TOTAL	97		81		82		77	
TREATMENT	Placebo		PGB 300 mg/d		PGB 600 mg/d		PGB 75 mg/d	
Any Increase	13	13.4%	7	8.6%	9	11.0%	8	10.4%
No Change	36	37.1%	23	28.4%	29	35.4%	26	33.8%
>0% Decrease	48	49.5%	51	63.0%	48	58.5%	42	54.5%
>=10% Decrease	39	40.2%	47	58.0%	46	56.1%	36	46.8%
>=20% Decrease	30	30.9%	40	49.4%	38	46.3%	32	41.6%
>=30% Decrease	24	24.7%	35	43.2%	29	35.4%	24	31.2%
>=40% Decrease	17	17.5%	32	39.5%	23	28.0%	17	22.1%
>=50% Decrease	15	15.5%	27	33.3%	20	24.4%	13	16.9%
>=60% Decrease	13	13.4%	19	23.5%	15	18.3%	8	10.4%
>=70% Decrease	8	8.2%	13	16.0%	9	11.0%	5	6.5%
>=80% Decrease	4	4.1%	7	8.6%	6	7.3%	5	6.5%
>=90% Decrease	1	1.0%	4	4.9%	3	3.7%	1	1.3%
=100% Decrease	1	1.0%	1	1.2%	3	3.7%	0	0.0%

Table 10. Percentage Change From Baseline in Endpoint Mean Pain Score: With BOCF (Study 131)

TOTAL	70		76	
TREATMENT	Placebo		PGB 300 mg/d	
Any Increase	20	28.6%	8	10.5%
No Change	14	20.0%	17	22.4%
>0% Decrease	36	51.4%	51	67.1%
>=10% Decrease	26	37.1%	49	64.5%
>=20% Decrease	20	28.6%	34	44.7%
>=30% Decrease	16	22.9%	28	36.8%
>=40% Decrease	11	15.7%	24	31.6%
>=50% Decrease	8	11.4%	18	23.7%
>=60% Decrease	4	5.7%	15	19.7%
>=70% Decrease	2	2.9%	9	11.8%
>=80% Decrease	0	0.0%	7	9.2%
>=90% Decrease	0	0.0%	5	6.6%
=100% Decrease	0	0.0%	2	2.6%

Table 11. Percentage Change From Baseline in Endpoint Mean Pain Score: With BOCF & MBI (Study 131)

TOTAL	70		76	
TREATMENT	Placebo		PGB 300 mg/d	
Any Increase	17	24.3%	[illegible]	[illegible]
No Change	21	30.0%	[illegible]	[illegible]
>0% Decrease	32	45.7%	[illegible]	[illegible]
>=10% Decrease	24	34.3%	40	52.6%
>=20% Decrease	19	27.1%	26	34.2%
>=30% Decrease	16	22.9%	20	26.3%
>=40% Decrease	11	15.7%	17	22.4%
>=50% Decrease	8	11.4%	13	17.1%
>=60% Decrease	4	5.7%	11	14.5%
>=70% Decrease	2	2.9%	7	9.2%
>=80% Decrease	0	0.0%	6	7.9%
>=90% Decrease	0	0.0%	4	5.3%
=100% Decrease	0	0.0%	2	2.6%

The averages of the responder rates of 300 mg/day in Studies 029 and 131 and 600 mg/d in Studies 014 and 029 using BOCF are 31% and 33% respectively. Corresponding averages of the responder rates of placebo group are 14% and 15% in comparing with 300 mg/d dose group and 600 mg/d dose group respectively. The responder rates from pregabalin groups are doubled comparing with the placebo group. The test for the difference in responder rates between pregabalin and placebo is very highly significant for both 300 mg/d dose and 600 mg/d dose with a p-value < 0.0001.

Based on BOCF & MBIR analyses, compared with the placebo group, on average approximate 6% more patients in pregabalin 300 mg/d dose groups or pregabalin 600 mg/d groups received at least 80% pain reduction. The study results show that the responder rates of 300 mg/d dose group and 600 mg/d dose group dropped to 25% and 24% respectively. Although the responder rate does not change much in placebo group (14% vs. 14%, and 12 % vs. 15%), the test for the difference in responder rates is still statistically significant for both 300 mg/d dose and 600 mg/d dose.

Note that the percentages in the categories *any increase* and *no increase* are not small.
The Wilcoxon rank sum test was performed to detect the improvement by using pregabalin for neuropathic pain associated with diabetic peripheral neuropathy in terms of the median percentage changes in endpoint mean pain score from the baseline by dose with BOCF or BOCF & MBIR. The p-values of the tests are listed in Table 12. Bonferroni method was used in the multiple comparisons. Using BOCF, both doses 300 mg/d and 600 mg/d showed significant improvement in pain relief comparing with placebo. However, in the use of BOCF & MBIR, the dose 300 mg/d failed to demonstrate efficacy in Study 131 with a p-value of 0.0308 (α=0.025) and the dose 600 mg/d failed to demonstrate efficacy in Study 029 with a p-value of 0.0202 (α=0.0083).

Table 12. Wilcoxon Rank Sum Test for the Difference in Median of Percentage Changes From Baseline (p-value)

Study	Method	75 mg	150 mg	300 mg	600 mg	Adjusted α*
014	BOCF		0.0074		0.0003	0.0125
	BOCF&MBIR		0.0137		0.0014	0.0125
029	BOCF	0.3984		0.0009	0.0003	0.0083
	BOCF&MBIR	0.4624		0.0048	0.0202	0.0083
131	BOCF			0.0010		0.0250
	BOCF&MBIR			0.0308		0.0250

* Adjusted α=0.025/# of comparisons (Bonferroni method)

3.2 Evaluation of Safety

On average, 86% of patients experienced AE in pregabalin 600 mg/d dose group, comparing with 77% and 61% of patients experienced AE in the pregabalin 300 mg/d and placebo groups, respectively. It is evident that the AE rate increases when the dose level increases. Based on the medical officer's report, skin ulcers and visual abnormalities in a dose dependent manner were observed from pregabalin treatment groups. However, there is no statistical evidence to support that the relationship exits between dose and skin ulcers. The statistical analysis regarding this issue can be found in Dr. Thomas Permutt's report. The following are the summaries of safety by studies:

Study 014: Seventy patients (85%) of the patients in the pregabalin 600 mg/d dose groups experienced adverse events compared with 56% and 57% in the pregabalin 150 mg/day dose group and the placebo group, respectively. Among patients given pregabalin 600 mg/d, the most common adverse event was dizziness. Other frequently occurring adverse events among pregabalin-treated patients were somnolence, peripheral edema and headache. Eight patients (5 pregabalin 600 mg/day, 1 pregabalin 150 mg/day and 2 placebo) experienced serious adverse events during the double blind phase of the study. The Sponsor claimed that none of the events were considered related to study medication. Thirteen patients (7 receiving 600 mg/d pregabalin, 2 receiving 150 mg/d pregabalin, and 4 receiving placebo) withdrew due to adverse events. There were no deaths during the study.

Study 029: Eighty-seven percent of the patients in the pregabalin 600 mg/d group experienced an adverse event as did 75%, 62% and 67% of the patients in the pregabalin 300 mg/d, pregabalin 75 mg/d and placebo groups, respectively. The most common adverse events among pregabalin-treated patients were dizziness, somnolence and peripheral edema. Eight patients (5 pregabalin, 3 placebo) experienced serious adverse events. The Sponsor claimed that none of these was considered related to treatment. Eighteen patients withdrew from the study due to adverse events. There were no deaths in this study.

Study 131: Seventy-nine percent of pregabalin-treated patients and 59% of patients in the placebo group experienced at least 1 adverse event. Most of the adverse events were mild to moderate in intensity. Dizziness was the most commonly occurring adverse event in both treatment groups. Other frequently occurring adverse events included somnolence, infection and peripheral edema. Two patients experienced a serious adverse event (1 pregabalin 300 mg/d, ischemic cardiac chest pain and 1 placebo, musculoskeletal chest pains). The Sponsor claimed that neither was considered related to study drug. Ten patients withdrew due to adverse events. There were no deaths in this study.

4. FINDING SPECIAL/SUBGROUP POPULATIONS

4.1 Race

Seventy nine percent of patients were white in each of placebo and pregabalin 600 mg/d treatment groups in Study 014. Ninety seven percent of patients were white in each treatment group in Study 029. In Study 131, the percentage of white is 91% and 84% for placebo group and pregabalin 300 mg/d dose group respectively. Since very few patients other than white participated the studies, there is no statistical conclusion can be made on race.

4.2 Gender

Based the applicant's LOCF analyses, it reported that the difference in primary endpoint between pregabalin and placebo patient is similar for females and males, in every treatment group.

The Table 13 is the summary of the use of rescue medication (including prohibited medication for pain) by gender.

Table 13. Summary of the Use of Rescue Medication by Gender

Study	ITT	NO RESCMED		RESCUEMED		
ID	N	Female (%)	Male (%)	Female (%)	Male (%)	p-value
014	246	75 (77.3)	127 (85.2)	22 (22.7)	22 (14.8)	0.0626
029	337	101(74.8)	166 (82.2)	34 (25.2)	36 (17.8)	0.0540
040	254	59 (54.6)	102 (69.9)	49 (45.4)	44 (30.1)	0.0062
131	146	50 (78.1)	70 (85.4)	14 (21.9)	12 (14.6)	0.1298
149	395	146 (83.9)	177 (84.3)	28 (16.1)	33 (15.7)	0.4575

It can be seen that except for failed Study 040, there is no significant difference in the use of rescue medication by gender at type I error rate of 0.05.

Since there is no stand out evidence in gender difference in taking rescue medication and dropouts, I did not pursue further for primary efficacy study by gender using BOCF or BOCF & MBIR on the variable of percentage change from baseline.

4.3 Age

Because relatively few PHN patients are in the youngest age category (21%), and very few DPN patients are in the oldest age category (7%), the applicant's analysis by age groups was based on all combined patients from both disease models.

Based on 3 separated ANCOVA models by age group, the applicant reported

- There may be a trend toward better efficacy with increasing age;
- There is a significant interaction (p-value=0.0124) between age group and treatment group, but this may be due to confounding between age and CLcr. After controlling for baseline CLcr, the difference between pregabalin and placebo patients is no longer significant (age group by dose interaction, p-value=0.1638).

Table 14. Summary of the Use of Rescue Medication by Age

		Rescue (Study 014)		Rescue (Study 029)		Rescue (Study 131)	
Age	N	No	Yes	No	Yes	No	Yes
21 - 30	4	2	0 (0%)	1	0 (0%)	1	0 (0%)
31 - 40	30	7	5 (42%)	9	3 (27%)	6	0 (0%)
41 - 50	110	32	9 (21%)	32	10 (24%)	18	9 (33%)
51 - 60	246	88	12 (12%)	87	21 (19%)	32	6 (16%)
61 - 70	225	55	15 (21%)	91	24 (21%)	35	5 (21%)
71 - 80	99	18	3 (14%)	43	11 (20%)	19	5 (21%)
81 - 85	4	0	0 (0%)	2	0 (0%)	2	0 (0%)

Table 14 gives the summary of the rescue medication used during the trial by age groups. The rescue medication includes both allowable and prohibited. It can be seen that very few patients in 21-30 or 81-85 category in Studies 014, 029 and 131. In the other age groups, there is no trend of increasing the use of rescue medication by age.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Neuropathic pain associated with diabetic peripheral neuropathy is a chronic disease. Excluding titration period (1-2 weeks), Studies 014 and 029 were on the fixed study doses only for 4 weeks. Although Study 131 was without titration period, it was an 8 week study only for pregabalin 300 mg/d dose. There was only one study to support 300

mg/d dose with 8 weeks duration. Therefore, the statistical inference is only meaningful for 4 weeks duration.

In the ITT population for Studies 014, 029 and 131, the percentages of patients who took either allowable rescue medication or prohibited rescue medication are 20%, 17% and 20% in placebo group, pregabalin 300 mg/d dose group and pregabalin 600 mg/d dose group respectively. Comparing the results from BOCF with that from BOCF & MBIR, the responder rate was decreased by 6–9% if the use of allowable or prohibited medication was taken into account in the study.

While the studies did show the efficacy in some degree, approximately 61% of the patients in the placebo group experienced adverse events compared to 77% and 86% in pregabalin 300 mg/d dose group and the pregabalin 600 mg/d dose group respectively. The difference in AE rates between placebo group and pregabalin dose groups is also very highly statistically significant (p-value=0.0002 and ≈ 0 for 300 mg/d dose and 600 mg/d dose respectively).

5.2 Conclusions and Recommendations

Overall, statistically the data support the applicant's claim that pregabalin is efficacious in pain relief in neuropathic pain associated with diabetic peripheral neuropathy, although the percentage of the patients that benefit from the pregabalin treatment is not large especially in BOCF & MBIR analyses. On average, approximately 6% more patients in pregabalin 300 mg/d dose groups or 600 mg/d groups received at least 80% pain reduction compared with placebo group in BOCF & MBIR analyses. Analyses of secondary variables, which are mostly alternate ways of measuring pain and pain reduction at the conclusion of the trials, also support the primary findings. However, the responder rates reported in the submitted draft labeling are not reliable since these results are from LOCF.

There is not enough evidence to support the efficacy and safety for the long term use of pregabalin due to the duration of the studies. Based on the medical officer's report, skin ulcers and visual abnormalities in a dose dependent manner were observed from pregabalin treatment groups. However, there is no statistical evidence to support that the relationship exits between dose and skin ulcers. The statistical analysis regarding this issue can be found in Dr. Thomas Permutt's report. I would like to suggest setting up a clinical margin for the efficacy testing in future studies for similar drug indications, which may help risk-benefit evaluations.

APPENDIX: Study 149

Study 149 evaluated the efficacy and safety of 3 doses of pregabalin in patients with painful diabetic neuropathy. It is a 12 week double-blind, placebo-controlled, parallel-group, multicenter trial. Following a 1 week baseline phase, 396 patients were randomized to receive placebo, 150, 300 or 300/600 mg/d pregabalin given twice a day (BID). Patients with a CLcr > 30 and ≤60 mL/min randomized to the 300/600 mg/day group received 300 mg/d and those with CLcr > 60 mL/min received 600 mg/d. A total of 395 patients received at least 1 dose of study medication. Pregabalin doses of 300 and 600 mg/d were titrated over 1 week. Patients were then maintained at their fixed dose for the remainder of the study.

Based on LOCF analyses the applicant reported that compared with placebo, treatment with 300/600 mg/d pregabalin resulted in a statistically significant improvement in endpoint mean pain score. No statistically significant difference was seen in primary endpoint for the 150 mg/d or the 300 mg/d dose groups. The weekly mean pain scores were significantly better than placebo at Weeks 2 through 12 and there was a statistically significant increase in the proportion of responders compared with placebo (46% vs 30%). However, Study 149 failed to demonstrate efficacy even for 600 mg/d dose in BOCF analysis.

Per medical officer's request, I separated the patients in Study 149 into two groups. One group included patients who had low CLcr and the other group included patients with CLcr > 60 mL/min. The BOCF and BOCF & MBIR analyses were performed on these two groups separately. The results from Wilcoxon rank sum test for the difference in median percentage change in endpoint mean pain score from baseline are given in Table 15.

Table 15. Wilcoxon Rank Sum Test for the Difference in Median of Percentage Changes From Baseline (p-values for Study 149)

Study	Method	75 mg	150 mg	300 mg	600 mg	Adjusted α***
149*	BOCF		0.5421	0.3949	0.0779	0.0083
	BOCF&MBIR		0.4438	0.4689	0.0763	0.0083
149**	BOCF		0.5347	0.7859		0.0125
	BOCF&MBIR		0.7017	0.8586		0.0125

* CLcr > 60 mL/min

** 30 mL/min ≤ CLcr ≤ 60 mL/min

***: Adjusted α = 0.025/# of comparisons

The adjusted α in Table 15 is based on Bonferroni method. It can be seen that Study 149 failed to demonstrate efficacy for all dose levels under the study regardless creatinine clearance level.

Summaries of percentage change in endpoint mean pain score from baseline are listed in Table 16–19.

Table 16. Percentage Change in Endpoint Mean Pain Score: With BOCF 149: (Study CLcr >60 mL/min)

TOTAL	84		87		90		88	
TREATMENT	Placebo		PGB 150 mg/d		PGB 300 mg/d		PGB 600 mg/d	
Any Increase	8	9.5%	10	11.5%	10	11.1%	6	6.8%
No Change	19	22.6%	22	25.3%	21	23.3%	21	23.9%
>0% Decrease	57	67.9%	55	63.2%	59	65.6%	61	69.3%
>=10% Decrease	52	61.9%	53	60.9%	55	61.1%	55	62.5%
>=20% Decrease	46	54.8%	41	47.1%	50	55.6%	50	56.8%
>=30% Decrease	31	36.9%	34	39.1%	39	43.3%	44	50.0%
>=40% Decrease	27	32.1%	29	33.3%	29	32.2%	37	42.0%
>=50% Decrease	21	25.0%	26	29.9%	25	27.8%	32	36.4%
>=60% Decrease	13	15.5%	17	19.5%	16	17.8%	22	25.0%
>=70% Decrease	6	7.1%	11	12.6%	12	13.3%	17	19.3%
>=80% Decrease	2	2.4%	8	9.2%	5	5.6%	8	9.1%
>=90% Decrease	0	0.0%	3	3.4%	1	1.1%	5	5.7%
=100% Decrease	0	0.0%	2	2.3%	0	0.0%	3	3.4%

Table 17. Percentage Change in Endpoint Mean Pain Score by Dose: With BOCF & MBIR (Study 149: CLcr >60 mL/min)

TOTAL	84		87		90		88	
TREATMENT	Placebo		PGB 150 mg/d		PGB 300 mg/d		PGB 600 mg/d	
Any Increase	7	8.3%	9	10.3%	10	11.1%	6	6.8%
No Change	20	23.8%	19	21.8%	20	22.2%	17	19.3%
>0% Decrease	51	60.7%	50	57.5%	59	65.6%	55	62.5%
>=10% Decrease	47	56.0%	48	55.2%	49	54.4%	49	55.7%
>=20% Decrease	41	48.8%	39	44.8%	44	48.9%	44	50.0%
>=30% Decrease	26	31.0%	32	36.8%	34	37.8%	40	45.5%
>=40% Decrease	23	27.4%	28	32.2%	26	28.9%	36	40.9%
>=50% Decrease	18	21.4%	25	28.7%	22	24.4%	31	35.2%
>=60% Decrease	11	13.1%	16	18.4%	13	14.4%	22	25.0%
>=70% Decrease	4	4.8%	10	11.5%	10	11.1%	17	19.3%
>=80% Decrease	2	2.4%	7	8.0%	5	5.6%	8	9.1%
>=90% Decrease	0	0.0%	3	3.4%	1	1.1%	5	5.7%
=100% Decrease	0	0.0%	2	2.3%	0	0.0%	3	3.4%

Table 18. Percentage Change in Endpoint Mean Pain Score: With BOCF (Study 149: CLcr ≤ 60 mL/min)

TOTAL	12		12		22	
TREATMENT	Placebo		PGB 150 mg/d		PGB 300 mg/d	
Any Increase	1	8.3%	0	0.0%	1	4.5%
No Change	2	16.7%	3	25.0%	10	45.5%
>0% Decrease	9	75.0%	9	75.0%	11	50.0%
>=10% Decrease	6	50.0%	9	75.0%	11	50.0%
>=20% Decrease	6	50.0%	6	50.0%	9	40.9%
>=30% Decrease	6	50.0%	5	41.7%	7	31.8%
>=40% Decrease	6	50.0%	3	25.0%	6	27.3%
>=50% Decrease	4	33.3%	3	25.0%	5	22.7%
>=60% Decrease	3	25.0%	2	16.7%	5	22.7%
>=70% Decrease	2	16.7%	2	16.7%	3	13.6%
>=80% Decrease	1	8.3%	2	16.7%	1	4.5%
>=90% Decrease	0	0.0%	1	8.3%	1	4.5%
=100% Decrease	0	0.0%	1	8.3%	0	0.0%

Table 19. Percentage Change in Endpoint Mean Pain Score: With BOCF & MBIR (Study 149: CLcr ≤ 60 mL/min)

TOTAL	12		12		22	
TREATMENT	Placebo		PGB 150 mg/d		PGB 300 mg/d	
Any Increase	1	8.3%	0	0.0%	1	4.5%
No Change	3	25.0%	5	41.7%	10	45.5%
>0% Decrease	8	66.7%	7	58.3%	11	50.0%
>=10% Decrease	6	50.0%	7	58.3%	9	40.9%
>=20% Decrease	6	50.0%	5	41.7%	8	36.4%
>=30% Decrease	6	50.0%	4	33.3%	6	27.3%
>=40% Decrease	6	50.0%	2	16.7%	5	22.7%
>=50% Decrease	4	33.3%	2	16.7%	4	18.2%
>=60% Decrease	3	25.0%	1	8.3%	4	18.2%
>=70% Decrease	2	16.7%	1	8.3%	2	9.1%
>=80% Decrease	1	8.3%	1	8.3%	1	4.5%
>=90% Decrease	0	0.0%	1	8.3%	1	4.5%
=100% Decrease	0	0.0%	1	8.3%	0	0.0%

It can be seen that the responder rate in low creatinine clearance group is much lower that those in CLcr > 60 mL/min group. It can also be noticed that the responder rate in placebo group increased compared with the results from other studies, which may be a cause of the failure on Study 149 for efficacy. Since Study 149 is the only study which

had BID regime and 12 weeks duration, it is not clear if the difference between Study 149 and others is due to the BID dosing or the long term duration of the study.

In order to clarify cloud in this study, I did a 6-week study for Study 149. Table 20 gives the p-values for Wilcoxon rank sum test for the difference in median percentage change from baseline based on data observed in the 6th week. It can be seen that pregabalin 600 mg/d dose with CLcr > 60 mL/min would pass the efficacy evaluation, if Study 149 had 6-week duration. Please also see Tables 21-24 for the summaries of percentage changes from baseline based on the 6th week's observations. From these tables one may see that the responder rates in pregabalin 600 mg/d dose group (with CLcr > 60 mL/min) are 2.9 and 2.5 folds of that in placebo group for BOCF and BOCF & MBIR respectively; the responder rates in pregabalin 300 mg/d dose group (with CLcr $\leq$ 60 mL/min) are 3.3 and 2.7 folds of that in placebo group for BOCF and BOCF & MBIR respectively. Notice that the responder rates in placebo groups are 21.4% for BOCF, 25.0% for BOCF & MBIR at the 6 week study for patients with a normal creatinine clearance, which are 8.3% and 9.5% higher than the corresponding results from 12 weeks study. For those patients had abnormal creatinine clearance, for both BOCF and BOCF & MBIR the responder rates of the placebo group are 8.3% and 33.3% in 12-week study and 6-week study respectively. Obviously, the responder rate in placebo group increased a lot along with time.

Table 20. Wilcoxon Rank Sum Test for the Difference in Median Percentage Change (p-value)

Study 149: 6-week results

Study	Method	150 mg	300 mg	600 mg	Adjusted α^{***}
149*	BOCF	0.2749	0.2058	0.0027	0.0083
	Reviewer	0.2953	0.2017	0.0025	0.0083
149**	BOCF	0.4769	0.6942		0.0125
	Reviewer	0.648	0.8343		0.0125

* CLcr > 60 mL/min

** 30 mL/min $\leq$ CLcr $\leq$ 60 mL/min

***: Adjusted α = 0.025/# of comparisons

Table 21. Percentage Change in Endpoint Mean Pain Score: With BOCF (Study 149: CLcr > 60 mL/min, 6 week results)

TOTAL	84		87		90		88	
TREATMENT	Placebo		PGB150 mg/d		PGB 300 mg/d		PGB 600 mg/d	
Any Increase	17	20.2%	20	23.0%	13	14.4%	11	12.5%
No Change	7	8.3%	6	6.9%	10	11.1%	11	12.5%
>0% Decrease	60	71.4%	61	70.1%	67	74.4%	66	75.0%
>=10% Decrease	53	63.1%	54	62.1%	55	61.1%	62	70.5%
>=20% Decrease	40	47.6%	43	49.4%	45	50.0%	53	60.2%
>=30% Decrease	30	35.7%	37	42.5%	37	41.1%	48	54.5%
>=40% Decrease	19	22.6%	32	36.8%	31	34.4%	44	50.0%
>=50% Decrease	13	15.5%	24	27.6%	19	21.1%	34	38.6%
>=60% Decrease	8	9.5%	17	19.5%	12	13.3%	24	27.3%
>=70% Decrease	5	6.0%	9	10.3%	6	6.7%	20	22.7%
>=80% Decrease	1	1.2%	4	4.6%	3	3.3%	10	11.4%
>=90% Decrease	0	0.0%	2	2.3%	1	1.1%	5	5.7%
=100% Decrease	0	0.0%	0	0.0%	0	0.0%	3	3.4%

Table 22. Percentage Change in Endpoint Mean Pain Score: With BOCF & MBIR (Study 149: CLcr > 60 mL/min, 6 week results)

TOTAL	84		87		90		88	
TREATMENT	Placebo		PGB 150 mg/d		PGB300 mg/d		PGB 600 mg/d	
Any Increase	14	16.7%	20	23.0%	13	14.4%	11	12.5%
No Change	19	22.6%	13	14.9%	19	21.1%	17	19.3%
>0% Decrease	51	60.7%	54	62.1%	58	64.4%	60	68.2%
>=10% Decrease	45	53.6%	48	55.2%	47	52.2%	56	63.6%
>=20% Decrease	34	40.5%	37	42.5%	41	45.6%	49	55.7%
>=30% Decrease	25	29.8%	32	36.8%	33	36.7%	45	51.1%
>=40% Decrease	16	19.0%	29	33.3%	27	30.0%	41	46.6%
>=50% Decrease	11	13.1%	22	25.3%	15	16.7%	33	37.5%
>=60% Decrease	6	7.1%	15	17.2%	10	11.1%	23	26.1%
>=70% Decrease	5	6.0%	8	9.2%	6	6.7%	19	21.6%
>=80% Decrease	1	1.2%	4	4.6%	3	3.3%	9	10.2%
>=90% Decrease	0	0.0%	2	2.3%	1	1.1%	5	5.7%
=100% Decrease	0	0.0%	0	0.0%	0	0.0%	3	3.4%

Table 23. Percentage Change in Endpoint Mean Pain Score: With BOCF (Study 149: CLcr ≤ 60 mL/min, 6 week results)

TOTAL	12		12		22	
TREATMENT	Placebo		PGB 150 mg/d		PGB 300 mg/d	
Any Increase	0	0.0%	0	0.0%	2	9.1%
No Change	1	8.3%	3	25.0%	7	31.8%
>0% Decrease	11	91.7%	9	75.0%	13	59.1%
>=10% Decrease	9	75.0%	8	66.7%	11	50.0%
>=20% Decrease	6	50.0%	6	50.0%	10	45.5%
>=30% Decrease	3	25.0%	4	33.3%	7	31.8%
>=40% Decrease	1	8.3%	3	25.0%	7	31.8%
>=50% Decrease	1	8.3%	2	16.7%	6	27.3%
>=60% Decrease	1	8.3%	1	8.3%	4	18.2%
>=70% Decrease	0	0.0%	1	8.3%	3	13.6%
>=80% Decrease	0	0.0%	1	8.3%	2	9.1%
>=90% Decrease	0	0.0%	1	8.3%	1	4.5%
=100% Decrease	0	0.0%	0	0.0%	0	0.0%

Table 24. Percentage Change in Endpoint Mean Pain Score: With BOCF & MBIR (Study 149: CLcr ≤ 60 mL/min, 6 week results)

TOTAL	12		12		22	
TREATMENT	Placebo		PGB 150 mg/day		PGB 300 mg/day	
Any Increase	0	0.0%	1	8.3%	2	9.1%
No Change	3	25.0%	4	33.3%	11	50.0%
>0% Decrease	9	75.0%	7	58.3%	9	40.9%
>=10% Decrease	7	58.3%	6	50.0%	8	36.4%
>=20% Decrease	5	41.7%	4	33.3%	7	31.8%
>=30% Decrease	2	16.7%	3	25.0%	6	27.3%
>=40% Decrease	1	8.3%	2	16.7%	6	27.3%
>=50% Decrease	1	8.3%	1	8.3%	5	22.7%
>=60% Decrease	1	8.3%	1	8.3%	3	13.6%
>=70% Decrease	0	0.0%	1	8.3%	3	13.6%
>=80% Decrease	0	0.0%	1	8.3%	2	9.1%
>=90% Decrease	0	0.0%	1	8.3%	1	4.5%
=100% Decrease	0	0.0%	0	0.0%	0	0.0%

Since there were not many patients who had abnormal creatinine clearance level in the study, I only compared the responder rates in 12-week study with those from 6-week study in detail for those patients who had normal creatinine clearance level in Table 25.

Table 25. Comparison in Responder Rates for Study 149 (BOCF with Rescue): CLcr >60 mL/min

Placebo

	6 week	
12 week	R	N
R	9.5%	11.9%*
N	3.6%	75.0%

PGB 150 mg/d

	6 week	
12 week	R	N
R	16.1%	12.6%
N	9.2%	62.1%

PGB 300 mg/d

	6 week	
12 week	R	N
R	12.2%	12.2%
N	4.4%	71.1%

PGB 600 mg/d

	6 week	
12 week	R	N
R	25.0%	10.2%**
N	12.5%**	52.3%

R in the table represents responder; and N means non-responder. It can be seen that the numbers in the cell with two stars are nearly the same. This may mean that, though there are people who were responders at week 6 but not at week 12, they are essentially balanced by people for whom it was the other way around. The reason the 6 week comparison to placebo is more significant than the 12 week one is found in the cell with one star. Placebo patients are getting better over the last 6 weeks.

There are two different interpretations for the two-star cells.

- The problem is not so much "tolerance" or loss of effect of the active drug. Rather, it may be decreased sensitivity of the assay. Patients in the study were those patients who needed help at entry. Three months later the population was not so highly enriched: it included a fair number of people who weren't so sick any more.
- A responder in 6 week but not a responder in 12 week may be due to the duration of the drug efficacy. The cell with one star suggests that some patients would get better without medication. Therefore, the percentage in N at 6 week and R at 12 week category may be a reflection of the cell with one star instead of due to the drug efficacy.

To make a firm conclusion on this issue, further investigation is needed.

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