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NDA 21-723

Statistical Review(s)

U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The applicant, Pfizer Inc., has proposed the use of LYRICA (pregabalin) for the management of neuropathic pain with herpes zoster (postherpetic neuralgia). The primary claim of the applicant is that treatment with pregabalin 150, 300, or 300/600 mg/d [BID and TID] results in a significant treatment effect compared to the placebo. The evidence taken collectively from studies reviewed indicated statistical support favoring pregabalin treatment over placebo in pain reduction. Although statistical differences in endpoint mean pain scores (i.e. Week 8 and Week 13, if available) were noted among these dosages the applicant studied, I defer discussion on the clinical relevance of these differences to Dr. Kashoki. Additional claims were made regarding treatment effect of pregabalin as early as within 3 days of treatment and within the first week. The evidence suggested that patients who took pregabalin received greater pain reduction than patients in the placebo group.

I conducted further analyses that included stratification of treatment groups based on creatinine clearance in studies 45, 127 and 196, and I carried out an in-depth analysis of treatment responders among patients in the pregabalin-treated groups and the placebo group.

Summary of Results from Study 45, 127, and 196

Study No.		Placebo	PGB 150[1]	PGB 150[2]	PGB 300[1]	PGB 300[2]	PGB 600[2]
Study 045 [TID]	N	81	42	39	45	31	
	Mean (se)	6.3 (0.2)	4.9 (0.3)	5.5 (0.3)	5.7 (0.3)	4.6 (0.3)	
	p-value[3]		0.0003	0.0587	0.0587	0.0003	
	Respond[5]	9%	29%	21%	11%	35%	
Study 127 [TID]	N	84			30		59
	Mean (se)	5.1 (0.2)			4.6 (0.4)		4.4 (0.3)
	p-value[3]				0.2346[4]		0.0302[4]
	Respond[5]	20%			30%		34%
Study 196 at Week 8 [BID]	N	93	26	61	59	65	64
	Mean (se)	6.1 (0.2)	5.8 (0.4)	5.0 (0.3)	5.2 (0.3)	5.3 (0.2)	4.7 (0.3)
	p-value[3]		0.4461	0.0024	0.0174	0.0174	0.0005
	Respond[5]	6%	8%	21%	17%	23%	30%
Study 196 at Week 13 [BID]	N	93	26	61	59	65	64
	Mean (se)	6.2 (0.2)	5.8 (0.4)	5.1 (0.3)	5.4 (0.3)	5.5 (0.3)	4.7 (0.3)
	p-value[3]		0.3514	0.0080	0.0582	0.1064	0.0005
	Respond[5]	6%	19%	28%	19%	20%	31%

[1] low creatinine clearance
[2] normal creatinine clearance
[3] using Hochberg's test of difference from placebo
[4] unadjusted p-value
[5] Percent responder at least 50% pain reduction

In general, there were substantial differences in percent responders between the pregabalin-treated groups and the placebo group, utilizing either the TID or BID dosing regimen. Furthermore, the endpoint mean pain scores among the pregabalin-treated groups are considerably lower than the endpoint mean pain scores among those treated with placebo. However, results from the statistical tests showed that only patients with normal creatinine clearance taking 300 mg/d or 600 mg/d are significantly different from the placebo, regardless of the dosing regimen utilized. The only other group that is shown to be significantly different at TID dosing is those patients with low creatinine clearance taking pregabalin 150 mg/d, while patients with low creatinine clearance taking pregabalin 300 mg/d and patients with normal creatinine clearance taking pregabalin 150 mg/d are the only other groups that are significantly different from the placebo at BID dosing. The inconsistencies of the test results generated could either be due to lack of power (i.e. inadequate number of samples), or this could be due to some tolerability issue in a number of patients to the study drug. I defer discussion on the clinical relevance of these differences to Dr. Kashoki.

Based on the graphical display of the proportion of responders by week in studies 045, 127 and 196 (Figures 3, 7, 11-14), pregabalin-treated patients not responding at Week 1 were likely to respond at Week 2. In addition, patients with normal creatinine clearance were likely to respond beyond Week 2.

Overall, the data support the applicant's claim that pregabalin is efficacious in reducing pain with herpes zoster.

1.2 Brief Overview of Clinical Studies

Background

Pregabalin [CI-1008 or (S)-3-isobutyl GABA, (S)-(+)-3-(aminomethyl)-5-methylhexanoic acid] was developed primarily as an antiepileptic agent. However, the applicant has found that pregabalin is effective in a variety of preclinical pain models of both neuropathic and nociceptive pain. According to the applicant, the safety of pregabalin has been demonstrated in single- and multiple-dose studies in healthy adults.

Currently, the applicant, Pfizer, Inc., is seeking FDA approval to market pregabalin capsules for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN), post-herpetic neuralgia (PHN), as adjunctive therapy for the treatment of partial seizures, and for generalized anxiety disorder. These were submitted as a single NDA but administratively split based on the indication; the present submission investigates the safety and efficacy of pregabalin for the management of neuropathic pain with herpes zoster (postherpetic neuralgia). Evidence is primarily derived from the five randomized, double-blind, multi-center trials conducted in the United States, Australia, and Europe.

The overall study objective across all studies was to evaluate the safety and efficacy of pregabalin in doses of 75 mg/d, 150 mg/d, 300 mg/d, and 300/600 mg/d compared to placebo for the treatment of pain in patients with post-herpetic neuralgia.

Study Design

The common design of the various studies comprised 2 phases:

1. Baseline: a one-week phase during which patients were screened for eligibility to enter the double-blind phase; and
2. Double-Blind: a 5- to 13-week phase at the beginning of which patients were randomly assigned to pregabalin or placebo treatment. Except for Study 030, pregabalin doses were titrated over a period of 2 to 12 days; the titration schedule varied from study to study. Patients remained at a fixed dose for the remainder of the double-blind phase (4 to 12 weeks).

Five double-blind, placebo-controlled, multi-center studies of pregabalin in patients with postherpetic neuralgia were conducted in the United States (US), Europe, Australia, South Africa, and Canada (Table 1). In three studies, the patients randomized to the 300/600 mg/d arm received a dose based on their creatinine clearance (CLcr). Patients whose estimated creatinine clearance was between 30 and 60 mL/min received the 300 mg/d dose, while subjects with estimated creatinine clearance of at least 60 mL/min will receive 600 mg/d dose. Meanwhile the remaining two studies had a single pregabalin treatment group correspond to a single pregabalin dose. Study 132 was terminated early due to a partial clinical hold placed by FDA. In Study 132, only two subjects received study medication for the entire double-blind treatment phase, and the rest were withdrawn prior to completing treatment.

Statistical Analysis:

In all five studies, the primary efficacy measure was the endpoint mean pain score, derived from a daily pain diary recorded by the patient using an 11-point numerical rating scale. Upon

awakening, the patient evaluated his/her pain for the previous 24 hours by circling the number of the scale that best described his/her pain. The scale ranged from 0 (no pain) to 10 (worst pain). The endpoint mean pain score was analyzed via an analysis of covariance model with treatment and cluster as fixed effects, and baseline mean pain score as covariate. Creatinine clearance strata were adjusted for in studies 127 and 196. The primary efficacy analysis included ITT patients who had one or more post-baseline pain scores. For patients who discontinued or did not complete the study, their endpoint mean score was based on the last set of pain scores they recorded (LOCF). Hochberg's method of adjustments for multiplicity was conducted.

The applicant also formulated numerous secondary variables, and conducted additional analyses on the primary efficacy variable. In consultation with Dr. Kashoki, the variable of focus in this review was the endpoint mean pain scores (at Week 8 and Week 13, if available) and the method of analysis was the analysis of covariance using baseline observation carried forward for early drop-outs, as well as the responder analysis.

Sponsor's Results and Conclusions:

In summary, of the five studies conducted by the applicant on post-herpetic neuralgia, the applicant claimed that three studies showed efficacy in patients treated with pregabalin (150, 300 and 300/600 mg/d [TID]; and 150, 300, and 300/600 mg/d [BID]) compared to placebo (Studies 045, 127 and 196). In addition, pregabalin-treated patients in the terminated study also showed efficacy compared to the placebo. A more detailed review of Sponsor's results and conclusions is provided in Section 2.

Table 1: Studies of Pregabalin in Patients with Post-herpetic Neuralgia

Study # [Regimen]	Design	No. of Primary Comparisons[d]	All Patients	Placebo	All PGB	Pregabalin group – by Dose (mg/day)			
						75	150	300	300/600 [a]
030 [TID]	5-week double-blind, placebo-controlled trial	2	255	88	167	84	83		
045 [TID]	8-week double-blind, placebo-controlled trial	2	238	81	157		81	76	
127 [TID]	8-week double-blind, parallel-group multicenter trial	1	173	84	89				89
132[b] [BID]	12-week double-blind, placebo-controlled trial	3	216[c]	52	164		51	62	51
196 [BID]	13-week double-blind, parallel-group multicenter trial	3	368	93	275		87	98	90
Total			**1250**	**398**	**852**	**84**	**302**	**236**	**230**

[a] Patients randomized to the 300/600 group received either 300 or 600 mg/day depending on their creatinine clearance (CLcr); Patients randomized to receive 300/600 mg/day will receive a dose of 300 mg/day if their estimated creatinine clearance (CLcr) is between 30 to 60 mL/min or a dose of 600 mg/day if their CLcr is greater than 60 mL/min

[b] PHN study that was terminated early due to partial clinical hold in the United States

[c] Only 2 patients out of 164 enrolled received study medication for the entire double-blind treatment phase.

[d] Hochberg procedure was used in studies with more than 1 primary comparison to protect the type 1 error rate at the 0.05 level

1.3 Statistical Issues and Findings

I conclude that treatment with pregabalin produces lower mean pain score at endpoint compared to placebo. A brief summary of the findings is displayed in Table 2. Furthermore, based on the responder analyses, when a less stringent definition of responders was used, pregabalin 150 mg/d was equally effective in treating patients with normal creatinine clearance as pregabalin 600 mg/d, but when more stringent criteria was used (>50% pain reduction) an additional benefit was seen at 600 mg/d. That is, patients appeared equally likely to have some response regardless of the dose, but higher doses tended to produce larger responses in more patients.

My conclusions were formulated after modification to the analysis conducted by the sponsor by stratifying treatment groups based on creatinine clearance in studies 45, 127 and 196, and by conducting in-depth analyses of treatment responders. These analyses were post-hoc; the purpose was to validate conclusions and to understand the treatment effects relative to creatinine clearance.

Table 2: Summary of Reviewer's Result for Studies 045, 127, and 196 using Analysis of Covariance on ITT Population (BOCF):

Study	Center	Dose	Duration (weeks)	Treatment group (mg/day)	ITT/Completed		Treatment Difference to Placebo	P-value	
					Placebo	PGB		Unadjusted	Hochberg's adjusted
45	Europe Australia	TID	8	150 [1]	81/61	42/36	-1.4		0.0003
				150 [2]		39/35	-0.8		0.0587
				300 [1]		45/30	-0.6		0.0587
				300 [2]		31/30	-1.7		0.0003
127	US	TID	8	300 [1]	84/74	30/17	-0.55	0.2346	
				600 [2]		59/41	-0.80	0.0302	
196	Europe Australia	BID	12	150 [1]	94/59	26/15	-0.43	0.3514	0.3514
				150 [2]		61/46	-1.07	0.0020	0.0080
				300 [1]		59/35	-0.81	0.0194	0.0582
				300 [2]		65/43	-0.65	0.0532	0.1064
				600 [2]		65/44	-1.47	<0.0001	0.0005

[1] low creatinine clearance
[2] normal creatinine clearance

2. INTRODUCTION

2.1 Overview

This is a review of the clinical data in patients with post-herpetic neuralgia as submitted in new drug application, NDA 21-446, serial number 000, for the use of pregabalin.

Pregabalin [CI-1008 or (S)-3-isobutyl GABA, (S)-(+)-3-(aminomethyl)-5-methylhexanoic acid] was developed primarily as an antiepileptic agent. However, the Applicant has found that pregabalin is effective in a variety of preclinical pain models of both neuropathic and nociceptive pain. According to the Applicant, the safety of pregabalin has been demonstrated in single- and multiple-dose studies in healthy adults.

Currently, the applicant, Pfizer Inc. is seeking FDA approval to market pregabalin capsules for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN), post-herpetic neuralgia (PHN), as adjunctive therapy for the treatment of partial seizures, and for generalized anxiety disorder. These were submitted as a single NDA but administratively split based on the indication; this review covers the treatment of post-herpetic neuralgia.

The focus of this statistical review is on the five clinical studies conducted in patients with post-herpetic neuralgia, and these are the following:

1.) Study 1008-030, a 5-week, double-blind, placebo-controlled TID trial of pregabalin (75 mg/d and 150 mg/day);
2.) Study 1008-045, an 8-week, double-blind, placebo-controlled TID trial of pregabalin (150 mg/d and 300 mg/day);
3.) Study 1008-127, an 8-week, double-blind, placebo-controlled TID trial of pregabalin (300 mg/d and 600 mg/day stratified by patient's creatinine clearance; and
4.) Study 1008-132, a 12-week, double-blind, placebo-controlled study of pregabalin twice a day (BID) (150 mg/d, 300 mg/d, or 300/600 mg/day stratified by patient's creatinine clearance;
5.) Study 1008-196, a 13-week, double-blind, placebo-controlled study of pregabalin twice a day (BID) (150 mg/d, 300 mg/d, or 300/600 mg/d).

2.2 Data Sources

This statistical review is based on data submitted in Studies 1008-030, 1008-045, 1008-127, 1008-132, 1008-196.

The electronic submission of this NDA can be found on the internal network drive of \\Cdsesub1\N21446\N_000\2003-10-30.

The clinical study report in for Studies 1008-030, 1008-045, 1008-127, 1008-132, 1008-196 is located at \\Cdsesub1\N21446\N_000\2003-10-30\clinstat.

The electronic datasets for all the studies are under \\Cdsesub1\N21446\N_000\2003-10-30\crt\datasets.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

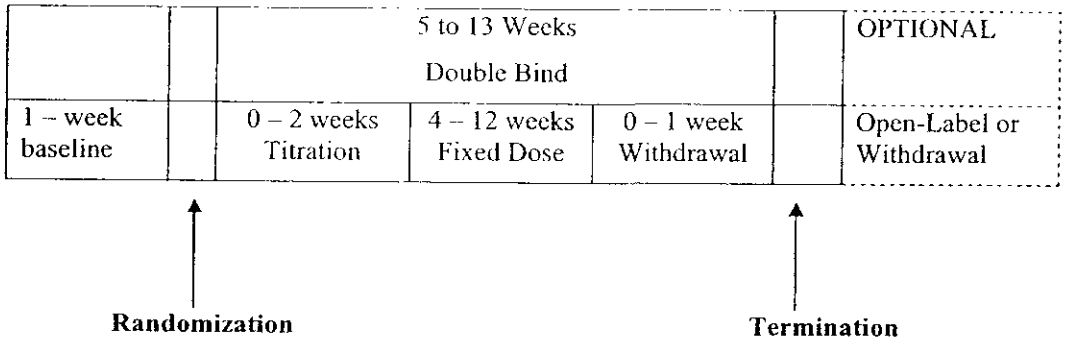
A total of five double-blind, placebo-controlled, multi-center studies of pregabalin in patients with postherpetic neuralgia were conducted in the United States (US), Europe, Australia, South Africa, and Canada (Table 1). In three studies, the patients were randomized to the 300/600 mg/d arm based on their creatinine clearance (CLcr). In other words, patients whose estimated creatinine clearance was between 30 and 60 mL/min received the 300 mg/d dose, while subjects with estimated creatinine clearance of at least 60 mL/min will receive 600 mg/d dose. Meanwhile the remaining two studies have a single pregabalin treatment group correspond to a single pregabalin dose. Study 132 was terminated early due to a partial clinical hold placed by FDA. In Study 132, only two subjects received study medication for the entire double-blind treatment phase, and the rest were withdrawn prior to completing treatment.

Study Design and Endpoints

The common design of the various studies is shown in Figure 1. All studies comprised 2 phases:

1. Baseline: a one-week phase during which patients were screened for eligibility to enter the double-blind phase; and
2. Double-Blind: a 5- to 13-week phase at the beginning of which patients were randomly assigned to pregabalin or placebo treatment. Except for Study 030, pregabalin doses were titrated over a period of 2 to 12 days; titration schedule varied from study to study. Patients remained at a fixed dose for the remainder of the double-blind phase (4 to 12 weeks).

Figure 1: Overall Study Design



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

Study Objective:

The overall study objective across all studies is to evaluate the safety and efficacy of pregabalin in doses of 75 mg/d, 150 mg/d, 300 mg/d, and 300/600 mg/d compared to placebo for the treatment of pain in patients with post-herpetic neuralgia.

Patient Population:

- Males or non-pregnant, non-lactating females of any race ≥ 18 years of age
- Must have completed at least four daily pain diary entries during baseline
- Must have a mean pain score of ≥ 4 over the 7-day baseline phase
- Must have 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)
- Must have pain at least three months after healing of a herpes zoster rash (six months in Study 045) and CLcr ≥ 30 mL/min
- Must have had a normal or stable chest x-ray within two years prior to the baseline visit.

Concomitant Medication:

Subjects were allowed to remain on a stable analgesic regimen (excluding concomitant anticonvulsants)

Efficacy Parameters

The primary efficacy variable was the endpoint mean pain score, derived from a daily pain diary recorded by the patient using an 11-point numerical rating scale. Upon awakening, the patient evaluated his/her pain for the previous 24 hours by circling the number of the scale that best described his/her pain. The scale ranged from 0 (no pain) to 10 (worst pain). The primary efficacy analysis includes ITT patients who had 1 or more post-baseline pain scores. For patients who discontinued or did not complete the study, their endpoint mean score was based on the last set of pain scores they recorded (LOCF).

Secondary Efficacy Analyses:

- Responder analysis (patients who had at least a 50% reduction from baseline in mean pain score at endpoint)
- Weekly analysis of pain scores
- Short Form McGill Pain Questionnaire (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
    - Euro QOL Health State Profile (EQ-5D)

Most of these secondary parameters were measured using patient self-assessment instruments. For the SF-MPQ, patients rated their pain intensity using Visual Analog Scale (VAS), present pain intensity (PPI), and pain descriptor scales. For all three scales, the highest number indicates worst pain.

Sample Size

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

Data Analysis Method

A brief overview of the statistical analyses used by the Applicant to assess the efficacy of pregabalin in the five clinical studies is presented in Table 3.

The following are the definition provided by the Applicant for the individual outcome measures collected in daily diaries:

- 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. Similar to the Baseline mean score, scores did not need to be recorded on consecutive days, and if fewer than 7 were recorded, the available scores were used to determine a mean

- 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, and so on.

- Change From Baseline: This is computed 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 $[(T - B)/B] \times 100 \leq -50$, where T represents the endpoint mean score and B represents baseline mean score.

The ITT population was the analysis population for all primary and secondary analyses for each study. The primary treatment group comparisons for each study are listed in Table 1.

As shown in Table 3, mean pain scores, SF-MPQ scores, mean sleep interference scores, SF-36 domains, and Quality of Life assessments were analyzed by the Applicant using an analysis of covariance (ANCOVA) main effects model, including treatment and center as factors and the corresponding baseline score as a covariate. In each case, adjusted (least squares) means were obtained from the model and 95% confidence intervals (CIs) on the difference in least-squares means between each pregabalin and placebo groups were constructed. For studies 127, 132 and 196, a dichotomous indicator variable for the CLcr stratum was also included in the every model. Language was included in the model for the SF-MPQ PPI for Study 045.

Also shown in Table 3, PGIC and CGIC data were analyzed using Cochran-Mantel-Haenszel (CMH) test with modified ridit scores, adjusting for center. The proportion of responders was analyzed using the CMH test with table scores, adjusting for center. As for the continuous outcome, a dichotomous variable for the CLcr stratum was also included in the responder analysis for Studies 127, 132, and 196.

Longitudinal (repeated measures) analysis of the weekly mean pain score was also conducted by the applicant. The observed values were analyzed using ANCOVA with treatment, center, CLcr strata (specifically for Studies 127, 132, and 196), baseline pain, and week as fixed effect terms in the model. The underlying covariance structure was estimated based upon maximizing Scharwtz' Bayesian Criterion.

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Table 3: Summary of Planned Efficacy Analyses

Analysis	Statistical Method	Comparison/Time Point	Population
Primary			
Endpoint Mean Pain Scores[a]	Analysis of Covariance (ANCOVA)	Each PGB dose vs. placebo/endpoint	ITT
Supplemental			
Responders[b]	Cochran-Mantel-Haenzel (CMH)	Each PGB dose vs. placebo/endpoint	ITT
Weekly Mean Pain Scores[c]	ANCOVA	Each PGC dose vs. placebo/each week	ITT-observed Cases
Secondary			
SF-MPQ			
Visual Analog Scale/Present Pain Intensity	ANCOVA	Each PGB dose vs. placebo/endpoint and specified time point	ITT
Pain Descriptors			
Sleep Interference	ANCOVA	Each PGB dose vs. placebo/endpoint and each week separately	ITT
PGIC/CGIC	CMH with modified ridit	Each PGB dose vs. placebo/termination	ITT
Quality of Life	ANCOVA	Each PGB dose vs. placebo/endpoint	ITT

[a] Mean of the last 7 daily 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

[b] Patients with 50% or greater reduction from baseline to endpoint mean pain scores. $\left[{}^{(T-B)}/_{B}\right] \times 100 \leq 50$, where T=Endpoint Mean pain score and B=baseline mean pain score;

Baseline mean pain score is defined as 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, available scores were used to determine the mean for all studies

[c] Mean of the diary entries for each week in the study. Since each diary entry reflected the previous 24-hour period. Week 1 mean was computed using all available entries from Days 2 to 8, etc

Applicant's Summary of Results of Individual Studies

Table 4 presents a summary of applicant's primary efficacy results from individual studies. Tables 5 and 6 present summaries of applicant's secondary efficacy results. Table 7 presents summary of adverse events from individual studies.

A. Study 032 - Failed Study

Efficacy:
The primary efficacy parameter was the endpoint mean pain score. No statistically significant differences were found in the comparison between the pregabalin and the placebo in either the primary efficacy outcome or any secondary efficacy measures (Tables 4 to 6). The endpoint mean pain scores (and standard deviations) for placebo, pregabalin 75 mg/d, and pregabalin 150 mg/d were 5.59 (0.21), 5.46 (0.21), and 5.52 (0.22), respectively.

Safety:
There was an increase in the number of subjects who experienced adverse events as the dosage increased: 52% placebo, 63% pregabalin 75, and 68% pregabalin 150 mg/d (Table 7). The most frequently reported adverse events among the pregabalin-treated patients at the 150 mg/d dose were dizziness, amblyopia, and somnolence. There were 6 out of 88 (7%) placebo patients who withdrew from the study due to adverse events, while only 2% in the pregabalin 75 mg/d and 6 % in the pregabalin 150 mg/d withdrew due to adverse events. Three pregabalin-treated patients and one placebo-treated patient withdrew due to serious adverse reactions. None of these were considered by the applicant to be related to the study drug. There were no deaths in this study.

B. Study 045

Efficacy:
The primary efficacy parameter was the endpoint mean pain score. Based on the applicant's report, there were improvements in the mean pain score in both pregabalin 150 mg/d and 300 mg/d compared to patients receiving placebo. The endpoint mean pain scores and standard deviations are: 6.33 (0.22) for placebo, 5.14 (0.22) for pregabalin 150mg/d and 4.76 (0.23) for pregabalin 300mg/d). These improvements (Table 4) were statistically significant. This was also evident when responder analysis, baseline-carried-forward analysis, and weekly mean pain analysis were used. Both pregabalin treatment groups also showed significant improvement in the SF-MPQ VAS scores as well as in sleep interference. In the SF-36 scales, there were significant improvements in mental health in both pregabalin150mg/d and pregabalin 300mg/d. Meanwhile significant improvements in bodily pain and vitality were found in subjects taking pregabalin 300mg/d compared to the placebo.

Safety:
There was an increase in the number of subjects who experienced adverse events as the dosage increased: 58% placebo, 65% pregabalin 150, and 83% pregabalin 300 mg/d (Table 7). The most frequently reported adverse events among the pregabalin-treated patients at the 150 and 300 mg/d dose were dizziness, somnolence and peripheral edema. Eight of 81 (10%) placebo patients withdrew from the study due to adverse events, while 11% in the pregabalin 150 mg/d and 16 % in the pregabalin 300 mg/d withdrew due to adverse events. Three pregabalin-treated patients and three placebo-treated patients withdrew due to serious adverse reactions. One placebo patient died during the study.

C. Study 127

Efficacy:
The primary efficacy parameter was the endpoint mean pain score. Based on the applicant's report, endpoint mean pain scores among pregabalin-treated patients were significantly different from those of patients taking placebo (Table 4). The result was consistent when baseline observation carried forward analysis and responder analysis were used. The applicant claimed improvement in the weekly mean pain score beginning at Week 1 and continuing through the study. There were also significant differences from placebo in secondary variables favoring the pregabalin-treated patients that included all subscales of SF-MPQ, mean sleep interference score at endpoint and at each week. There was also significant difference in bodily pain and general health perception domains of the SF-36 between the pregabalin-treated patients and patients taking placebo. The applicant also reported differences in CGIC and PGIC scales favoring pregabalin-treated patients.

Safety:
There was an increase in the number of subjects who experienced adverse events as the dosage increased: 63% placebo, 87% pregabalin 300/600 mg/d (Table 7).

D. Study 196

Efficacy:
The primary efficacy parameter was the endpoint mean pain score. Based on the applicant's report, there were improvements in the mean pain score in all three pregabalin- treated groups (150, 300 and 300/600 mg/d) compared to patients receiving placebo (Tables 4 to 6). These improvements were statistically significant. This was also evident when responder analysis, baseline-carried-forward analysis, and weekly mean pain analysis were used. Pregabalin 300 and 300/600 mg/d treatment groups showed significant improvement in the SF-MPQ VAS scores as well as in sleep interference. In the SF-36 scales, there were significant improvements in bodily pain scores in the pregabalin 300/600 mg/d compared to the placebo group.

Safety:
There was an increase in the number of subjects who experienced adverse events with increasing dose and the increase often occurred among the treated subjects compared to those treated with placebo (Table 7).

D. Study 132 – Terminated Study

Efficacy:
Because the study was terminated early, any conclusion from this study should be interpreted with caution. The primary efficacy parameter was the endpoint weekly mean pain score computed from a numerical pain rating scale collected in a daily pain diary. Based on the result described in Table 3, there were improvements in the mean pain score in all three pregabalin 150 mg/d, 300 mg/d and 300/600 mg/d treated groups compared to patients receiving placebo. No responder analysis, baseline-carried-forward analysis, and weekly mean pain analysis were conducted.

Safety:
There was an increase in the number of subjects who experienced adverse events as the dosage increases and this often occurred among the treated group than the placebo (Table 7).

In summary, of the five studies conducted by the applicant on post-herpetic neuralgia, the applicant claimed that three studies showed efficacy in patients treated with pregabalin [150, 300 mg/d and 300/600 mg/d at TID dosing per day; and 150, 300, and 300/600 mg/d at BID per day] compared to placebo (Studies 045, 127 and 196). In addition, pregabalin-treated patients in the terminated study also showed efficacy compared to the placebo. In the next section of this review, I will review and explore this claim. Upon consultation with Dr. Kashoki (medical reviewer), only the efficacy part of studies 45, 127, and 196 will be reviewed. This is because not only did study 030 fail to show efficacy, but also the duration of study was short (i.e. 5 weeks) compared to the other three studies. Study 173, which was terminated early, did not furnish any information requiring detailed review. In addition, it was determined that there were no safety issues in studies 45, 127, and 196 needing statistical evaluation.

Table 4: Summary of Applicant's Results for Studies 030, 045, 1127, 132, and 196:

Study	Center	Dose	Duration (weeks)	Treatment group (mg/day)	N		ITT/Completed		P-value		
					Placebo	PGB	Placebo	PGB	ANCOVA – ITT (LOCF)	ANCOVA –ITT (BOCF)	Responder Analysis
30	US	TID	5	75	87	83	88/79	84/79	0.6361		0.439
				150		82		83/76	0.7999		0.465
45	Europe Australia	TID	8	150	81	81	81/61	81/71	0.0002	0.0003	0.006
				300		76		76/60	0.0001	0.0004	0.003
127	US	TID	8	300/600	84	88	84/74	89/58	0.0001	0.0166	0.001
196	Europe Australia	BID	12	150	93	87	93/59	87/61	0.0077	0.0051	0.001
				300		98		98/62	0.0008	0.0201	0.001
				300/600		88		90/60	0.0001	0.0001	0.001
132*	US	BID	12	150	52	51	52/0	51/0	0.0015		
				300		62		62/2	0.0002		
				300/600		50		51/0	0.0001		

* PHN study that was terminated early due to partial clinical hold in the United States

Table 5: Summary of Applicant's Secondary Efficacy Results

Study	Treatment group (mg/day)	N		Unadjusted P-value					
		Placebo	PGB	VAS Scores	PPI Scores	Sensory Scores	Affective Scores	Total SF-MPQ	Sleep
30	75	87	83	0.7719	0.9372	0.5100	0.1446	0.3147	0.9212
	150		82	0.9869	0.5466	0.0322	0.3498	0.0524	0.0414
45	150	81	81	0.006	0.2372	NA	NA	NA	0.0003
	300		76	0.0003	0.2653				0.0001
127	300/600	84	88	0.0001	0.0127	0.0002	0.0047	0.0002	0.0001
196	150	93	87	0.0898	0.0612	NA	NA	NA	0.0007
	300		98	0.0144	0.0496				0.0001
	300/600		88	0.0001	0.0039				0.0001

Table 6: Summary of Statistically Significant SF-36 QOL Results

Study	Treatment group (mg/day)	N		Significance							
		Placebo	PGB	Physical	Role Limit	Social	Pain	Mental	Emotional	Vitality	General health
30	75	87	83								
	150		82								
45	150	81	81					*			
	300		76				*	*		*	
127	300/600	84	88				*				*
196	150	93	87								
	300		98								
	300/600		88				*				

* $p < 0.05$

Table 7: Summary of Adverse Events

Study No	Description	Placebo	Pregabalin total daily dose					
			75 mg/d	150 mg/d		300 mg/d		300/600 mg d
			TID	BID	TID	BID	TID	BID TID
030	Total Patients	88	84		83			
	No. (%) of Patients with AE All AE's	46 (52.3)	53 (63.1)		56 (67.5)			
	Associated AE's	22 (25.0)	27 (32.1)		34 (41.0)			
	No. (%) of Patients withdrawn due to AE							
	All AE's	6 (6.8)	2 (2.4)		5 (6.0)			
	Associated AE's	2 (2.3)	1 (1.2)		5 (6.0)			
	No. (%) of Patients withdrawn due to serious AE							
	All AE's	1 (1.1)	2 (2.4)		1 (1.2)			
	Associated AE's	0 (0.0)	0 (0.0)		0 (0.0)			
045	Total Patients	81			81		76	
	No. (%) of Patients with AE							
	All AE's	47 (58.0)			53 (65.4)		63 (82.9)	
	Associated AE's	32 (39.5)			41 (50.6)		51 (67.1)	
	No. (%) of Patients withdrawn due to AE							
	All AE's	8 (9.9)			9 (11.1)		12 (15.8)	
	Associated AE's	4 (4.9)			9 (11.1)		9 (11.8)	
	No. (%) of Patients withdrawn due to serious AE							
	All AE's	3 (3.7)			3 (3.7)		0 (0.0)	
	Associated AE's	1 (1.2)			3 (3.7)		0 (0.0)	

Table 7 (Continued)

Study No	Description	Placebo	Pregabalin total daily dose					
			75 mg/d	150 mg/d		300 mg/d		300/600 mg d
			TID	BID	TID	BID	TID	BID TID
127	Total Patients	84						89
	No. (%) of Patients with AE							
	All AE's	53 (63.1)						77 (86.5)
	Associated AE's	31 (36.9)						65 (73.0)
	No. (%) of Patients withdrawn due to AE							
	All AE's	4 (4.8)						28 (31.5)
	Associated AE's	2 (2.4)						24 (27.0)
	No. (%) of Patients withdrawn due to serious AE							
	All AE's	1 (1.2)						1 (1.1)
	Associated AE's	0 (0.0)						0 (0.0)
196	Total Patients	93		87		98		90
	No. (%) of Patients with AE							
	All AE's	53 (57.0)		60 (69.0)		70 (71.4)		76 (84.4)
	Associated AE's	37 (39.8)		52 (59.8)		63 (64.3)		67 (74.4)
	No. (%) of Patients withdrawn due to AE							
	All AE's	5 (5.4)		7 (8.0)		15 (15.3)		19 (21.1)
	Associated AE's	4 (4.3)		6 (6.9)		15 (15.3)		16 (17.8)
	No. (%) of Patients withdrawn due to serious AE							
	All AE's	0 (0.0)		0 (0.0)		1 (1.0)		2 (2.2)
	Associated AE's	0 (0.0)		0 (0.0)		1 (1.0)		1 (1.1)

Table 7 (Continued):

Study No	Description	Placebo	Pregabalin total daily dose					
			75 mg/d	150 mg/d		300 mg/d		300/600 mg/d
			TID	BID	TID	BID	TID	BID TID
132*	Total Patients	52		51		62		51
	No. (%) of Patients with AE							
	All AE's	28 (53.8)		33 (64.7)		45 (72.6)		41 (80.4)
	Associated AE's	18 (34.6)		28 (54.9)		37 (59.7)		33 (64.7)
	No. (%) of Patients withdrawn due to AE							
	All AE's	3 (5.8)		8 (15.7)		6 (9.7)		12 (23.5)
	Associated AE's	2 (3.8)		7 (13.7)		5 (8.1)		10 (19.6)
	No. (%) of Patients withdrawn due to serious AE **							
	All AE's	1 (1.9)		1 (2.0)		0 (0.0)		0 (0.0)
	Associated AE's	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)

* terminated early

** includes both TESS and non-TESS events

Detailed Review of Individual Studies

3.3.1 Study 1008-045

Study 1008-045 was a randomized, double-blind, placebo-controlled, parallel group, multi-center comparison of pregabalin 150 mg/d (50 mg TID), 300 mg/d (100 mg TID), and placebo for the treatment of adult patients with PHN. The study consisted of a one-week baseline phase and an 8-week double-blind treatment phase including a one-week titration period and a 7-week fixed dose period.

In order to detect a difference of 1.3 in endpoint weekly mean pain score between the placebo and pregabalin treatment with an overall standard deviation of 2.35, and assuming two-sided testing at the 0.025 level (to control for multiple comparison) and 90% power, a sample size of 240 (80 per treatment group) was proposed. The study was conducted at 53 sites, with most of sites having less than 18 patients. Therefore, these small centers were combined into clusters after the study was completed, but before the blind was broken. There were a total of 11 study clusters.

In this study, 55% of the participants were female, almost all were Caucasian (99%), and more than 80% were over 65 (mean 72, range 32 to 96). Of the 307 patients who entered the baseline phase, 238 participants completed the baseline phase and were randomized into the three treatment groups (placebo 81, PGB150 81, PGB300 76). Demographic and baseline characteristics did not differ among the three treatment groups. Most importantly, the baseline mean pain scores shown below among these groups are not different (Table 8).

Table 8: Summary of Baseline Mean Pain Score (Intent-to-treat population)

	Placebo	Pregabalin		All Patients
		150 mg/d	300 mg/d	
N	81	81	76	238
Mean (SD)	6.6 (1.6)	6.9 (1.7)	7.0 (1.6)	6.8 (1.6)
Median	6.7	7.1	7.0	7.0
Range	4.0 to 10.0	4.0 to 10.0	4.0 to 10.0	4.0 to 10.0

Source: Table 8 of Applicant's Report [RR 720-04356]

Of the 238 randomized patients, 33 (86%) had major protocol violations that warranted exclusion from the Per Protocol patient population (placebo 73, PGB150 67, PGB300 65). The primary reason for exclusion was the intake of prohibited medications or unstable concurrent medications (29 of 33 patients).

All of the 238 patients that were randomized took at least one dose of study medication (Table 9). A total of 192 (80%) patients completed the 8-week study. Among the 46 patients who withdrew from the study, 29 (63%) withdrew due to adverse events (placebo 8, PGB150 9, PGB300 12). Eight patients withdrew due to lack of efficacy. Seven of these eight patients were from the placebo group and only one from the PGB 300 group.

Table 9: Summary of Patient Disposition [Number (%) of Patients]

Disposition N.(%)	Placebo	Pregabalin		All Patients
		150 mg/day	300 mg/day	
Entered Baseline Phase				307[a]
Completed Baseline Phase				238 (77.5)
Withdrawn During Baseline Phase:				69 (22.5)
Did Not Meet Criteria				54 (17.6)
Other				15 (4.9)
Randomized	81	81	76	238
Intent-To-Treat	81	81	76	238
Completed Study	61 (75.3)	71 (87.7)	60 (78.9)	192 (80.7)
Withdrawn During Treatment Phase:	20 (24.7)	10 (12.3)	16 (21.1)	46 (19.3)
Adverse Event	8 (9.9)	9 (11.1)	12 (15.8)	29 (12.2)
Lack of Compliance	2 (2.5)	0 (0)	1 (1.3)	3 (1.3)
Lack of Efficacy	7 (8.6)	0 (0)	1 (1.3)	8 (3.4)
Other	3 (3.7)	1 (1.2)	2 (2.6)	6 (2.5)
Entered Open Label[b]	52 (64.2)	52 (64.2)	53 (69.7)	157 (66.0)

[a] Includes 2 patients that were re-screened.

[b] Number is taken from patient status at end of double-blind. Because of delay in approval of the open-label study by Ethics Committees and other factors, 3 patients listed here never took open-label study medication.

Source: Table 10 from Applicant's report [RR 720-04356]

The applicant's analysis of the primary efficacy variable using data from the ITT population showed that endpoint mean pain scores for both the pregabalin 150 mg/d group and the pregabalin 300 mg/d group were significantly different from the placebo group, while no difference was found between the pregabalin 300 mg/d group and the pregabalin 150 mg/d group (Table 10). The analysis imputed missing data using a last observation carried forward (LOCF) scheme, and employed analysis of covariance with treatment and cluster as fixed effects, and with the baseline mean pain score as covariate.

Table 10: Endpoint[a] Mean Pain Scores: Results of Analysis of Covariance (ITT Population)

Treatment	N	Least-Squares Means	SE	Treatment Comparisons (Pregabalin — Placebo)			
				Difference	95% CI	Unadjusted p-Value	Adjusted[b] p-Value
Placebo	81	6.33	0.22				
Pregabalin 150	81	5.14	0.22	-1.20	(-1.81, -0.58)	0.0002	0.0002
Pregabalin 300	76	4.76	0.23	-1.57	(-2.20, -0.95)	0.0001	0.0002
PGB 150 vs PGB 300	--	--	--	-0.38	(-1.00, 0.24)	0.2323	0.2323

SE = Standard error; CI = Confidence interval.

[a] Endpoint = Last 7 available scores while on study medication, up to and including day after last dose.

[b] Adjustment based on Hochberg's procedure for the 2 pairwise comparisons versus placebo.

Source: Table 12 from Applicant's report

Additional analyses were performed by the applicant demonstrating the generalizability of the results. These comprise repeating the analysis by including treatment-by-cluster interaction term; testing the assumption of parallel slopes by including treatment-by-baseline interaction; testing the assumption of normality; exclusion of protocol violators or analyzing using Per Protocol population; using baseline observation carried forward (BOCF) scheme for missing data; computing and comparing weekly mean pain scores; conducting responder analysis; and analysis of longitudinal data. All these analyses supported

the claim of efficacy of pregabalin 150 mg/d and pregabalin 300 mg/d TID dosing in the treatment of pain due to PHN.

To further understand the efficacy claim, upon consultation with Dr. Kashoki (medical reviewer) I carried out additional analyses including weekly responder analyses based on percent decrease in mean pain score from baseline. The percent decrease was classified in 10-percent increments. In these analyses, weekly mean pain score for patients who withdrew from the study regardless of the reason of withdrawal were given the baseline pain score, so that these patients were always classified as non-responders. Otherwise, weekly mean pain scores for all patients who completed the study are calculated based on the average pain scores per week defined as:

Week	Days
1	2 – 8
2	9 – 15
3	16 – 22
4	23 – 29
5	30 – 36
6	37 – 43
7	44 – 50
8	51 – 57

Table 11 presents the results from the analysis of covariance with weekly pain scores and endpoint pain scores as outcome variables. The analyses include treatment and cluster as fixed effects with baseline mean pain score as covariate. Although there was a significant difference between the pregabalin-treated groups and the placebo group at all time points, the difference in mean pain scores between the treatment groups was more pronounced after Week 1. At Week 1, there was only 0.6 of a point reduction in mean pain scores among the pregabalin-treated groups and the placebo group that could be attributed to treatment titration. Patients in the treated group began the fixed dose regimen only after Week 1.

Table 11: Least Square Mean Pain Score by Dose (BOCF) – ITT population

	Placebo N=81	PGB 150 N=81		PGB 300 N=76	
	mean (SD)	mean (SD)	P value[1]	Mean (SD)	P value[1]
Week 1	6.6 (0.1)	6.0 (0.1)	0.0034	6.1 (0.1)	0.0053
Week 2	6.5 (0.2)	5.7 (0.2)	0.0005	5.5 (0.2)	0.0002
Week 3	6.5 (0.2)	5.6 (0.2)	0.0001	5.6 (0.2)	0.0001
Week 4	6.5 (0.2)	5.6 (0.2)	0.0002	5.4 (0.2)	0.0002
Week 5	6.3 (0.2)	5.5 (0.2)	0.0015	5.3 (0.2)	0.0004
Week 6	6.4 (0.2)	5.5 (0.2)	0.0017	5.2 (0.2)	0.0002
Week 7	6.2 (0.2)	5.4 (0.2)	0.0038	5.3 (0.2)	0.0020
Week 8[2]	6.3 (0.2)	5.2 (0.2)	0.0005	5.2 (0.2)	0.0005
Endpoint[3]	6.3 (0.2)	5.2 (0.2)	0.0004	5.2 (0.2)	0.0004

[1] using Hochberg's test of difference from control (placebo)
[2] Week 8= baseline mean pain score for non-completers, and average of day 51 to day 57 pain scores for completers
[3] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose

Additional analyses were performed to assess the sensitivity of the weekly mean pain scores to different extrapolation techniques on missing observations within a given week for completers, as well as the imputation of weekly mean pain scores for non-completers. There were no important differences in the results between methods (Appendix I). In addition, the use of rescue medication and/or prohibited

medications was also examined. Based on the supplemental data provided by the sponsor on June 7, 2004, there are 20 out of 238 subjects that took prohibited medications (placebo 5, PGB150 10, PGB300 5). Meanwhile, 47 out of 238 subjects took rescue medication at least once (placebo 13, PGB150 19, PGB300 15). Of these 47 subjects, 39 took the rescue medication from beginning to the end of the study treatment, three subjects took rescue medication in the middle of the study to the end of the study period, three subjects took the rescue once or twice in the middle of study, and two of these took only during baseline period. All these 47 subjects' pain scores did not differ from the day before rescue were taken or the day after it was taken, so the rescue could not have affected the average pain scores much. Furthermore, only five out of these 47 subjects dropped out due to adverse event, and all these five took rescue medication from the beginning of the study to the end of the study period (or to the day they dropped-out). No additional analyses were conducted using rescue medication.

Based on the analysis of endpoint mean pain score and the analysis of week 8 mean pain score, there is a significant difference between the pregabalin treated-groups and the placebo (Table 10). Furthermore, comparing the change from baseline mean pain score to endpoint mean pain score between the pregabalin-treated groups and the placebo showed significant difference in pain reduction. There is at least 1.6 points reduction in pain among the pregabalin 150 and pregabalin 300 groups compared to only 0.5 of a point reduction among the patients in the placebo group (Table 12). The same conclusion was reached when week 8 pain scores were used instead of the endpoint mean pain scores.

Table 12: Change in Mean Pain Scores: Results of Analysis of Covariance

	Placebo	Pregabalin 150	Pregabalin 300
Baseline[1]	6.64 (1.6)	6.93 (1.7)	6.98 (1.6)
Endpoint[2]	6.15 (2.1)	5.31 (2.5)	5.34 (2.6)
Change[3]	0.50 (1.5)	1.63 (2.0)	1.64 (2.3)
lsmeans	0.53 (0.2)	1.65 (0.2)	1.64 (0.2)
p-value[4]		0.0004	0.0004
Week 8[5]	6.14 (2.2)	5.28 (2.5)	5.32 (2.6)
Change[6]	0.51 (1.5)	1.63 (2.01)	1.66 (2.4)
lsmeans	0.54 (0.2)	1.65 (0.2)	1.66 (0.2)
p-value[4]		0.0005	0.0005

[1] Baseline = Last 7 available scores before taking study medication, up to and including Day 1
[2] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose
[3] Change= Baseline – Endpoint
[4] using Hochberg's test of difference from control (placebo)
[5] Week 8= baseline mean pain score for non-completers, and average of day 51 to day 57 pain scores for completers
[6] Change= Baseline – Week 8

Using the definition of weekly mean pain scores outlined above (i.e. assigning baseline pain scores to non-completers), responders based on the percent pain reduction were identified. Figure 2 presents the proportion of responders with 10% – 80% pain reduction in their mean pain score by treatment groups over the 8-week period. Using the definition provided by the applicant for the endpoint proportion of responders, (i.e. percent of patients who had a 50% or greater reduction in mean pain score from baseline to endpoint) there was difference between pregabalin-treated groups and the placebo, favoring the pregabalin-treated patients (Figure 2). The graph (at 50% pain reduction) also showed no difference in treatment effect between pregabalin 150 mg/d and pregabalin 300 mg/d. Based on this graph alone, it seemed that dosage of pregabalin 150 mg/d would be adequate to achieve efficacy. However, upon careful examination of the other graphs using a different definition of responder (based on different percent pain reduction), there is evidence suggesting some benefit in pain reduction among those subjects in the pregabalin 300 mg/d over those subjects taking pregabalin 150 mg/d dosage, particularly for more stringent definitions of responder (pain reduction over 50%).

Figure 2: Percent Mean Pain Reduction

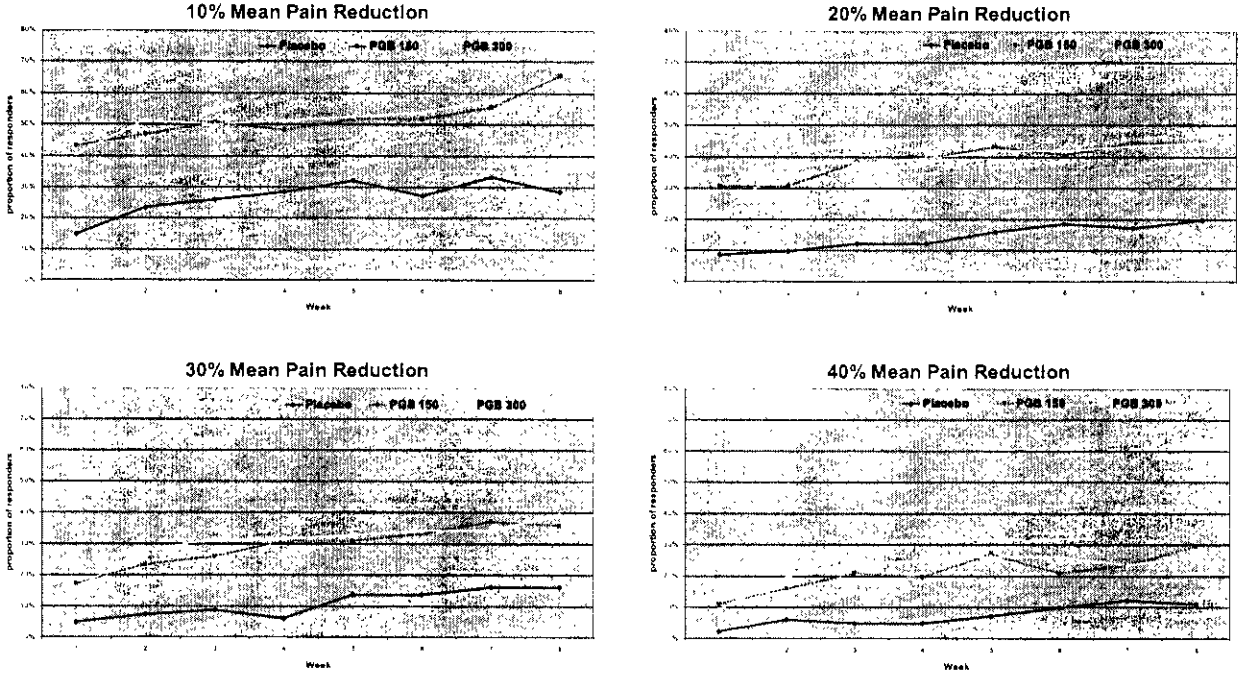
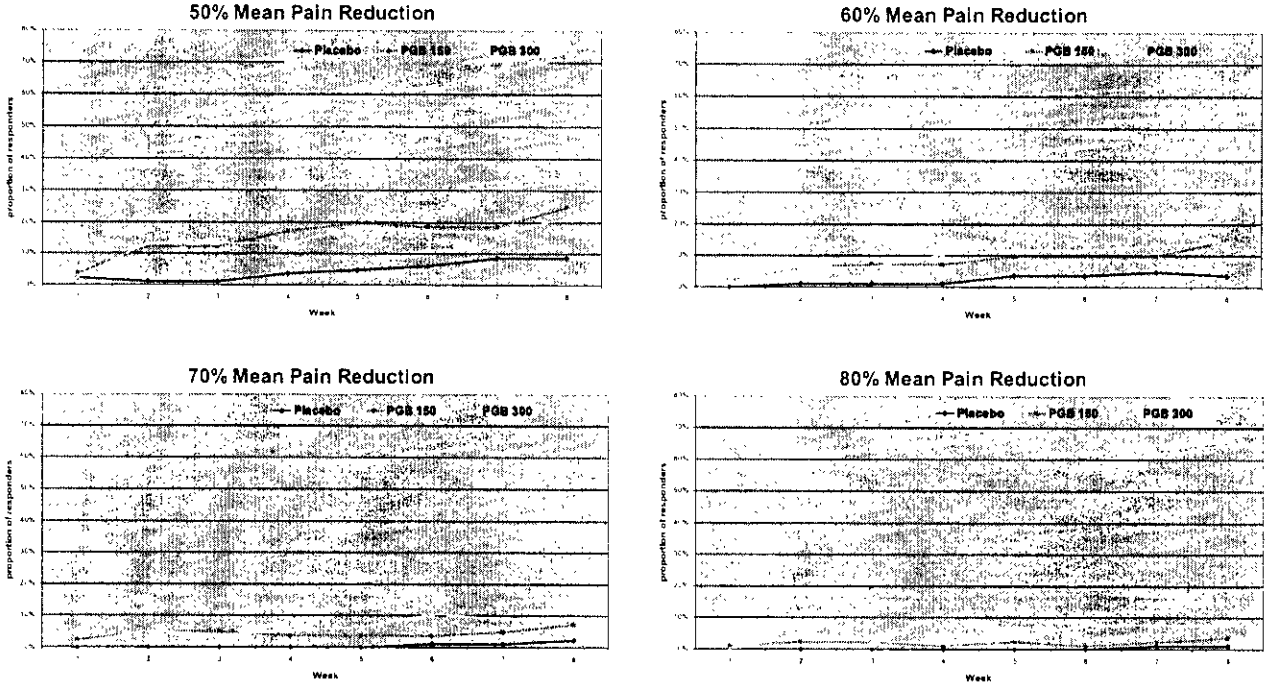
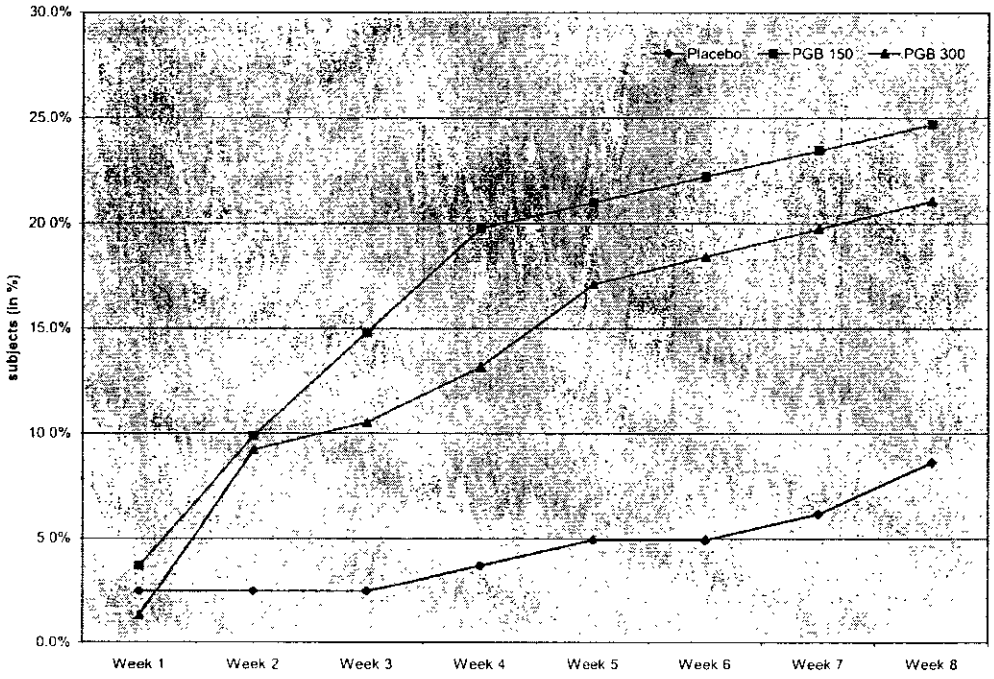


Figure 2 (Continued)



There were a total of 43 subjects (completer) who had 50% mean pain reduction at the end of the study. Figure 3 displays the distribution of these patients from the beginning of the study (week 1) to the end of the study (week 8). The graph shows an increasing trend of responders. This suggests that patient who did not respond at week 1 has a potential to respond until week 4 in the pregabalin-treated 150mg/d group, and patient in the pregabalin 300 mg/d group has a chance to respond until week 5; after which the chance slowly diminishes. Meanwhile, patients in the placebo group did not show any trend.

Figure 3: Proportion of Responders by Week



For a single time point the information in Figure 2 can be summarized in a single graph. Figure 4 shows the proportions of responders at endpoint for all the various definitions of responder considered. A higher proportion of subjects in the pregabalin-treated groups were treatment responders compared to the placebo-treated group (Table 13 and Figure 4). There was also a small difference in the proportion of responders between the pregabalin 150 mg/d group and pregabalin 300 mg/d group. The difference slightly favored the 150 mg/d group when less stringent definitions of responder were used (less than 30% reduction), and the difference slightly favored the 300 mg/d group when more stringent definitions of responder were used (30 – 60%).

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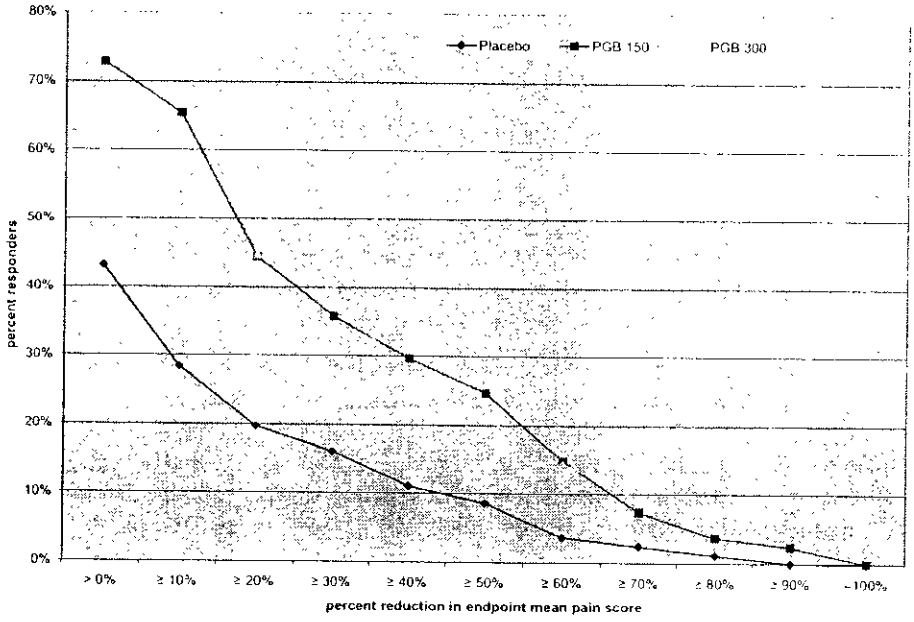
Table 13: Percentage change in endpoint mean pain score by dose (BOCF) ITT population

	TOTAL		PLACEBO		PGB150		PGB300	
	Total	%	Total	%	Total	%	Total	%
Any increase	39	16%	19	23%	11	14%	9	12%
None	59	25%	27	33%	11	14%	21	28%
> 0 % decrease	140	59%	35	43%	59	73%	46	61%
≥ 10%	115	48%	23	28%	53	65%	39	51%
≥ 20%	86	36%	16	20%	36	44%	34	45%
≥ 30%	72	30%	13	16%	29	36%	30	39%
≥ 40%	53	22%	9	11%	24	30%	20	26%
≥ 50%	**43**	**18%**	**7**	**9%**	**20**	**25%**	**16**	**21%**
≥ 60%	26	11%	3	4%	12	15%	11	14%
≥ 70%	15	6%	2	2%	6	7%	7	9%
≥ 80%	10	4%	1	1%	3	4%	6	8%
≥ 90%	6	3%	0	0%	2	2%	4	5%
=100%	1	0%	0	0%	0	0%	1	1%

Figure 4: Response Profile at Endpoint



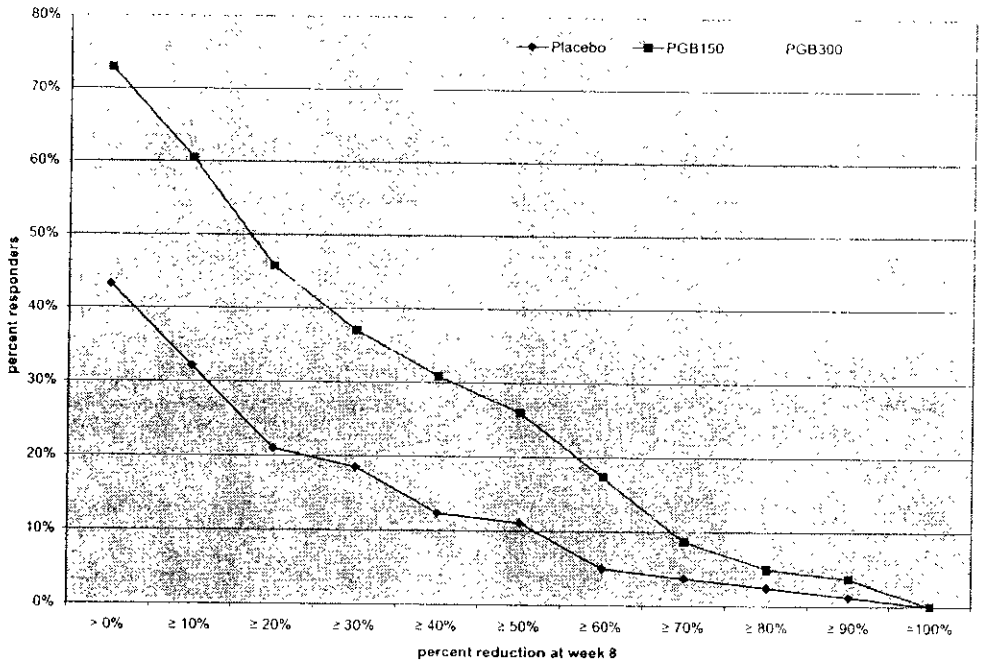
Upon the request of Dr. Kashoki, response profile at Week 8 was also calculated. Week 8 is defined as the average of day 51 to day 57 pain scores for the completers and baseline mean pain score for the non-completers. Based on Week 8 pain score, a higher proportion of subjects in the pregabalin-treated groups were treatment responders compared to the placebo-treated group (Table 14 and Figure 5). There was also a small difference in the proportion of responders between the pregabalin 150 mg/d group and pregabalin 300 mg/d group. The difference slightly favored the 150 mg/d group when less stringent definitions of responder were used (less than 30% reduction), and the difference slightly favors the 300 mg/d group when more stringent definitions of responder were used (40 – 60%). There was only a very slight difference between the percent responders when endpoint mean pain scores or week 8 mean pain scores

are used. The small difference could be due to the fact that of the 192 patients who completed the study, 70 patients completed earlier than Day 56, resulting in exposure to study medication of less than 8 weeks.

Table 14: Percentage change in Week 8 mean pain score by dose (BOCF) - ITT population

	TOTAL		PLACEBO		PGB150		PGB300	
	Total	%	Total	%	Total	%	Total	%
Any increase	39	16%	20	25%	10	12%	9	12%
None	60	25%	26	32%	12	15%	22	29%
> 0 % decrease	139	58%	35	43%	59	73%	45	59%
≥ 10%	113	47%	26	32%	49	60%	38	50%
≥ 20%	88	37%	17	21%	37	46%	34	45%
≥ 30%	75	32%	15	19%	30	37%	30	39%
≥ 40%	56	24%	10	12%	25	31%	21	28%
≥ 50%	**45**	**19%**	**9**	**11%**	**21**	**26%**	**15**	**20%**
≥ 60%	29	12%	4	5%	14	17%	11	14%
≥ 70%	18	8%	3	4%	7	9%	8	11%
≥ 80%	12	5%	2	2%	4	5%	6	8%
≥ 90%	8	3%	1	1%	3	4%	4	5%
=100%	2	1%	0	0%	0	0%	2	3%

Figure 5: Response Profile at Week 8



Additional analyses were performed as per request by Dr. Winchell and Dr. Kashoki. These are done by re-assignment treatment groups based on patients' baseline creatinine clearance. The results are presented in Appendix II. Furthermore, statistical tests were conducted in the percentage change at endpoint and on Week 8 by dose (Tables 13 and 14), and the results are presented in Appendix III.

3.3.2 Study 1008-127

Study 1008-127 was a randomized, double-blind, placebo-controlled, parallel-group, multi-center comparison of pregabalin to placebo for the treatment of adult patients with PHN. The study consisted of a one-week baseline phase followed by an 8-week double-blind treatment phase comprising one week of titration and a 7-week fixed dose period. Randomization was stratified by the creatinine clearance (CLcr) of each patient. The pregabalin dose was 600 mg/d (200 mg TID) for patients with CLcr above 60 mL/min (normal creatinine clearance) and 300 mg/d (100 mg TID) for patients with CLcr between 30 and 60 mL/min (low creatinine clearance). According to the applicant, pharmacokinetic modeling of data from previous pregabalin pain protocols indicated that a dose of 300 mg/d in patients with low creatinine clearance is equivalent with respect to steady-state concentrations to a dose of 600 mg/d in patients with normal creatinine clearance. The study was therefore designed and analyzed to test the efficacy of a treatment regimen with dose based on creatinine clearance. Nevertheless, in consultation with Dr. Kashoki (medical reviewer), I consider it worthwhile to explore the claim of equal effects of the different doses in the two strata.

In order to detect a difference of 1.3 in endpoint weekly mean pain score between the placebo and pregabalin treatment with an overall standard deviation of 2.35, and assuming two-sided testing at the 0.05 level and 90% power, a sample size of 152 (76 per treatment group) was proposed. The study was conducted at 25 sites, with most of sites having less than 18 patients. Therefore, these small centers were combined into clusters after the study was completed, but before the blind was broken. There were a total of 18 study clusters.

In this study, 53% of the participants were female, almost all were Caucasian (95%), and more than 80% were over 65 (mean 72, range 31 to 100). Of the 245 patients who entered the baseline phase, 173 participants completed the baseline phase and were randomized into two treatment groups (placebo 84, PGB300/600 89). Demographic and baseline characteristics did not differ between the two treatment groups. Most importantly, the baseline mean pain scores shown below between these two are not different (Table 15).

Table 15: Mean Pain Scores: Descriptive Statistics (Study 127)

Time point	Placebo			Pregabalin		
	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max
Baseline[a]	84	6.4 (1.5)	4, 10	89	6.3 (1.4)	3.7, 9.1
Endpoint[b]	84	5.3 (2.6)	0, 10	88	3.6 (2.3)	0, 9.6
Change[c]	84	-1.1 (2.0)	-6.6, 3.9	88	-2.7 (2.1)	-7.3, 2.4

SD = Standard deviation.

[a] Baseline = Last 7 available scores before taking study medication, up to and including Day 1.

[b] Endpoint = Last 7 available scores while on study medication, up to and including day after last dose.

[c] Change is from baseline to endpoint

Source: Table 11 of Applicant's Report [RR 720-04457]

Of the 89 randomized subjects in the PGB 300/600 group, 30 subjects had low creatinine clearance and 59 subjects had normal creatinine clearance (Table 16). Because the sample size calculation was based on two-sample analysis at the 0.05 level, the number of subjects in the study may not be sufficient to detect a treatment difference from placebo in the two pregabalin-treated groups separately. Assuming two-sided testing at the 0.025 level (to control for multiple comparisons), a sample size of 240 (80 per treatment group) would have been needed to achieve 90% power. Nonetheless, these separate analyses are important to explore the efficacy of pregabalin based on patient's creatinine clearance.

Table 16: Summary of Baseline Mean Pain Score (Intent-to-treat population)

	Placebo	Pregabalin		All Patients
		300 mg/d	600 mg/d	
N	84	30	59	173
Mean (SD)	6.43 (1.51)	6.60 (1.41)	6.13 (1.44)	6.36 (1.48)
Median	6.43	6.43	6.14	6.29
Range	[redacted]			

Of the 173 randomized patients, 36 patients (21%) had major protocol violations that warranted exclusion from the Per Protocol patient population (Placebo 66, PGB300 25, and PGB600 48). Patient disposition is summarized in Table 17. All patients took at least one dose of study medication. A total of 132 (76%) patients completed the 8-week study. Of the 41 patients who withdrew from the study, 32 (78%) withdrew due to adverse events (Placebo 4, PGB300 11, PGB600 17). Six patients, all from the placebo group, withdrew due to lack of efficacy. The remaining three patients withdrew either due to lack of compliance or withdrawal of consent.

Table 17: Summary of Patient Disposition [Number (%) of Patients]

Disposition N,(%)	Treatment Group		
	Placebo	Pregabalin	All Patients
Entered Baseline Phase			245
Completed Baseline Phase			173 (70.6)
Withdrawn During Baseline Phase:			72 (29.4)
Did not meet criteria			57 (23.3)
Other			2 (0.8)
Patient withdrew consent			13 (5.3)
Randomized	84	89	173
Intent-to-Treat	84	89	173
Completed Study	74 (88.1)	58 (65.2)	132 (76.3)
Withdrawn During Treatment Phase:	10 (11.9)	31 (34.8)	41 (23.7)
Adverse Event	4 (4.8)	28 (31.5)	32 (18.5)
Lack of Compliance	0 (0)	2 (2.2)	2 (1.2)
Lack of Efficacy	6 (7.1)	0 (0)	6 (3.5)
Patient withdraws consent	0 (0)	1 (1.1)	1 (0.6)
Entered Open Label Treatment	63 (75.0)	62 (69.7)	125 (72.3)

[a] Those who withdrew early from the study could elect to enter open-label treatment.

Source: Table 10 from Applicant's report [RR 720-04457]

The applicant's analysis of the primary efficacy variable (i.e. endpoint mean pain scores) using data from the ITT population showed that the pregabalin-treated group was significantly different from the placebo group (Tables 18A and 18B). Missing data were imputed using a last observation carried forward (LOCF) scheme (Table 18A) and a baseline observation carried forward (BOCF) scheme (Table 18B). The table was generated based on an analysis of covariance with treatment and cluster as fixed effects and with the baseline mean pain score as a covariate.

Table 18A: Endpoint[a] Mean Pain Scores: Results of Analysis of Covariance (ITT Population) - LOCF method

Treatment	N	Least Squares Mean	SE	Treatment Comparisons (Pregabalin—Placebo) Difference	95% CI	p-value
Placebo	84	5.29	0.24			
Pregabalin	88	3.60	0.24	-1.69	(-2.33, -1.05)	0.0001

SE = Standard error; CI = Confidence interval

[a] Endpoint = Last 7 available scores while on study medication (if less than 7 then whatever scores are available).

Source: Table 12 from Applicant's report

Table 18B: Endpoint Mean Pain scores: Analysis of Covariance (BOCF)

Treatment	N	Least Squares Means	SE	Treatment Comparisons (Pregabalin – Placebo) Difference	95% CI	p-Value
Placebo	84	5.15	0.23			
Pregabalin	88	4.36	0.24	-0.79	(-1.44, -0.15)	0.0166

SE = Standard error; CI = Confidence interval

[a] Endpoint = Last 7 available scores while on study medication, up to and including day after last dose.

Source: Appendix D.3 from Applicant's report

Additional analyses were performed by the applicant to explore the sensitivity of the results by repeating the analyses and testing for treatment-by-cluster interaction; by testing the assumption of parallel slopes using treatment-by-baseline interaction; testing the assumption of normality; exclusion of protocol violators or analyzing using Per Protocol population; computing and comparing weekly mean pain scores; conducting responder analysis; and analysis of longitudinal data. All these analyses supported the claim of efficacy of pregabalin 300/600 mg/d (100/200 mg TID) dosing in the treatment of pain due to PHN.

To further understand the efficacy claim, upon consultation with Dr. Kashoki, I carried out additional analyses including endpoint mean pain score analysis on each pregabalin-treated group (PGB 300 and PGB 600). Weekly responder analyses based on percent decrease in mean pain score from baseline were also conducted. The percent decrease was classified in 10-percent increments. In these analyses, weekly mean pain score for patients who withdrew from the study regardless of the reason were given the baseline pain score, so that these patients were always classified as non-responders. Otherwise, weekly mean pain scores for all patients who completed the study are calculated based on the average pain scores per week defined as:

Week	Days
1	2 – 8
2	9 – 15
3	16 – 22
4	23 – 29
5	30 – 36
6	37 – 43
7	44 – 50
8	51 – 57

Table 19: Endpoint[1] Mean Pain Scores: Results of Analysis of Covariance[2] on ITT population using BOCF

Treatment	N	Baseline Mean	Least-Squares Mean	SE	Treatment Comparisons (Pregabalin – Placebo)	
					Differences	p-value
Placebo	84	6.43	5.22	0.24		
Pregabalin 300/600	89	6.29	4.42	0.23	-0.8	0.0137

[1] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline pain score for non-completers

[2] Analysis include treatment, center, and creatinine clearance strata as fixed effects, with baseline mean pain score as covariate, and the interaction between baseline pain score and treatment.

Table 20: Endpoint[1] Mean Pain Scores: Results of Analysis of Covariance on ITT population using New Treatment Assignment (BOCF)

Treatment	N	Baseline Mean	Least-Squares Mean	SE	Treatment Comparisons (Pregabalin – Placebo)	
					Differences	p-value[2]
Placebo	84	6.43	5.16	0.23		
PGB 300	30	6.60	4.61	0.39	-0.55	0.2346
PGB 600	59	6.13	4.36	0.29	-0.80	0.0302
PGB 300 vs. PGB 600					-0.25	0.6084

[1] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline pain score for non-completers

[2] using pair-wise comparison test

Tables 19 and 20 present the results from the analysis of covariance with endpoint mean pain scores as outcome variables. The analyses include treatment and cluster as fixed effects, with baseline mean pain score as covariate, and the interaction between baseline pain score and treatment. Table 19 showed a significant difference between pregabalin 300/600 and placebo using the BOCF method, similar to the result provided by the applicant. However, when pregabalin 300/600 patients were stratified into two groups based on creatinine clearance, there was a significant difference only between the pregabalin 600 and the placebo ($p = 0.03$ using pairwise comparison test). Pregabalin 300 showed no significant difference from the placebo at the 0.05 level. Again, this study was not designed to compare the separate strata to the placebo. Nevertheless, quantitatively, a greater benefit in pregabalin 600 mg/d among normal creatinine clearance patients than those in pregabalin 300 mg/d with low creatinine clearance, suggesting that a dose of 300 mg/d in patients with low creatinine clearance may not be equivalent to a dose of 600 mg/d in patients with normal creatinine clearance as claimed by the applicant. This claim will be explored further using weekly responder analyses and in Study 196.

Tables 21 and 22 display results from the analysis of covariance with weekly mean pain scores and endpoint mean pain scores as outcome variables. The analyses include treatment, cluster and creatinine clearance strata (for Table 21 only) as fixed effects and the baseline mean pain score as a covariate. An interaction term (treatment by baseline score) was included in the analyses. Overall, patients taking pregabalin 300/600mg/d had significantly lower weekly mean pain score compared to the placebo (Table 21). When the pregabalin-group was stratified, patients in the pregabalin 600 mg/d had lower weekly mean pain score than pregabalin 300 mg/d and the placebo after week 1 (Table 22). Although the evidence for an effect of pregabalin 300/600mg/d was compelling (Table 21), the comparisons between

the strata (Table 22) may not be reliable due to lack of power, particularly in the pregabalin 300 mg/d group.

Table 21: Least Square Mean Pain Score by Dose (BOCF) – ITT population

	Placebo N=84	PGB 300/600 N=89	
	Mean (SD)	Mean (SD)	P value
Week 1	5.96 (0.1)	5.25 (0.1)	0.0002
Week 2	5.77 (0.2)	4.74 (0.2)	<0.0001
Week 3	5.61 (0.2)	4.57 (0.2)	0.0001
Week 4	5.62 (0.2)	4.68 (0.2)	0.0007
Week 5	5.46 (0.2)	4.54 (0.2)	0.0026
Week 6	5.50 (0.2)	4.52 (0.2)	0.0009
Week 7	5.42 (0.2)	4.50 (0.2)	0.0041
Week 8[1]	5.16 (0.2)	4.40 (0.2)	0.0224
Endpoint[2]	5.22 (0.2)	4.42 (0.2)	0.0137

[1] Week 8= baseline mean pain score for non-completers, and average of day 51 to day 57 pain scores for completers
[2] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline pain score for non-completers

Table 22: Least Square Mean Pain Score by Dose (BOCF) using New Treatment Assignment – ITT population

	Placebo N=84	PGB 300 N=30		PGB 600 N=59	
	Mean (SD)	mean (SD)	P value[1]	mean (SD)	P value[1]
Week 1	5.94 (0.1)	5.26 (0.2)	0.0121	5.27 (0.2)	0.0019
Week 2	5.71 (0.2)	5.00 (0.3)	0.0306	4.56 (0.2)	<0.0001
Week 3	5.54 (0.2)	4.91 (0.3)	0.0999	4.34 (0.2)	<0.0001
Week 4	5.54 (0.2)	4.93 (0.3)	0.1126	4.55 (0.2)	0.0013
Week 5	5.41 (0.2)	4.71 (0.4)	0.1007	4.48 (0.3)	0.0066
Week 6	5.41 (0.2)	4.78 (0.4)	0.1229	4.39 (0.3)	0.0019
Week 7	5.34 (0.2)	4.75 (0.4)	0.1769	4.41 (0.3)	0.0087
Week 8[2]	5.08 (0.2)	4.62 (0.4)	0.3334	4.28 (0.3)	0.0333
Endpoint[3]	5.14 (0.2)	4.61 (0.4)	0.2346	4.36 (0.3)	0.0302

[1] using pair-wise comparison test
[2] Week 8= baseline mean pain score for non-completers, and average of day 51 to day 57 pain scores for completers
[3] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline pain score for non-completers

Additional analyses were performed to assess the sensitivity of the weekly mean pain scores to different extrapolation techniques on missing observations within a given week for completers, as well as the imputation of weekly mean pain scores for non-completers. There were no important differences in the results between methods. In addition, the use of rescue medication and/or prohibited medications was also examined. Based on the supplemental data provided by the sponsor on June 7, 2004, only one (in the placebo group) of the 173 subjects randomized took prohibited medications. Meanwhile, 26 of 173 subjects took rescue medication at least once (placebo 14, PGB300 4, PGB600 8). Of these 26 subjects, 21 took the rescue medication from beginning to the end of the study treatment, three subjects took rescue medication from the middle of the study to the end of the study period, only one subject took the rescue once or twice in the middle of study, and only one subject took the rescue only during the baseline period. All these 26 subjects' pain scores did not differ from the day before rescue were taken or the day after it was taken, so the rescue could not have affected the average pain scores much. Furthermore, only three out of these 26 subjects dropped out due to an adverse event and two of these three subjects two rescue

medication from the beginning of the study to the end of the study period (or to the day they dropped out). Also, only three out of the 26 subjects dropped out due to lack of efficacy, and these subjects took rescue from the beginning of the study to the day they dropped out. Therefore, no additional analyses were conducted using rescue medication.

The analysis of endpoint mean pain score and the analysis of week 8 mean pain score showed statistically significant difference between the pregabalin treated-group and the placebo (Tables 21), and when the pregabalin group was stratified based on creatinine clearance, pregabalin 600mg/d showed significant difference compared to the placebo (Table 22). The conclusion is similar when change from baseline mean pain score is used instead (Table 23). Quantitatively, the pregabalin 600 group showed a more favorable pain reduction score than the pregabalin 300 group.

Table 23: Change in Mean Pain Scores: Results of Analysis of Covariance[1]

	Placebo	Pregabalin 300/600	Pregabalin 300	Pregabalin 600
Baseline[2]	6.43 (1.5)	6.29 (1.4)	6.60 (1.4)	6.13 (1.4)
Endpoint[3]	5.25 (2.5)	4.42 (2.4)	4.76 (2.4)	4.24 (2.4)
Change[4]	1.18 (1.9)	1.87 (2.2)	1.84 (2.6)	1.89 (2.1)
lsmeans	1.21 (0.2)	1.93	1.75 (0.4)	2.00 (0.3)
p-value[5]		0.0137	0.2346	0.0302
Week 8[6]	5.20 (2.6)	4.42 (2.4)	4.85 (2.5)	4.21 (2.4)
Change[7]	1.25 (1.9)	1.85 (2.2)	1.74 (2.6)	1.90 (2.1)
lsmeans	1.28 (0.2)	1.96	1.73 (0.4)	2.07 (0.3)
p-value[5]		0.0224	0.3334	0.0333

[1] Analysis include treatment, center, and creatinine clearance strata (for pregabalin 300/600 only group) as fixed effects, with baseline mean pain score as covariate, and the interaction between baseline pain score and treatment.
[2] Baseline = Last 7 available scores before taking study medication, up to and including Day 1
[3] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline pain score for non-completers
[4] Change= Baseline – Endpoint
[5] using Dunnett's test of difference from control (placebo)
[6] Week 8= baseline mean pain score for non-completers, and average of day 51 to day 57 pain scores for completers
[7] Change= Baseline – Week 8

Using the definition of weekly mean pain scores outlined above (i.e. assigning baseline pain scores to non-completers), responders based on the percent pain reduction were identified. Figure 6 presents the proportion of responders with 10% – 80% pain reduction in their mean pain score by treatment group over the 8-week period. Using the definition provided by the applicant for the endpoint proportion of responders, (i.e. percent of patients who had a 50% or greater reduction in mean pain score from baseline to endpoint) there was difference between pregabalin-treated groups and the placebo. The graph also showed a greater benefit in pregabalin 600 mg/d among normal creatinine clearance patients than those in pregabalin 300 mg/d with low creatinine clearance, particularly at the beginning of the dose period. Furthermore, when different definitions of responder (based on different percent pain reduction) were used, there was compelling evidence suggesting treatment benefit in pain reduction among those subjects with normal creatinine clearance taking pregabalin 600 mg/d over those subjects with low creatinine clearance taking pregabalin 300mg/d dosage particularly for less stringent definitions of responder (pain reduction less than 50%). Only when the percentage of pain reduction was higher than 50% then the conclusion is uncertain. For more stringent definitions of responder, the difference between strata was less pronounced and appeared mainly in the beginning of the treatment period.

Figure 6: Percent Mean Pain Reduction

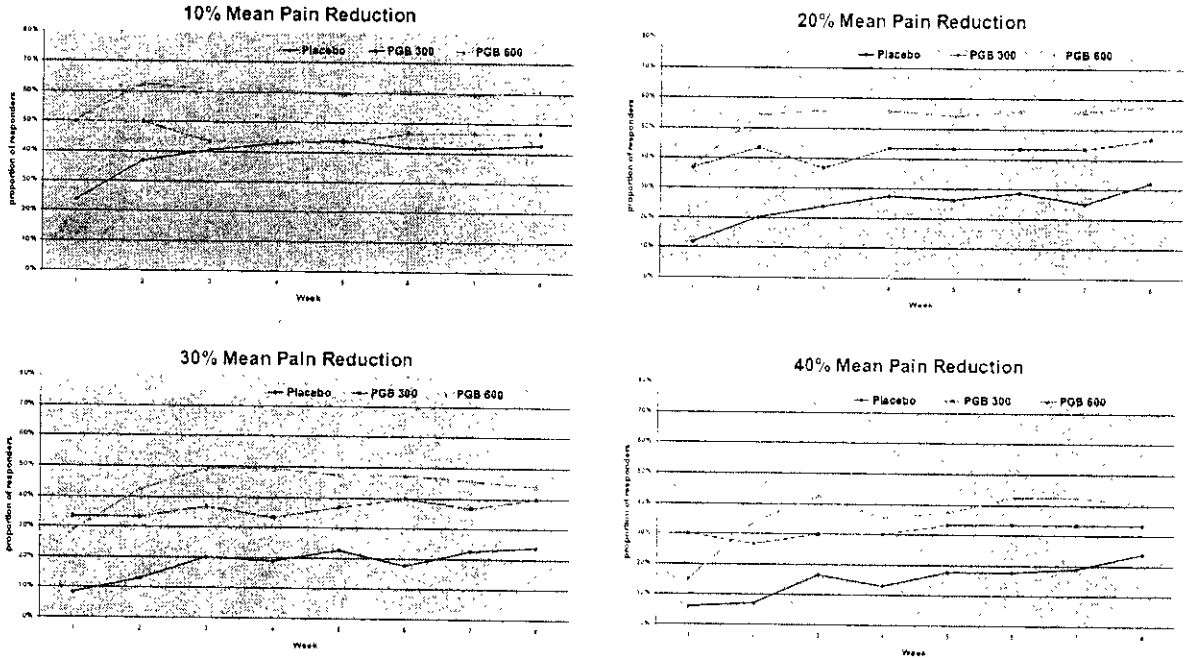
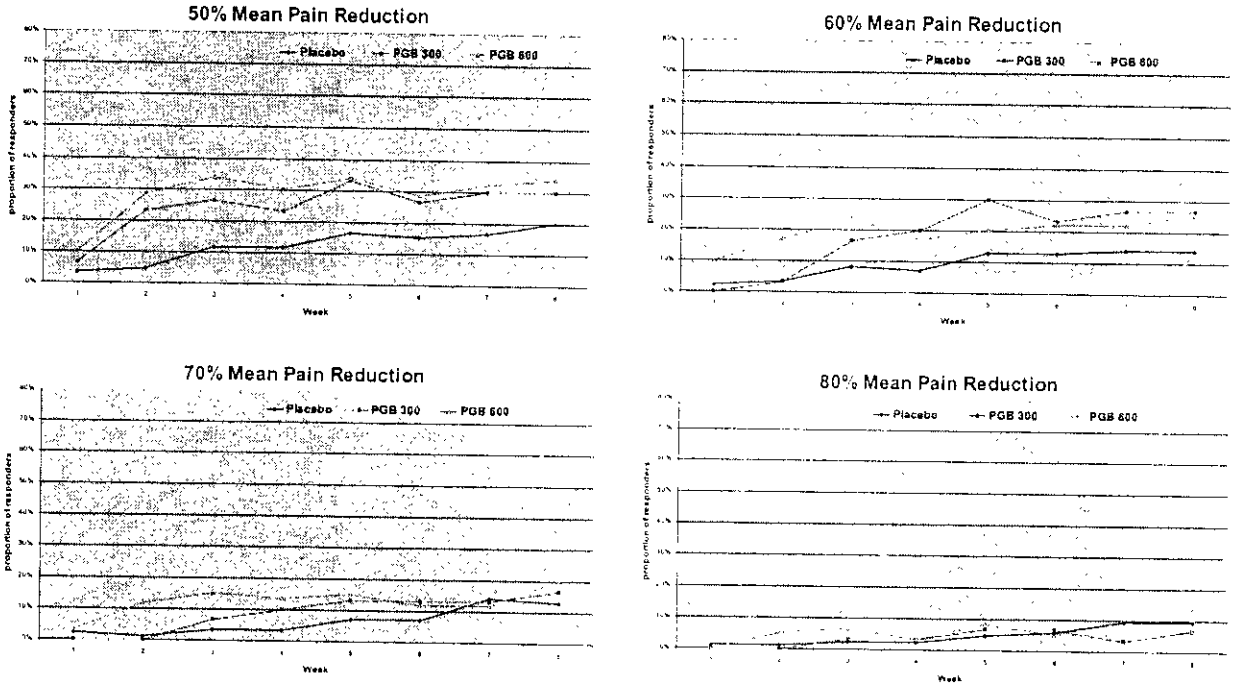
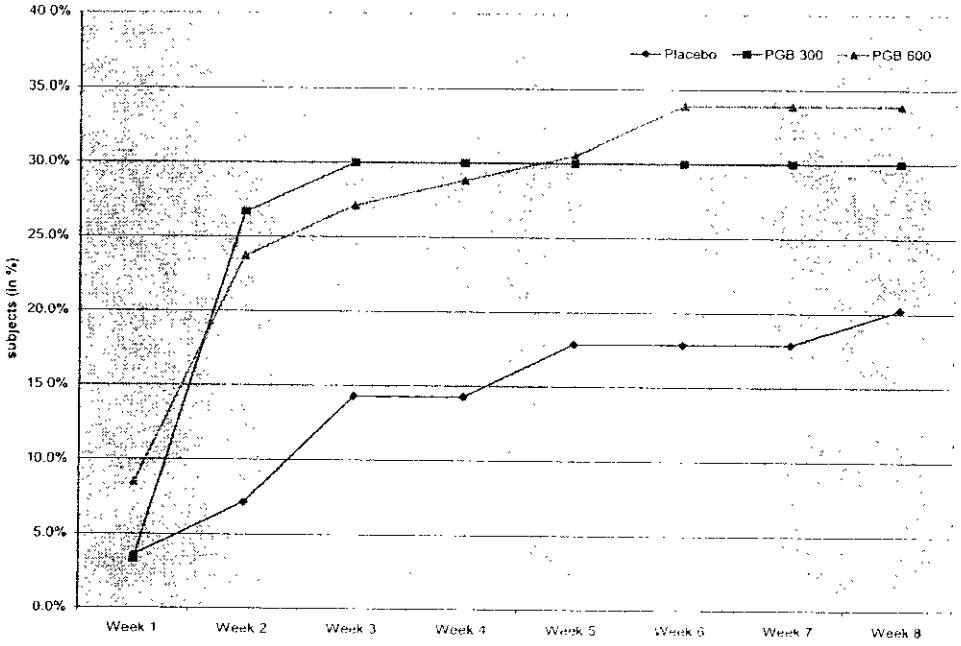


Figure 6 (Continued)



There were a total of 46 subjects (completer) who had 50% mean pain reduction at the end of the study. Figure 7 presents the distribution of these patients from the beginning of the study (week 1) to the end of the study (week 8). Patients who did not respond in Week 1 are likely to respond in Week 2 in both pregabalin 300 mg/d and 600mg/d. However, in the pregabalin 300 mg/d group, any subjects who did not respond at Week 3 will not likely respond beyond that week. On the other hand, subjects taking pregabalin 600 mg/d who did not respond initially still have a chance to respond until Week 6. Patients in the placebo group did not show any noteworthy trends.

Figure 7: Proportion of Responders by Week

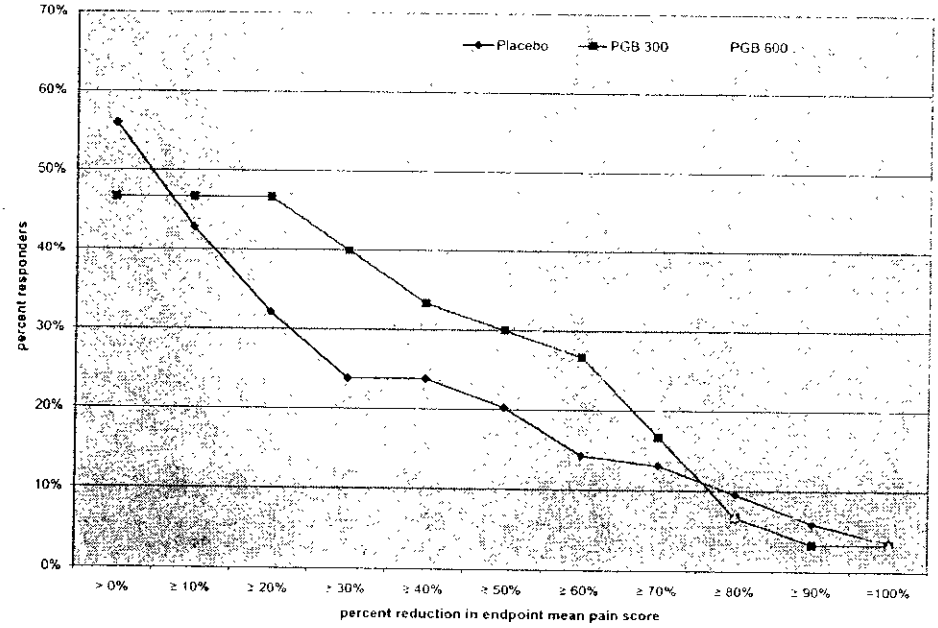


For a single time point the information in Figure 6 can be summarized in a single graph. Figure 8 shows the proportions of responders at endpoint for all the various definitions of responder considered. A higher proportion of subjects in the pregabalin-treated groups were treatment responders compared to the placebo-treated group. For the less stringent definitions of responder (less than 50% pain reduction), pregabalin 600 mg/d group showed a much higher reduction in pain compared to either pregabalin 300mg/d or the placebo (Table 24 and Figure 8). However, for more stringent definitions (50–70% reduction), pregabalin 300 mg/d and pregabalin 600 mg/d showed only a small difference, but still favored the pregabalin 600mg/d group. Few patients in any group achieved more than 70% reduction in pain.

Table 24: Percentage change in endpoint mean pain score by dose (BOCF) - ITT population

	TOTAL		PLACEBO		PGB300		PGB600	
	Total	%	Total	%	Total	%	Total	%
Any increase	22	12.7	16	19.1	3	10.0	3	5.1
None	52	30.1	21	25.0	13	43.3	18	30.5
> 0 % decrease	99	57.3	47	56.0	14	46.7	38	64.4
≥ 10%	86	49.7	36	42.9	14	46.7	36	61.0
≥ 20%	75	43.4	27	32.1	14	46.7	34	57.6
≥ 30%	58	33.5	20	23.8	12	40.0	26	44.1
≥ 40%	54	31.2	20	23.8	10	33.3	24	40.7
≥ 50%	**46**	**26.6**	**17**	**20.2**	**9**	**30.0**	**20**	**33.9**
≥ 60%	35	20.2	12	14.3	8	26.7	15	25.4
≥ 70%	28	16.2	11	13.1	5	16.7	12	20.3
≥ 80%	14	8.1	8	9.5	2	6.7	4	6.8
≥ 90%	10	5.8	5	6.0	1	3.3	4	6.8
=100%	6	3.5	3	3.6	1	3.3	2	3.4

Figure 8: Response Profile at Endpoint



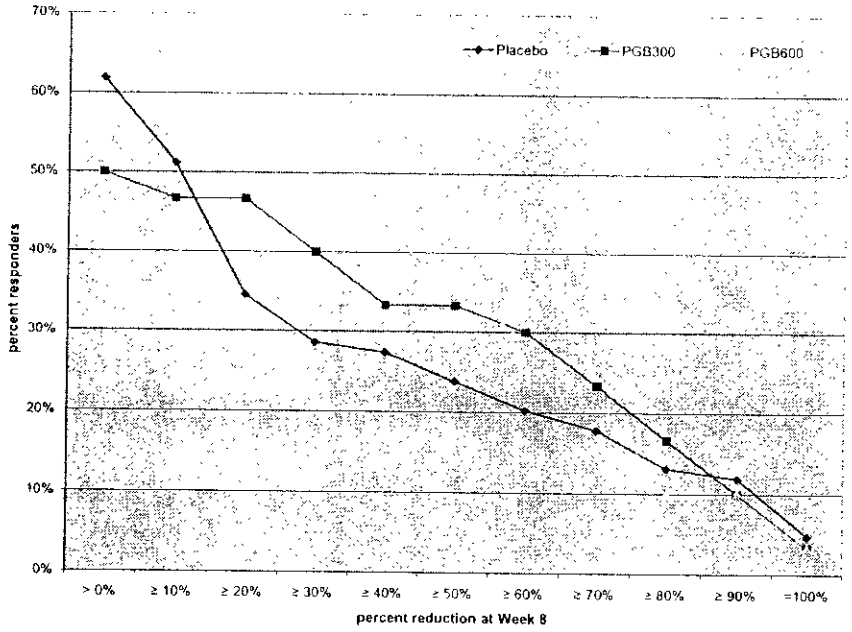
Upon the request of Dr. Kashoki, response profile at Week 8 was also calculated. Week 8 is defined as the average of day 51 to day 57 pain scores for the completers and baseline mean pain score for the non-completers. A higher proportion of subjects in the pregabalin-treated groups were treatment responders compared to the placebo-treated group at endpoint. For the less stringent definitions of responder (less than 50% pain reduction), the pregabalin 600 mg/d group showed a much higher reduction in pain compared to either pregabalin 300mg/d or the placebo (Table 23 and Figure 9). However, for more stringent definitions (50–70% reduction), pregabalin 300 mg/d and pregabalin 600 mg/d showed only a small difference, favoring the pregabalin 300mg/d group. This is slightly different from the conclusion based on endpoint mean pain score. Furthermore, the responder rates using Week 8 pain score (Table 23) are different (slightly higher) than the responder rates when endpoint mean pain score is used (Table 25).

The difference could be due to the fact that of the 132 patients who completed the study, 45 patients had completed earlier than Day 56, resulting in exposure to study medication of less than 8 weeks.

Table 25: Percentage change in Week 8 mean pain score by dose (BOCF) ITT population

	TOTAL		PLACEBO		PGB300		PGB600	
	Total	%	Total	%	Total	%	Total	%
Any increase	19	11%	14	17%	2	7%	3	5%
None	49	28%	18	21%	13	43%	18	31%
> 0 % decrease	105	61%	52	62%	15	50%	38	64%
≥ 10%	94	54%	43	51%	14	47%	37	63%
≥ 20%	78	45%	29	35%	14	47%	35	59%
≥ 30%	65	38%	24	29%	12	40%	29	49%
≥ 40%	58	34%	23	27%	10	33%	25	42%
≥ 50%	**51**	**29%**	**20**	**24%**	**10**	**33%**	**21**	**36%**
≥ 60%	43	25%	17	20%	9	30%	17	29%
≥ 70%	35	20%	15	18%	7	23%	13	22%
≥ 80%	22	13%	11	13%	5	17%	6	10%
≥ 90%	19	11%	10	12%	3	10%	6	10%
=100%	7	4%	4	5%	1	3%	2	3%

Figure 9: Response Profile at Week 8



Statistical tests were conducted in the percentage change at endpoint and on Week 8 by dose (Tables 24 and 25), and the results are presented in Appendix III.

3.3.3 Study 1008-196

Study 1008-196 was a randomized, double-blind, placebo-controlled, parallel group, multi-center comparison of pregabalin to placebo for the treatment of adult patients with PHN. The study consisted of one-week baseline phase, followed by a 13-week double-blind treatment phase comprising one-week of titration for the 300 and 300/600 mg/d dose groups, and a 12-week fixed dose phase. In this study, patients were randomized to 1 of 4 treatment groups (placebo, 150, 300, 300/600 mg/d pregabalin) and the maximum pregabalin dose was dependent upon creatinine clearance. Subjects with CLcr above mL/min (normal creatinine clearance) in the pregabalin 300/600 group received pregabalin dose of 600 mg/d (300 mg BID), and subjects with creatinine clearance between 30 and 60 mL/min (low creatinine clearance) received pregabalin dose of 300 mg/d (150 mg BID). Similar to Study 127, this study was designed and analyzed to test the efficacy of a treatment regimen with dose based on creatinine clearance. In consultation with Dr. Kashoki (medical reviewer), I consider it worthwhile to explore the claim of equal effects of the different doses in the two strata by re-classifying the treatment groups into:

1. "low" pregabalin 150mg/d on subjects with low creatinine clearance;
2. "normal" pregabalin 150mg/d on subjects with normal creatinine clearance;
3. "low" pregabalin 300mg/d on subjects with low creatinine clearance;
4. "normal" pregabalin 300mg/d on subjects with normal creatinine clearance; and
5. "normal" pregabalin 600 mg/d based on subjects with normal creatinine clearance

In order to detect a difference of at least 1.3 in endpoint weekly mean pain score between the placebo and at least one pregabalin treatment group with a common standard deviation of 2.15, and assuming two-sided testing at the 0.0167 level (to control for multiple comparisons) and 90% power, sample size of 352 (88 per treatment group) was proposed. The study was conducted at 76 sites, with most of sites having less than 20 patients. Therefore, these small centers were combined into clusters after the study was completed, but before the blind was broken. There are a total of 14 study clusters.

Patient disposition is summarized in Table 26. Of the total 435 patients who entered the baseline phase, 370 participants completed the baseline phase and were randomized to treatment, and 368 went on to receive study medication (placebo 93, PGB150 87, PGB300 98, and PGB300/600 90). A total of 242 (66%) patients completed the 13-week study. Among the 126 patients who withdrew from the study, 46 (36.5%) withdrew due to adverse events (Placebo=5, PGB150=7, PGB300=15, PGB300/600=19). Meanwhile, 57 patients withdrew due to lack of efficacy (Placebo=22, PGB150=16, PGB300=13, PGB300/600=6). The remaining 23 patients withdrew either due to lack of compliance or consent withdrawal.

Furthermore, 96 (26%) of the 368 randomized subjects had protocol deviations. Forty were confirmed protocol deviations and 56 were further categorized as protocol violations. These 56 individuals warranted exclusion from the Per Protocol patient population. This resulted in a per protocol population of 312 patients (Placebo 78, PGB150-low 22, PGB150-normal 52, PGB300-low 51, PGB300-normal 55, PGB600 54)

Table 26: Summary of Patient Disposition [Number (%) of Patients]

Disposition N (%)	Placebo	Pregabalin 150 mg/day	Pregabalin 300 mg/day	Pregabalin 300 600 mg/day	All Patients
Entered Baseline Phase					435
Completed Baseline Phase					370 (85.1)
Withdrawn During Baseline Phase[a]:					65 (14.9)
Adverse Event					1 (0.2)
Did Not Meet Criteria					48 (11.0)
Other					16 (3.7)
Entered Double-Blind (Randomized)	94	87	98	91	370
Intent-to-Treat Patients	93	87	98	90	368
Withdrawn During Treatment Phase:	34 (36.6)	26 (29.9)	36 (36.7)	30 (33.3)	126 (34.2)
Adverse Event	5 (5.4)	7 (8.0)	15 (15.3)	19 (21.1)	46 (12.5)
Lack of Compliance	0 (0.0)	0 (0.0)	1 (1.0)	1 (1.1)	2 (0.5)
Lack of Efficacy	22 (23.7)	16 (18.4)	13 (13.3)	6 (6.7)	57 (15.5)
Other/Administrative	7 (7.5)	3 (3.4)	7 (7.1)	4 (4.4)	21 (5.7)
Completed Study	59 (63.4)	61 (70.1)	62 (63.3)	60 (66.7)	242 (65.8)
Entered Open Label (1008-198)	74 (79.6)	68 (78.2)	70 (71.4)	63 (70.0)	275 (74.7)

[a] The denominator for percentages of "Withdrawn during baseline" category and sub-categories is the number of patient entered in Baseline; the denominator for all other percentages is, respectively, for each column the number of ITT patients.

Source: Table 10 from Applicant's report [RR 720-30191]

In this study, 54% of the participants were female, majority were Caucasian (99%), and at least 76% were more than 65 years of age (mean 71, range 18 to 92). The mean estimated baseline creatinine clearance was 75.7 mL/min for all patients, with a range of 32 to 229 mL/min. Upon stratification, 252 patients (69%) were categorized as having normal creatinine clearance status and 116 patients (32%) have low creatinine clearance level. Table 27 presents the summary of baseline estimated creatinine clearance by creatinine clearance strata. Other demographic and baseline characteristics did not differ among the four treatment groups. Most importantly, the baseline mean pain scores shown below (Table 28) among these groups are not different.

Table 27: Summary of baseline creatinine clearance score by strata

Estimated Creatinine Clearance at Baseline (mL/min)	Placebo (N=93)		Pregabalin 150 mg/day (N=87)		Pregabalin 300 mg day (N=98)		Pregabalin 300 600 mg day (N=90)	
	Low	Normal	Low	Normal	Low	Normal	Low	Normal
N	31	62	26	61	33	65	26	64
Mean (STD)	50.0 (7.9)	90.2 (30.6)	51.5 (7.8)	84.1 (17.1)	50.0 (7.6)	88.2 (22.7)	49.9 (9.0)	87.1 (22.6)
Median	53	83.5	53	82	50	85	51.5	79.5
Range	32 to 60	44 to 229	36 to 71	61 to 126	37 to 69	61 to 201	33 to 62	47 to 152

[a] Creatinine clearance (CLcr) stratum was 'Normal' for patients with CLcr >60 mL/min, and 'Low' for patients with CLcr >30 and ≤60 mL/min.

Source: Table 12 of applicant's Report [RR 720-30191]

Table 28: Mean Pain Scores: Descriptive Statistics

Baseline Mean Pain Score					
N	93	87	98	90	368
Mean (SD)	6.85 (1.49)	6.44 (1.58)	6.72 (1.41)	6.65 (1.44)	6.67 (1.48)
Median	7	6.57	6.93	6.71	6.79
Range	1.71 to 10.00	2.57 to 10.00	3.71 to 9.71	3.86 to 10.00	1.71 to 10.00

Source: Table 13 of applicant's Report [RR 720-30191]

Of the 87 randomized subjects in the pregabalin 150 group, 26 subjects had low creatinine clearance, and 61 had normal creatinine clearance; of the 188 randomized subjects in the pregabalin 300 and pregabalin

300/600 groups, 59 subjects had low creatinine clearance and 65 subjects had normal creatinine clearance taking pregabalin 300 mg/d; Meanwhile, 64 subjects had normal creatinine clearance who were taking pregabalin 600mg/d (Table 29). Because the sample size calculation was based on a four-arm study at the 0.0167 level, the number of subjects required in the six-arm study may not be sufficient to detect treatment difference from placebo in the five pregabalin-treated groups separately. In assuming a two-sided testing at the 0.01 level (to control for multiple comparison), sample size of 576 (96 per treatment group) are needed in order to achieve a 90% power. Nonetheless, these separate analyses are important to explore the efficacy of pregabalin based on patient's creatinine clearance.

Table 29: Summary of the Intent-to-treat population

		Pregabalin				
	Placebo	150 mg/d		300 mg/d		600 mg/d
		Low[1]	Normal[2]	Low[1]	Normal[2]	Normal[2]
N	93	26	61	59	65	64

[1]Low = creatinine clearance is between 30 and 60 mL/min
[2]Normal = creatinine clearance >60 mL/min

The applicant's analysis of the primary efficacy variable using endpoint mean pain scores (Tables 30 and 31) and using Week 8 mean pain scores (Table 32) data from the ITT population showed that the pregabalin-treated groups were significantly different from the placebo group. Missing data were imputed using last observation carried forward (LOCF) scheme (Tables 30 and 32) and baseline observation carried forward scheme (Table 31). The table was generated based on the analysis of covariance with treatment, cluster and creatinine clearance strata as fixed effects, and with the baseline mean pain score as covariate.

Table 30: Endpoint[a] Mean Pain Scores: Results of Analysis of covariance (ITT Population)

Treatment (mg/day)	N	Least-Squares Means	SE	Treatment Comparisons (Pregabalin — Placebo)			
				Difference	95% CI	Unadjusted p-Value	Adjusted[b] p-Value
Placebo	93	6.14	0.23				
PGB 150 mg	87	5.26	0.24	-0.88	(-1.53, -0.23)	0.0077	0.0077
PGB 300 mg	98	5.07	0.23	-1.07	(-1.70, -0.45)	0.0008	0.0016
PGB 300/600 mg	88	4.35	0.24	-1.79	(-2.43, -1.15)	0.0001	0.0003
Interactions treatment by:							
• Cluster (Generalizability)		p = 0.2965					
• CLcr Stratum		p = 0.3991					
• Baseline Score		p = 0.4771					

SE = Standard error; CI = Confidence interval; PGB = Pregabalin.
[a] Based on LS Means using ANCOVA model (including effects for treatment, cluster, CLcr stratum and the baseline score value as covariate).
[b] Adjustment based on Hochberg's procedure.

Source: Table 16 from applicant's report

Table 31:

Table 7. Endpoint [a] Mean Pain Scores – BCF : Results of Analysis of Covariance - Intent-To-Treat Analysis

Treatment Group	N	Least Squares Means	SE	Treatment Comparisons (Pregabalin - Placebo) Difference	95% CI	Unadjusted p-Value	Adjusted p-Value [b]
Placebo	93	6.22	0.22				
PGB 150 mg	87	5.35	0.23	-0.87	(-1.48, -0.27)	0.0051	0.0102
PGB 300 mg	98	5.52	0.21	-0.70	(-1.29, -0.11)	0.0201	0.0201
PGB 300/600 mg	88	4.89	0.23	-1.33	(-194, -0.73)	0.0001	0.0003

SE = Standard error; CI = Confidence interval

[a] Based on LS Means using ANCOVA model (including effects for treatment, cluster, Creatinine clearance stratum and the baseline score value as covariate).

[b] Adjusted p-value based on Hochberg's procedure for the 3 pairwise comparisons versus placebo.

Table 32: Week 8 Endpoint Mean pain scores:

Treatment Group (mg/day)	N	Least-Squares Means	SE	Treatment Comparisons (Pregabalin — Placebo) Difference	95% CI	Unadjusted p-Value	Adjusted p-Value[b]
Placebo	93	6.08	0.22				
PGB 150 mg	87	5.19	0.22	-0.88	(-1.48, -0.28)	0.0040	0.0040
PGB 300 mg	98	5.03	0.21	-1.04	(-1.62, -0.46)	0.0005	0.0010
PGB 300/600 mg	88	4.45	0.22	-1.63	(-2.22, -1.03)	0.0001	0.0003

SE = Standard error; CI = Confidence interval.

[a] Based on LS Means using ANCOVA model (including effects for treatment, cluster, CLcr stratum and the baseline score value as covariate).

[b] Adjusted p-value based on Hochberg's procedure for the 3 pairwise comparisons versus placebo.

Additional analyses were performed by the applicant to explore the sensitivity of the results by repeating the analyses and testing for treatment-by-cluster interaction; by testing the assumption of parallel slopes using treatment-by-baseline interaction; testing the assumption of normality; exclusion of protocol violators or analyzing using Per Protocol population; computing and comparing weekly mean pain scores; conducting responder analysis; and analysis of longitudinal data. All these analyses supported the claim of efficacy of pregabalin (150, 300, or 300/600 mg/d) dosing, given BID, in the treatment of pain due to PHN.

To further understand the efficacy claim, upon consultation with Dr. Kashoki, I carried out additional analyses including endpoint mean pain score analysis on each pregabalin-treated groups (PGB150 – low, PGB150 – normal, PGB300 – low, PGB300 – normal, PGB600). Weekly responder analyses based on percent decrease in mean pain score from baseline were also conducted. The percent decrease was classified in 10-percent increments. In these analyses, weekly mean pain score for patients who withdrew from the study regardless of the reason were given the baseline pain score, so that these patients were always classified as non-responders. Otherwise, weekly mean pain scores for all patients who completed the study are calculated based on the average pain scores per week defined as:

Week	Days
1	2 - 8
2	9 – 15
3	16 – 22
4	23 – 29
5	30 – 36
6	37 – 43
7	44 – 50
8	51 – 57
9	58 – 64
10	65 – 71
11	72 – 78
12	79 – 85
13	86 – 92

Re-analysis of endpoint mean pain scores using BOCF scheme showed significant difference between pregabalin-treated groups (150, 300 and 300/600 mg/d) and the placebo group (Table 33), similar to Table 31 from the applicant's result.

Table 33: Endpoint[1] Mean Pain Scores: Results of Analysis of covariance on ITT population using BOCF

Treatment	N	Baseline Mean	Least-Squares Mean	SE	Treatment Comparisons (Pregabalin – Placebo)		
					Difference	p-value[2]	p-value[3]
Placebo	93	6.85	6.22	0.22			
PGB 150	87	6.44	5.35	0.23	-0.87	0.0055	0.0110
PGB 300	98	6.72	5.52	0.21	-0.70	0.0205	0.0205
PGB 300/600	88	6.65	4.94	0.22	-1.28	<0.0001	0.0003

[1] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline mean pain score for non-completers
[2] unadjusted p-values
[3] Adjustment based on Hochberg's procedure for the two pairwise comparisons versus placebo

Summary of baseline mean pain score when pregabalin-treated groups were divided based on the creatinine clearance is displayed in Table 34. The result showed that the baseline pain scores are homogenous across subgroups except for pregabalin 150-normal.

Table 34: Summary of Baseline Mean Pain Score (Intent-to-treat population) – Up to Week 13

	Placebo	Pregabalin				
		150 mg/d		300 mg/d		600 mg/d
		Low[1]	Normal[2]	Low[1]	Normal[2]	Normal[2]
N	93	26	61	59	65	64
Mean (SD)	6.85 (1.49)	6.77 (1.72)	6.30 (1.51)	6.84 (1.42)	6.60 (1.44)	6.64 (1.42)
Median	7.0	7.0	6.29	7.0	6.86	6.66
Range	1.7 – 10.0	3.14 – 10.0	2.57 – 10.0	4.14 – 9.71	3.71 – 9.14	3.86 – 10.0

[1]Low = creatinine clearance is between 30 and 60 mL/min
[2]Normal = creatinine clearance >60 mL/min

Table 35: Week 8[1] Mean Pain Scores: Results of Analysis of Covariance on ITT population using BOCF

Treatment	N	Baseline Mean	Least-Squares Mean	SE	Treatment Comparisons (Pregabalin - Placebo)		
					Differences	p-value[2]	p-value[3]
Placebo	93	6.85	6.11	0.20			
PGB 150							
Low[4]	26	6.77	5.79	0.38	-0.31	0.4461	0.4461
Normal[5]	61	6.30	5.00	0.25	-1.11	0.0006	0.0024
PGB 300							
Low[4]	59	6.84	5.22	0.26	-0.89	0.0066	0.0174
Normal[5]	65	6.60	5.29	0.24	-0.82	0.0087	0.0174
PGB 600	64	6.64	4.74	0.25	-1.37	<0.0001	0.0005

[1] Week 8= Average of available scores between day 51 to day 57, except when subject dropped out before or during that week then it will be baseline pain score
[2] unadjusted p-values
[3] Adjustment based on Hochberg's procedure for the six pairwise comparisons versus placebo
[4]Low = creatinine clearance is between 30 and 60 mL/min
[5]Normal = creatinine clearance >60 mL/min

Table 36: Endpoint[1] Mean Pain Scores: Results of Analysis of Covariance on ITT population using BOCF

Treatment	N	Baseline Mean	Least-Squares Mean	SE	Treatment Comparisons (Pregabalin – Placebo)		
					Differences	p-value[2]	p-value[3]
Placebo	93	6.85	6.19	0.22			
PGB 150							
Low[4]	26	6.77	5.76	0.41	-0.43	0.3514	0.3514
Normal[5]	61	6.30	5.12	0.27	-1.07	0.0020	0.0080
PGB 300							
Low[4]	59	6.84	5.38	0.27	-0.81	0.0194	0.0582
Normal[5]	65	6.60	5.54	0.26	-0.65	0.0532	0.1064
PGB 600	64	6.64	4.72	0.26	-1.47	<0.0001	0.0005

[1] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline mean pain score for non-completers
[2] unadjusted p-values
[3] Adjustment based on Hochberg's procedure for the two pairwise comparisons versus placebo
[4]Low = creatinine clearance is between 30 and 60 mL/min
[5]Normal = creatinine clearance >60 mL/min

The results from the analysis of covariance with Week 8 mean pain scores (Table 35) and endpoint mean pain scores (Table 36) as outcome variables are presented. The analyses include treatment and cluster as fixed effects, and with baseline mean pain score as covariate. As shown, subjects who have normal creatinine clearance and were treated with pregabalin (150 or 600 mg/d) up to week 13 were significantly different than placebo. Subjects in the pregabalin 300 group with either low or normal creatinine clearance level were also different than the placebo up to week 8, but only subjects with low creatinine clearance group were significantly different to the placebo at week 13 based on the definition of endpoint mean pain score, suggesting that pregabalin 300 was more beneficial to those with low creatinine

clearance. One caveat in analyzing these results is that the study was not designed to compare the separate strata to the placebo. Nevertheless quantitatively, a treatment benefit in pregabalin 600 mg/d is shown among patients with normal creatinine clearance. Furthermore, patients taking pregabalin 600mg/d achieved on average lower mean pain score compared to patients with low creatinine clearance taking pregabalin 300 mg/d. Meanwhile, patients with low creatinine clearance taking pregabalin 300 mg/d showed on average a lower mean pain score than those taking pregabalin 150 mg/d.

Tables 37 and 38 present the results from the analysis of covariance with weekly pain scores and endpoint pain scores as outcome variables. The analyses include treatment and cluster as fixed effects with baseline mean pain score as covariate. There was evidently a statistically significant difference between the pregabalin-treated groups and placebo over time (Tables 37), and when treatment groups were stratified based on creatinine clearance, there was also evidence of treatment difference between pregabalin-treated groups and placebo over time, except on subjects who have low creatinine clearance treated with pregabalin 150 mg/d (table 38). On the other hand, when applicant's definition of endpoint-mean-pain score was used (Week 13 endpoint), there was difference in the result from the Week 13 mean pain score in the pregabalin 300 group with normal creatinine clearance. This was apparently due to higher mean pain score in the placebo group when week 13 pain score was calculated based on the average of the available scores from day 86 to day 92 for completers, compared to when endpoint mean pain score was calculated based on the average of the last 7 available scores including day after last dose for completers. Furthermore, 17 of the 242 who completed the study have completed earlier than day 92, resulting in exposure to study medication of less than 13 weeks. Nevertheless, there was clear evidence that pregabalin 600 mg/d and pregabalin 150 mg/d for normal creatinine clearance subjects were effective in reducing pain compared to the placebo, and that pregabalin 300 mg/d, regardless of creatinine clearance level, also appeared to be beneficial in reducing pain compared to the placebo.

Table 37: Weekly[1] Least Square Mean Pain Score by Dose (BOCF) – ITT population

	Placebo Mean (SD)	Mean (SD)	PGB 150 p-value[2]	p-value[3]	Mean (SD)	PGB 300 p-value[2]	p-value[3]	Mean (SD)	PGB 600 p-value[2]	p-value[3]
Week 1	6.5 (0.1)	5.8 (0.1)	<0.0001	<0.0001	5.8 (0.1)	<0.0001	<0.0001	5.7 (0.1)	<0.0001	<0.0001
Week 2	6.4 (0.2)	5.7 (0.2)	0.0033	0.0033	5.5 (0.2)	<0.0001	0.0002	5.4 (0.2)	<0.0001	0.0002
Week 3	6.4 (0.2)	5.6 (0.2)	0.0014	0.0014	5.5 (0.2)	0.0002	0.0004	5.2 (0.2)	<0.0001	0.0003
Week 4	6.4 (0.2)	5.6 (0.2)	0.0006	0.0006	5.4 (0.2)	<0.0001	0.0002	5.2 (0.2)	<0.0001	0.0002
Week 5	6.5 (0.2)	5.4 (0.3)	<0.0001	0.0001	5.6 (0.2)	0.0004	0.0004	5.1 (0.2)	<0.0001	0.0002
Week 6	6.3 (0.2)	5.3 (0.2)	0.0003	0.0006	5.6 (0.2)	0.0060	0.0060	5.2 (0.2)	<0.0001	0.0003
Week 7	6.3 (0.2)	5.4 (0.2)	0.0005	0.0010	5.4 (0.2)	0.0043	0.0043	5.1 (0.2)	<0.0001	0.0003
Week 8	6.2 (0.2)	5.3 (0.2)	0.0014	0.0028	5.6 (0.2)	0.0151	0.0151	5.0 (0.2)	<0.0001	0.0003
Week 9	6.3 (0.2)	5.4 (0.2)	0.0008	0.0016	5.6 (0.2)	0.0126	0.0126	5.0 (0.2)	<0.0001	0.0003
Week 10	6.3 (0.2)	5.4 (0.2)	0.0005	0.0010	5.7 (0.2)	0.0173	0.0173	4.9 (0.2)	<0.0001	0.0003
Week 11	6.3 (0.2)	5.4 (0.2)	0.0026	0.0052	5.6 (0.2)	0.0180	0.0180	4.9 (0.2)	<0.0001	0.0003
Week 12	6.3 (0.2)	5.3 (0.2)	0.0011	0.0022	5.6 (0.2)	0.0134	0.0134	5.0 (0.2)	<0.0001	0.0003
Week 13	6.3 (0.2)	5.4 (0.4)	0.0028	0.0056	5.6 (0.2)	0.0135	0.0135	5.0 (0.2)	<0.0001	0.0003
Week 8 Endpain[4]	6.2 (0.2)	5.3 (0.2)	0.0030	0.0031	5.3 (0.2)	0.0031	0.0031	4.9 (0.2)	<0.0001	0.0003
Endpain[5]	6.2 (0.2)	5.3 (0.2)	0.0055	0.0110	5.5 (0.2)	0.0205	0.0205	4.9 (0.2)	<0.0001	0.0003

[1] Weekly pain score= Average of the available scores per week for completers, and baseline mean pain scores for non-completers
[2] unadjusted p-values
[3] Adjustment based on Hochberg's procedure for the six pairwise comparisons versus placebo
[4] Week 8= Average of the last 7 available scores up to day 57, and baseline mean pain scores for non-completers at week 8 and onwards
[5] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline mean pain score for non-completers

Table 38: Weekly[1] Least Square Mean Pain Score by Dose (BOCF) using new treatment groups– ITT population

Treatment	Least-Squares Mean (SE)	Change from baseline LS mean (SE)	Treatment Comparisons (Pregabalin - Placebo)		
			Differences	p-value[2]	p-value[3]
Week 1					
Placebo	6.51 (0.1)	0.16 (0.1)			
PGB 150[4]	5.97 (0.2)	0.71 (0.2)	-0.54	0.0311	0.0311
PGB 150[5]	5.74 (0.1)	0.93 (0.1)	-0.77	<0.0001	0.0004
PGB 300[4]	5.64 (0.1)	1.04 (0.1)	-0.87	<0.0001	0.0004
PGB 300[5]	5.87 (0.1)	0.80 (0.1)	-0.64	0.0005	0.0010
PGB 600[5]	5.82 (0.1)	0.86 (0.1)	-0.69	0.0002	0.0006
Week 2					
Placebo	6.40 (0.2)	0.26 (0.2)			
PGB 150[4]	5.93 (0.3)	0.73 (0.3)	-0.47	0.1593	0.1593
PGB 150[5]	5.65 (0.2)	1.02 (0.2)	-0.75	0.0027	0.0054
PGB 300[4]	5.46 (0.2)	1.21 (0.2)	-0.94	0.0002	0.0008
PGB 300[5]	5.60 (0.2)	1.07 (0.2)	-0.80	0.0010	0.0030
PGB 600[5]	5.23 (0.2)	1.44 (0.2)	-1.17	<0.0001	0.0005
Week 3					
Placebo	6.37 (0.2)	0.30 (0.2)			
PGB 150[4]	5.90 (0.3)	0.77 (0.3)	-0.47	0.1766	0.1766
PGB 150[5]	5.49 (0.2)	1.18 (0.2)	-0.88	0.0007	0.0021
PGB 300[4]	5.40 (0.2)	1.27 (0.2)	-0.97	0.0003	0.0012
PGB 300[5]	5.60 (0.2)	1.07 (0.2)	-0.77	0.0027	0.0054
PGB 600[5]	5.04 (0.2)	1.63 (0.2)	-1.33	<0.0001	0.0005
Week 4					
Placebo	6.40 (0.2)	0.27 (0.2)			
PGB 150[4]	5.77 (0.3)	0.90 (0.3)	-0.63	0.0922	0.0922
PGB 150[5]	5.41 (0.2)	1.25 (0.2)	-0.99	0.0004	0.0012
PGB 300[4]	5.51 (0.2)	1.15 (0.2)	-0.89	0.0018	0.0036
PGB 300[5]	5.34 (0.2)	1.33 (0.2)	-1.06	0.0001	0.0004
PGB 600[5]	4.99 (0.2)	1.68 (0.2)	-1.41	<0.0001	0.0004
Week 5					
Placebo	6.41 (0.2)	0.25 (0.2)			
PGB 150[4]	5.63 (0.3)	1.04 (0.3)	-0.78	0.0366	0.0366
PGB 150[5]	5.26 (0.2)	1.41 (0.2)	-1.15	<0.0001	0.0004
PGB 300[4]	5.61 (0.2)	1.06 (0.2)	-0.80	0.0044	0.0088
PGB 300[5]	5.51 (0.2)	1.16 (0.2)	-0.90	0.0010	0.0030
PGB 600[5]	4.80 (0.2)	1.87 (0.2)	-1.61	<0.0001	0.0004

Table 38 (Continued):

Treatment	Least-Squares Mean (SE)	Change from baseline LS mean (SE)	Treatment Comparisons (Pregabalin – Placebo)		
			Differences	p-value[2]	p-value[3]
Week 6					
Placebo	6.28 (0.2)	0.40 (0.2)			
PGB 150[4]	5.58 (0.3)	1.09 (0.3)	-0.70	0.0765	0.0765
PGB 150[5]	5.17 (0.2)	1.50 (0.2)	-1.11	0.0002	0.0008
PGB 300[4]	5.62 (0.2)	1.06 (0.2)	-0.66	0.0261	0.0522
PGB 300[5]	5.55 (0.2)	1.13 (0.2)	-0.73	0.0109	0.0327
PGB 600[5]	4.96 (0.2)	1.72 (0.2)	-1.32	<0.0001	0.0005
Week 7					
Placebo	6.26 (0.2)	0.41 (0.2)			
PGB 150[4]	5.76 (0.4)	0.91 (0.4)	-0.50	0.2165	0.2165
PGB 150[5]	5.10 (0.2)	1.58 (0.2)	-1.16	0.0001	0.0004
PGB 300[4]	5.54 (0.2)	1.13 (0.2)	-0.72	0.0186	0.0372
PGB 300[5]	5.51 (0.2)	1.16 (0.2)	-0.75	0.0107	0.0321
PGB 600[5]	4.86 (0.2)	1.81 (0.2)	-1.40	<0.0001	0.0004
Week 8					
Placebo	6.18 (0.2)	0.50 (0.2)			
PGB 150[4]	5.71 (0.4)	0.97 (0.4)	-0.47	0.2643	0.2643
PGB 150[5]	5.06 (0.2)	1.61 (0.2)	-1.12	0.0004	0.0016
PGB 300[4]	5.47 (0.3)	1.20 (0.3)	-0.71	0.0277	0.0544
PGB 300[5]	5.44 (0.2)	1.23 (0.2)	-0.74	0.0164	0.0492
PGB 600[5]	4.82 (0.2)	1.85 (0.2)	-1.36	<0.0001	0.0005
Week 9					
Placebo	6.22 (0.2)	0.44 (0.2)			
PGB 150[4]	5.63 (0.4)	1.04 (0.4)	-0.59	0.1423	0.1423
PGB 150[5]	5.16 (0.2)	1.51 (0.2)	-1.06	0.0005	0.0020
PGB 300[4]	5.53 (0.2)	1.14 (0.2)	-0.69	0.0243	0.0486
PGB 300[5]	5.54 (0.2)	1.13 (0.2)	-0.68	0.0200	0.0486
PGB 600[5]	4.81 (0.2)	1.86 (0.2)	-1.41	<0.0001	0.0005
Week 10					
Placebo	6.28 (0.2)	0.39 (0.2)			
PGB 150[4]	5.50 (0.4)	1.17 (0.4)	-0.78	0.0604	0.0604
PGB 150[5]	5.20 (0.2)	1.47 (0.2)	-1.08	0.0006	0.0024
PGB 300[4]	5.60 (0.2)	1.07 (0.2)	-0.68	0.0306	0.0604
PGB 300[5]	5.57 (0.2)	1.10 (0.2)	-0.71	0.0192	0.0576
PGB 600[5]	4.67 (0.2)	1.99 (0.2)	-1.61	<0.0001	0.0005

Table 38 (Continued):

Treatment	Least-Squares Mean (SE)	Change from baseline LS mean (SE)	Treatment Comparisons (Pregabalin – Placebo)		
			Differences	p-value[2]	p-value[3]
Week 11					
Placebo	6.23 (0.2)	0.44 (0.2)			
PGB 150[4]	5.58 (0.4)	1.10 (0.4)	-0.65	0.1446	0.1446
PGB 150[5]	5.20 (0.3)	1.48 (0.3)	-1.03	0.0021	0.0084
PGB 300[4]	5.52 (0.3)	1.15 (0.3)	-0.71	0.0357	0.0714
PGB 300[5]	5.48 (0.2)	1.19 (0.2)	-0.75	0.0226	0.0678
PGB 600[5]	4.68 (0.3)	1.99 (0.3)	-1.55	<0.0001	0.0005
Week 12					
Placebo	6.27 (0.2)	0.41 (0.2)			
PGB 150[4]	5.59 (0.4)	1.09 (0.4)	-0.68	0.1372	0.1372
PGB 150[5]	5.10 (0.3)	1.58 (0.3)	-1.17	0.0007	0.0028
PGB 300[4]	5.44 (0.3)	1.24 (0.3)	-0.83	0.0163	0.0489
PGB 300[5]	5.56 (0.3)	1.19 (0.3)	-0.71	0.0333	0.0666
PGB 600[5]	4.75 (0.3)	1.93 (0.3)	-1.52	<0.0001	0.0005
Week 13					
Placebo	6.28 (0.2)	0.40 (0.2)			
PGB 150[4]	5.87 (0.4)	0.82 (0.4)	-0.41	0.3705	0.3705
PGB 150[5]	5.10 (0.3)	1.59 (0.3)	-1.18	0.0007	0.0028
PGB 300[4]	5.41 (0.3)	1.27 (0.3)	-0.87	0.0131	0.0393
PGB 300[5]	5.52 (0.3)	1.17 (0.3)	-0.76	0.0252	0.0504
PGB 600[5]	4.77 (0.3)	1.91 (0.3)	-1.51	<0.0001	0.0005
Week 8 Endpoint[6]					
Placebo	6.11 (0.2)	0.56 (0.2)			
PGB 150[4]	5.79 (0.4)	0.89 (0.4)	-0.32	0.4461	0.4461
PGB 150[5]	5.00 (0.2)	1.67 (0.2)	-1.11	0.0006	0.0024
PGB 300[4]	5.22 (0.3)	1.45 (0.3)	-0.89	0.0066	0.0174
PGB 300[5]	5.29 (0.2)	1.38 (0.2)	-0.82	0.0087	0.0174
PGB 600[5]	4.74 (0.2)	1.93 (0.2)	-1.37	<0.0001	0.0005
Week 13 Endpoint[7]					
Placebo	6.19 (0.2)	0.48 (0.2)			
PGB 150[4]	5.76 (0.4)	0.91 (0.4)	-0.43	0.3514	0.3514
PGB 150[5]	5.12 (0.3)	1.55 (0.3)	-1.07	0.0020	0.0080
PGB 300[4]	5.38 (0.3)	1.29 (0.3)	-0.81	0.0194	0.0582
PGB 300[5]	5.54 (0.3)	1.13 (0.3)	-0.65	0.0532	0.1064
PGB 600[5]	4.72 (0.3)	1.96 (0.3)	-1.47	<0.0001	0.0005

[1]Weekly pain score= Average of the available scores per week for completers, and baseline mean pain scores for non-completers
[2]unadjusted p-values
[3]Adjustment based on Hochberg's procedure for the six pairwise comparisons versus placebo
[4]Low = creatinine clearance is between 30 and 60 mL/min
[5]Normal = creatinine clearance >60 mL/min
[6] Week 8= Average of the last 7 available scores up to day 57 and baseline mean pain scores for non-completers at week 8 and onwards
[7] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline mean pain score for non-completers

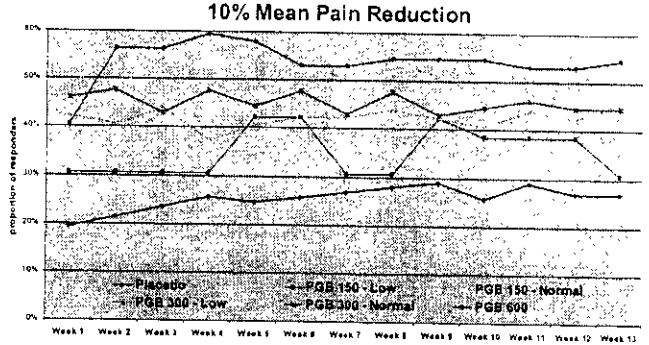
Additional analyses were performed to assess the sensitivity of the weekly mean pain scores to different extrapolation techniques on missing observations within a given week for completers and imputation of weekly mean pain scores for non-completers. The results were generally similar to those already discussed. In addition, the use of rescue medication and/or prohibited medications was also examined. Based on the supplemental data provided by the sponsor on June 7, 2004, there were eight subjects in the placebo group out of the total 368 subjects randomized to treatments who took prohibited medications. There were six subjects in pregabalin 150 group (3 in each creatinine clearance strata), 10 subjects in pregabalin 300 (5 in each creatinine clearance strata), and five subjects in the pregabalin 600 group who took at least one prohibited medication. Meanwhile, 94 out of 368 subjects took rescue medication at least once (placebo 24, PGB150-Low 8, PGB150-Normal 13, PGB300-Low 17, PGB300-Normal 18, and PGB600 14). Of these 94 subjects, 77 (82%) took the rescue medication from beginning to the end of the study treatment, eight subjects took rescue medication in the middle of the study to the end of the study period, seven subjects took the rescue once or twice in the middle of study, and only one subject took it only during the baseline period. All these 94 subjects' pain scores did not differ from the day before rescue was taken or the day after it was taken, so the rescue could not have affected the average pain scores much. Furthermore, only nine out of these 94 subjects dropped out due to an adverse event, and eight of these nine subjects took rescue medication from the beginning of the study to the end of the study period (or to the day they dropped-out). Meanwhile, 14 of the 94 subjects dropped out due to lack of efficacy, and 12 of these subjects took rescue from the beginning of the study to the day they dropped out. Therefore, no additional analyses were conducted using rescue medication.

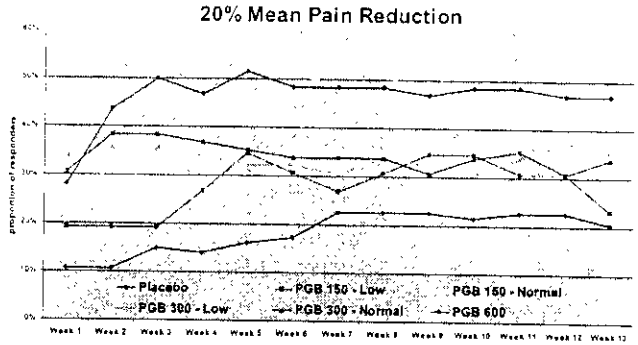
Using the definition of weekly mean pain scores outlined above (i.e. assigning baseline pain scores to non-completers), responders based on the percent pain reduction were identified. Figure 10 presents the proportion of responders with 10% – 80% pain reduction in their mean pain score by treatment group over the 13-week period. Using the definition provided by the applicant for the endpoint proportion of responders, (i.e. percent of patients who had a 50% or greater reduction in mean pain score from baseline to endpoint) there was difference between pregabalin-treated groups and the placebo. The graph suggests a clear benefit in pregabalin 600mg/d over the other pregabalin-treated groups beginning at week 5. There was also clear evidence of treatment benefit among subjects with normal creatinine clearance taking pregabalin 150mg/d towards the end of the study period. Subjects with normal creatinine clearance taking pregabalin 300 mg/d also showed higher proportion of responders compared to those in the low creatinine clearance taking same dosage form.

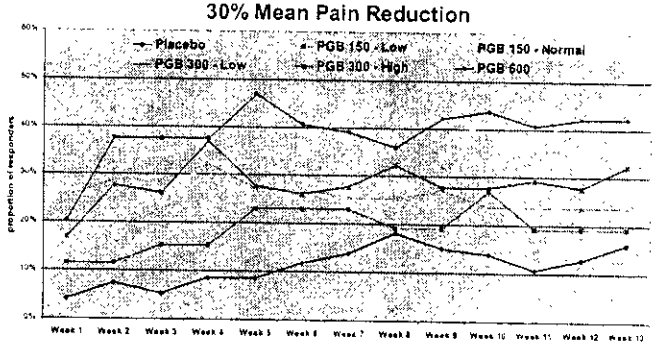
When different definitions of responder (based on different percent pain reduction) were used, there was evidence suggesting treatment benefit in pain reduction among those subjects in the pregabalin 600 mg/d over those subjects taking either pregabalin 150 or pregabalin 300 mg/d dosage. Although the difference in the proportion of responders was negligible between the pregabalin 600 mg/d group and the pregabalin 150 group (with normal creatinine clearance) for less stringent definitions of responder (pain reduction less than 30%), there was evidence that this difference increases as the definitions of responder become more stringent. There was also evidence that pregabalin 300 mg/d (with normal creatinine clearance) is better than the pregabalin 150 (with normal creatinine clearance) at 60% pain reduction.

Nevertheless, pregabalin 600 mg/d is the winner in reducing pain, followed by pregabalin 150 mg/d for subjects with normal creatinine clearance level, and pregabalin 300 mg/d for subjects with normal creatinine clearance level.

Figure 10: Percent Mean Pain Reduction







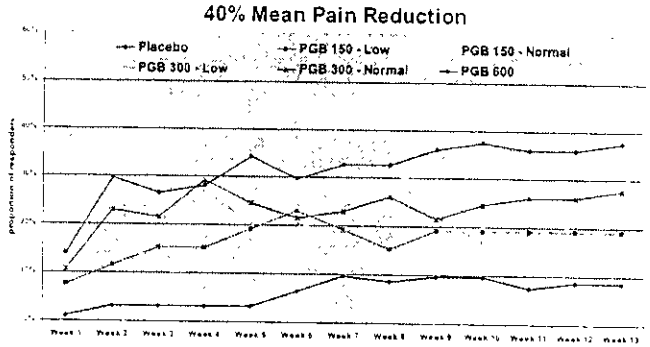
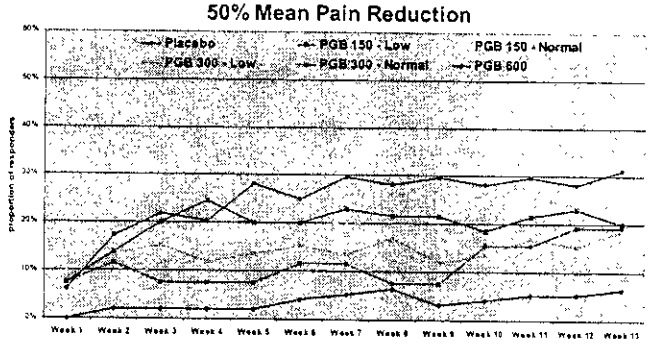
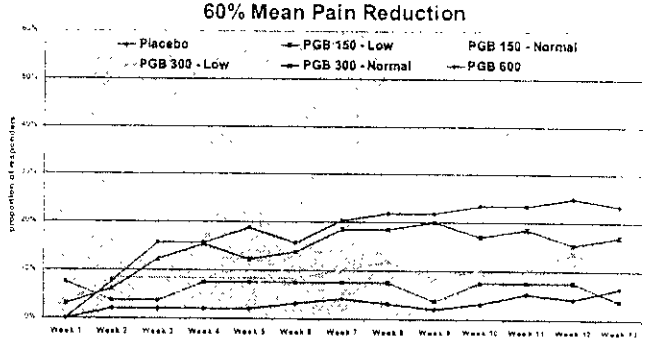
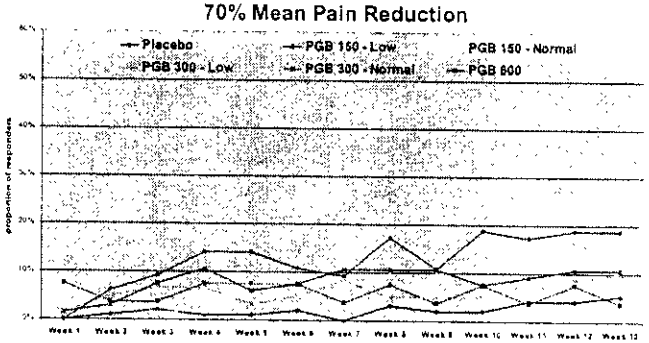
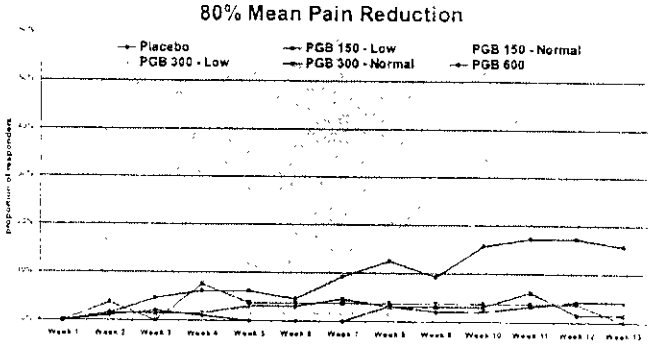


Figure 10 (Continued)



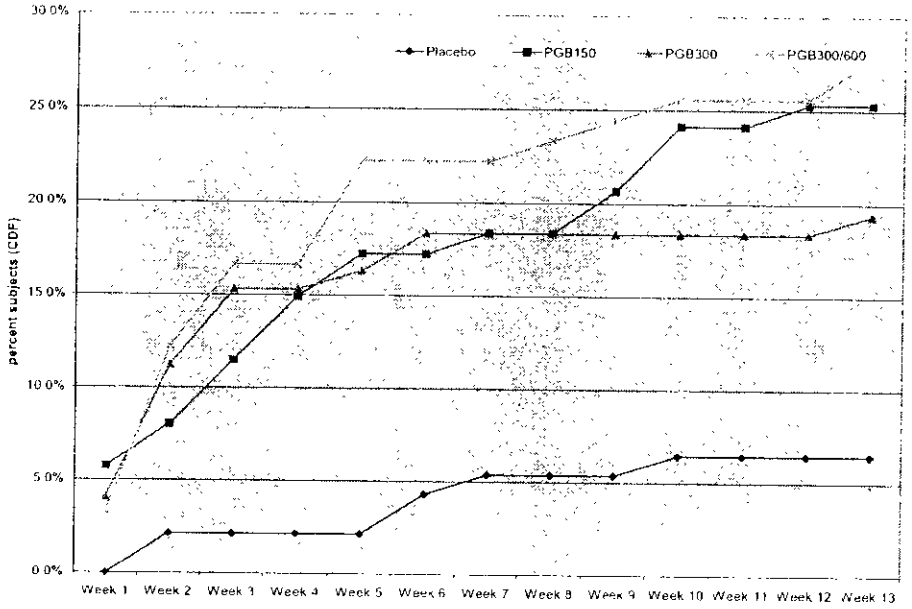






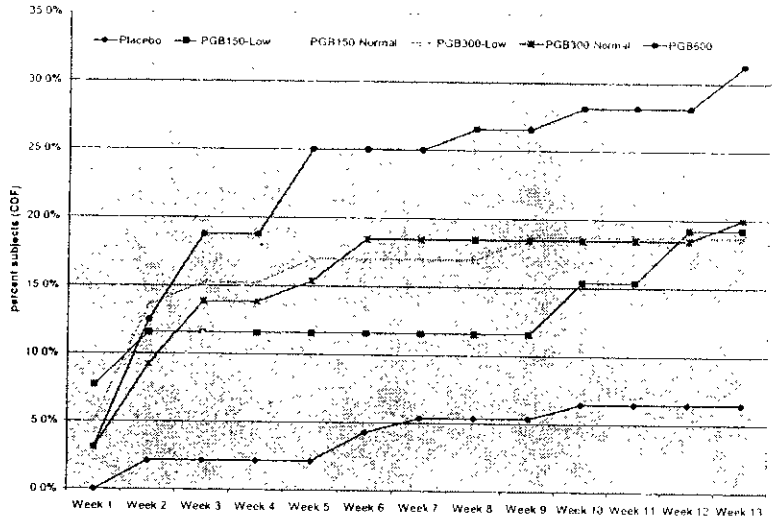
There were a total of 72 subjects (completer) who had 50% mean pain reduction by the end of the 13-week study. Figure 11 present the distribution of these patients from the beginning of the study (week 1) to the end of the study (week 13). The graph showed evidence that patients who did not respond to pregabalin 150 mg/d or pregabalin 300/600 mg/d at Week 1 were likely to respond at Week 2 and beyond. However, in the pregabalin 300 mg/d group, any subjects who did not respond at Week 6 will not likely respond beyond that week. Patients in the placebo group did not show any noteworthy trends.

Figure 11: Proportion of responders by week up to Week 13



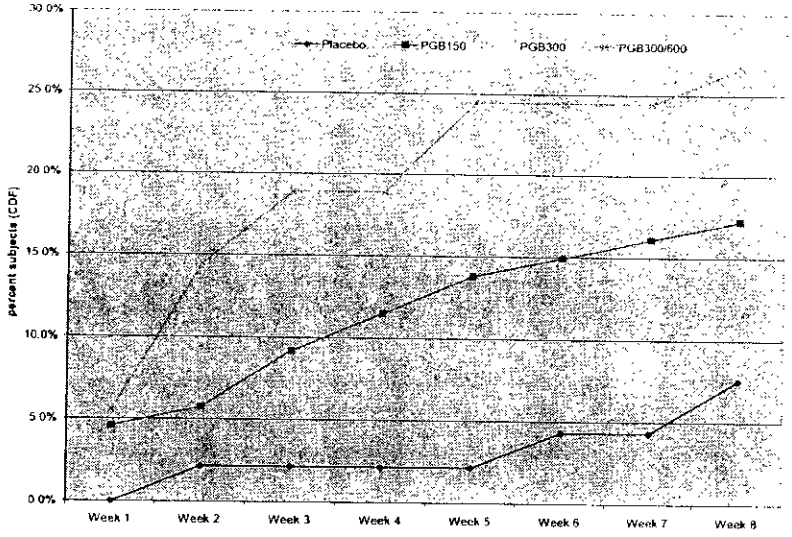
Similar findings were found when subjects in the pregabalin-treated groups were re-classified based on their creatinine clearance (Figure 12). The graph showed evidence that patients who did not respond to pregabalin at Week 1 were likely to respond at Week 2. However, only subjects with normal creatinine clearance were likely to respond beyond week 2 (up to Week 10 for PGB150, and up to Week 13 for PGB 600).

Figure 12: Proportion of responders by week up to Week 13 using new treatment groups based on creatinine clearance



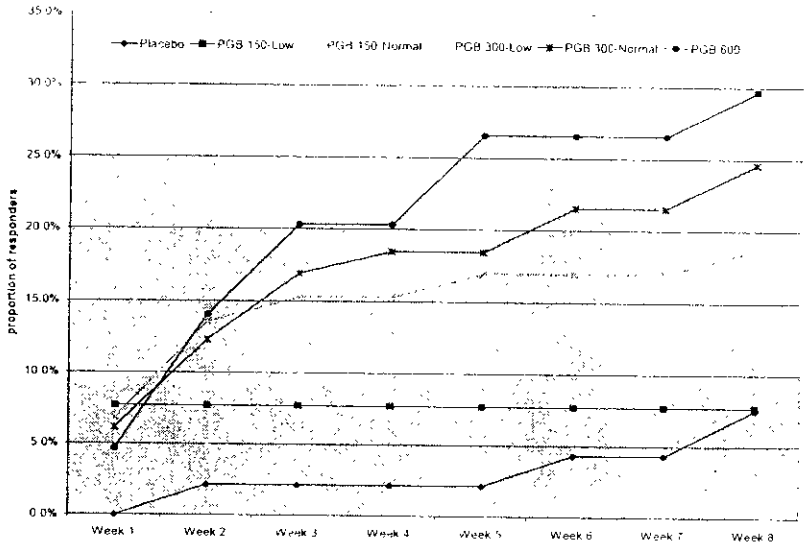
There were a total of 68 subjects (completer) who had 50% mean pain reduction by the end of the 8-week study. Figure 13 present the distribution of these patients from the beginning of the study (week 1) up to week 8. The graph showed evidence that patients who did not respond to pregabalin at Week 1 were likely to respond at Week 2 and beyond, regardless of the dosage use. Patients in the placebo group did not show any noteworthy trends.

Figure 13: Proportion of responders by week up to Week 8



Similar findings were found when subjects in the pregabalin-treated groups were re-classified based on their creatinine clearance (Figure 14). The graph showed evidence that patients who did not respond to pregabalin at Week 1 were likely to respond at Week 2. Only subjects with low creatinine clearance taking pregabalin 150 were not likely to respond beyond week 2.

Figure 14: Proportion of responders by week up to Week 8 using new treatment groups based on creatinine clearance



For a single time point the information in Figure 10 can be summarized in a single graph. Figures 15 and 16 shows the proportions of responders for all the various definitions of responder considered using week 8 and week 13 mean pain scores, respectively. A higher proportion of subjects in the pregabalin-treated groups (except on patients with low creatinine clearance taking pregabalin 150mg/d) were treatment responders compared to the placebo-treated group. When less stringent definitions of responder (less than 30% reduction) was used, there was evidence that patients with normal creatinine taking either pregabalin 150 mg/d or pregabalin 600 mg/d were responding favorably to the treatment (Figures 15 and 16). However, when more stringent definition of responders was used (more than 30% reduction), there was a faster decline in treatment responders in the pregabalin 150 mg/d group compared to the pregabalin 600mg/d group. Furthermore, at greater than 50% pain reduction, the graphs showed only slight difference in treatment response between patients with normal creatinine clearance taking pregabalin 150mg/d and patients taking pregabalin 300mg/d. Therefore, in can be concluded that the response rate was best at pregabalin 600 mg/d, good at pregabalin 150 mg/d with normal creatinine clearance in less stringent definition of responders, and good at either pregabalin 150 with normal creatinine clearance or pregabalin 300 in a more stringent definition of responders. Few patients in any group achieved more than 70% reduction in pain. Tabular summaries of the graphs are displayed in Tables 39 and 40.

Statistical tests were conducted in the percentage change at endpoint (i.e. Week 13) and on Week 8 by dose (Tables 39 and 40), and the results are presented in Appendix III.

Figure 15:

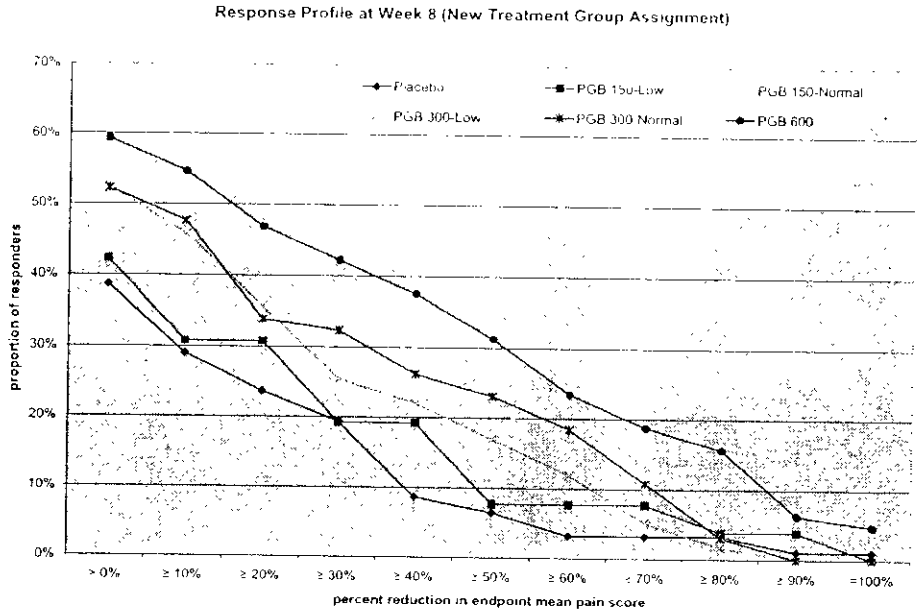


Figure 16:

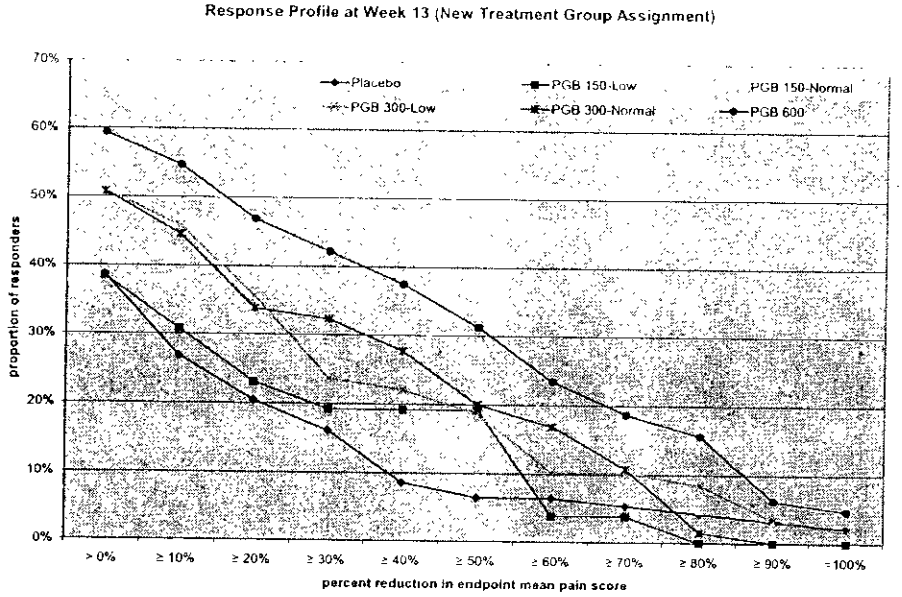


Table 39: Percentage change in Week 8 mean pain score by dose using new treatment assignment based on creatinine clearance (BOCF) – ITT population

	TOTAL		PLACEBO		PGB 150[1]		PGB 150[2]		PGB 300[1]		PGB 300[2]		PGB 600	
	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%
Any increase	38	10%	18	19%	2	8%	5	8%	2	3%	8	12%	3	5%
None	140	38%	39	42%	13	50%	17	28%	26	44%	23	35%	22	34%
> 0 % decrease	190	52%	36	39%	11	42%	39	64%	31	53%	34	52%	39	61%
≥ 10%	165	45%	27	29%	8	31%	36	59%	27	46%	31	48%	36	56%
≥ 20%	137	37%	22	24%	8	31%	31	51%	21	36%	22	34%	33	52%
≥ 30%	109	30%	18	19%	5	19%	26	43%	15	25%	21	32%	24	38%
≥ 40%	83	23%	8	9%	5	19%	18	30%	13	22%	17	26%	22	34%
≥ 50%	65	18%	**6**	**6%**	**2**	**8%**	**13**	**21%**	**10**	**17%**	**15**	**23%**	**19**	**30%**
≥ 60%	48	13%	3	3%	2	8%	10	16%	7	12%	12	18%	14	22%
≥ 70%	32	9%	3	3%	2	8%	6	10%	3	5%	7	11%	11	17%
≥ 80%	17	5%	3	3%	1	4%	2	3%	1	2%	2	3%	8	13%
≥ 90%	6	2%	1	1%	1	4%	0	0%	0	0%	0	0%	4	6%
=100%	2	1%	1	1%	0	0%	0	0%	0	0%	0	0%	1	2%

[1]Low = creatinine clearance is between 30 and 60 mL/min
[2]Normal = creatinine clearance >60 mL/min

Table 40: Percentage change in endpoint mean pain score by dose using new treatment assignment based on creatinine clearance (BOCF) – ITT population

	TOTAL		PLACEBO		PGB 150[1]		PGB 150[2]		PGB 300[1]		PGB 300[2]		PGB 600	
	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%
Any increase	48	13%	21	23%	2	8%	9	15%	2	3%	8	12%	6	9%
None	137	37%	36	39%	14	54%	16	26%	27	46%	24	37%	20	31%
> 0 % decrease	183	50%	36	39%	10	38%	36	59%	30	51%	33	51%	38	59%
≥ 10%	155	42%	25	27%	8	31%	31	51%	27	46%	29	45%	35	55%
≥ 20%	128	35%	19	20%	6	23%	30	49%	21	36%	22	34%	30	47%
≥ 30%	107	29%	15	16%	5	19%	25	41%	14	24%	21	32%	27	42%
≥ 40%	87	24%	8	9%	5	19%	19	31%	13	22%	18	28%	24	38%
≥ 50%	**72**	**20%**	**6**	**6%**	**5**	**19%**	**17**	**28%**	**11**	**19%**	**13**	**20%**	**20**	**31%**
≥ 60%	50	14%	6	6%	1	4%	11	18%	6	10%	11	17%	15	23%
≥ 70%	38	10%	5	5%	1	4%	7	11%	6	10%	7	11%	12	19%
≥ 80%	23	6%	4	4%	0	0%	3	5%	5	8%	1	2%	10	16%
≥ 90%	11	3%	3	3%	0	0%	2	3%	2	3%	0	0%	4	6%
=100%	8	2%	2	2%	0	0%	2	3%	1	2%	0	0%	3	5%

[1]Low = creatinine clearance is between 30 and 60 mL/min
[2]Normal = creatinine clearance >60 mL/min

Results and Conclusions

I conclude that treatment with pregabalin produces significantly lower mean pain score at Week 8 (endpoint) compared to placebo except pregabalin 150 mg/d on patients with low creatinine clearance. In addition, upon careful examination of the treatment responders in each study, I find that the greatest treatment benefit was among patients with normal creatinine clearance taking pregabalin 600 mg/d (study 127 and 196). When a less stringent definition of responders was used, pregabalin 150mg/d was equally effective in treating patients with normal creatinine clearance as pregabalin 600 mg/d, but when a more stringent criterion was used (>50% pain reduction) an additional benefit was apparent with pregabalin 600 mg/d. There also appeared to be no difference between pregabalin 300 mg/d and pregabalin 150 mg/d, regardless of patient's creatinine clearance.

In consultation with Dr. Kashoki, we determined that there were no safety issues needing statistical evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Age, Race, and Hormonal Status

4.1.1 Sex

Exploring the relationships between sex and treatment, ANCOVA analysis adjusting for the interaction term was conducted. The new model included endpoint pain scores as outcome variables; treatment, and cluster as fixed effects; baseline mean pain score as a covariate; and sex-by-treatment and age-by-treatment as interaction terms. In Study 045 the interaction between sex and treatment was not statistically significant. A similar conclusion was reached in Study 127 using the original data with pregabalin 300/600 group and the placebo group, as well as using the stratified data based on creatinine clearance. In Study 196, there was also no significant interaction between sex and treatment at Week 8 or Week 13, whether or not stratified data based on creatinine clearance was used.

4.1.2 Age

Exploring the relationships between age and treatment, ANCOVA analysis adjusting for the interaction term was conducted. Age was dichotomized into two groups: ≤ 65 and > 65 years. The new model included endpoint pain scores as outcome variables; treatment, and cluster as fixed effects; baseline mean pain score as a covariate; and sex-by-treatment and age-by-treatment as interaction terms. In Study 045, interaction between age and treatment was statistically significant. In Study 127, the interaction between age and treatment was statistically significant, either by using the original data with pregabalin 300/600 group and the placebo group ($p=0.0342$), or by using the stratified data based on creatinine clearance ($p=0.0082$). In Study 196, no significant interaction between age and treatment at Week 8 or Week 13 are found.

4.1.3 Race

Of the 238 subjects randomized in study 045, 236 (99%) were white. Ninety five percent of patients were white in Study 127 (164 out of 173), and in Study 196, 99% were white (364 out of 368). Because of the small numbers of nonwhites, any claims of parity in terms of patient's race are essentially unsupported.

4.1.4 Hormonal Status

Among those 131 subjects who had hormonal status information in Study 045, majority of them (126) were postmenopausal. Ninety five percent (87 out of 92) subjects and 96% (191 out of 200) subjects were postmenopausal in Study 127 and in Study 196, respectively. Because of the small numbers of pre-menopausal women, any claims of parity between these subgroups are essentially unsupported.

4.2 Pooled Data (Study 045, 127 and 196)

Pooling the data from Study 045, Study 127 and Study 196, ANCOVA analyses adjusting for the interaction terms were conducted. Exploring the relationships between sex and treatment and between age and treatment, the new models included the week 8 mean pain scores and the endpoint mean pain scores as outcome variables; treatment, and cluster as fixed effects; baseline mean pain score as a covariate; and sex-by-treatment and age-by-treatment as interaction terms. Treatment was defined as taking pregabalin versus the placebo.

Neither the interaction between age and treatment nor the interaction between sex and treatment are statistically significant at week 8 or at endpoint when data were pooled.

In conclusion, the claim of no differences in endpoint mean pain score based on age or sex is shown to be correct except only in study 127.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Even when some of the results from different studies using the new treatment assignment showed no significant difference between pregabalin and placebo, most of these samples that were used to generate the results were too small to expect significant findings. In fact, most of the pregabalin doses that were shown to have no significant difference compared to the placebo have substantially smaller sample sizes compared to those that have shown statistical difference. As a result, the outcomes from the statistical tests were inconsistent across different studies as shown in Table 41.

Another reason for the inconsistencies could be the different dosing regimens utilized (i.e. Studies 045 and 127 are TID, and Study 196 is BID). As an example, endpoint mean pain scores of patients with low baseline creatinine clearance taking pregabalin 300 mg/d were statistically different compared to the placebo when given BID dosing. Alternatively, endpoint mean pain scores of patients with low creatinine clearance taking pregabalin 150 mg/d were statistically different to the placebo when given TID dosing.

Although it appears that there are inconsistencies with the results from different studies, based on the overall finding, as well as findings from the responder analysis, I conclude that pregabalin 150 or 300 mg/d is an effective treatment regardless of patient's baseline creatinine clearance. Furthermore, for patients with normal creatinine clearance, pregabalin 600 mg/d is also an effective treatment in reducing pain. The question about the safety and tolerability of the drug, particularly at dosage 600 mg/d, will be discussed in detail by Dr. Kashoki.

Table 41: Collective Evidence - Least Square Mean Pain Score (SE) by Dose and by Study

Summary of Results from Study 45, 127, and 196

Study No.		Placebo	PGB 150[1]	PGB 150[2]	PGB 300[1]	PGB 300[2]	PGB 600[2]
Study 045 [TID]	N	81	42	39	45	31	
	Mean (se)	6.3 (0.2)	4.9 (0.3)	5.5 (0.3)	5.7 (0.3)	4.6 (0.3)	
	p-value[3]		0.0003	0.0587	0.0587	0.0003	
Study 127 [TID]	N	84			30		59
	Mean (se)	5.1 (0.2)			4.6 (0.4)		4.4 (0.3)
	p-value[3]				0.2346[4]		0.0302[4]
Study 196 at Week 8 [BID]	N	93	26	61	59	65	64
	Mean (se)	6.1 (0.2)	5.8 (0.4)	5.0 (0.3)	5.2 (0.3)	5.3 (0.2)	4.7 (0.3)
	p-value[3]		0.4461	0.0024	0.0174	0.0174	0.0005
Study 196 at Week 13 [BID]	N	93	26	61	59	65	64
	Mean (se)	6.2 (0.2)	5.8 (0.4)	5.1 (0.3)	5.4 (0.3)	5.5 (0.3)	4.7 (0.3)
	p-value[3]		0.3514	0.0080	0.0582	0.1064	0.0005

[1] low creatinine clearance
[2] normal creatinine clearance
[3] using Hochberg's test of difference from placebo
[4] unadjusted p-value

5.2 Conclusions and Recommendations

In view of the statistical findings generated from the analyses conducted by the applicant and by me, I conclude that pregabalin 150, 300, and 300/600 mg/d are efficacious for the management of neuropathic pain with postherpetic neuralgia.

6. Labelling Claims

PHN LABEL CLAIMS:

1. [redacted]
2. Significant reduction in pain by Week 1

6.1 Study 1008-045

Using the available pain scores for the first week, regardless of the status of subjects at the end of the study, daily pain scores and three day pain scores were summarized and presented in Table 42.

Table 42: Mean Pain Score by Dose (BOCF)

	Placebo N=81	PGB 150 N=81	PGB 300 N=76
Baseline	6.64 (1.6)	6.93 (1.7)	6.98 (1.6)
Day 2	6.35 (1.9)	6.36 (2.1)	6.21 (2.2)
Day 3	6.40 (1.9)	6.12 (2.2)	6.07 (2.2)
Day 4	6.34 (2.0)	6.05 (2.2)	6.07 (2.2)
Day 5	6.42 (2.1)	5.80 (2.4)	5.71 (2.2)
Day 6	6.43 (2.1)	5.90 (2.4)	5.64 (2.2)
Day 7	6.29 (2.2)	5.85 (2.3)	5.29 (2.4)
Day 8	6.24 (2.2)	5.82 (2.3)	5.41 (2.4)
First 3 Days[1]	6.36 (1.8)	6.18 (2.0)	6.11 (2.1)
Week 1[2]	6.36 (1.8)	5.99 (2.1)	5.77 (2.0)

[1] First 3 days = day2 + day3 +day4
[2] Week 1= average of day 2 to day 8 pain scores regardless of status (completers or non-completers)

Table 43: Least Square Mean Pain Score by Dose (BOCF)

	Placebo N=81	PGB 150 N=81		PGB 300 N=76	
	mean (SD)	mean (SD)	P value[2]	mean (SD)	P value[2]
Day 2	6.54 (0.1)	6.30 (0.1)	0.4252	6.09 (0.2)	0.0664
Day 3	6.60 (0.2)	6.05 (0.2)	0.0265	5.92 (0.2)	0.0055
Day 4	6.56 (0.2)	5.97 (0.2)	0.0205	5.93 (0.2)	0.0155
Day 5	6.63 (0.2)	5.71 (0.2)	0.0008	5.57 (0.2)	0.0001
Day 6	6.59 (0.2)	5.81(0.2)	0.0119	5.53 (0.2)	0.0006
Day 7	6.48 (0.2)	5.75 (0.2)	0.0258	5.17 (0.2)	<0.0001
Day 8	6.43 (0.2)	5.76 (0.2)	0.0440	5.28 (0.2)	0.0003
First 3 days[1]	**6.57 (0.1)**	**6.10 (0.1)**	**0.0300**	**5.98 (0.1)**	**0.0053**
Week 1	6.56 (0.1)	5.92 (0.1)	0.0027	5.64 (0.1)	<0.0001

[1] First 3 days = day2 + day3 +day4
[2] using Hochberg's test of difference from control (placebo)

Table 43 presents the results from the Analysis of Covariance with daily pain scores, first 3 days pain score, and week 1 pain score as outcome variables. The analyses include treatment and cluster as fixed effects, and with baseline mean pain score as covariate. Although there are significant differences in pain reduction within the first three days of treatment and by Week 1, the differences are quantitatively small to warrant a convincing claim.

6.2 Study 1008-127:

Using the available pain scores for the first week, regardless of status of the subjects at the end of the study, daily pain scores and three day pain scores were summarized and presented in Table 44.

Table 44: Mean Pain Score by Dose (BOCF)

	Placebo N=84	PGB300/600 N=89	PGB 300 N=30	PGB 600 N=59
Baseline	6.43 (1.5)	6.29 (1.4)	6.60 (1.4)	6.13 (1.4)
Day 2	6.08 (2.0)	5.53 (1.8)	5.76 (1.6)	5.42 (1.9)
Day 3	5.99 (2.1)	5.18 (2.0)	5.04 (2.2)	5.24 (1.9)
Day 4	6.12 (1.9)	4.62 (2.0)	4.32 (1.8)	4.76 (2.0)
Day 5	5.96 (2.1)	4.59 (2.1)	4.64 (1.8)	4.57 (2.2)
Day 6	5.83 (2.2)	4.23 (2.3)	4.37 (2.0)	4.16 (2.4)
Day 7	5.86 (2.1)	4.18 (2.3)	4.33 (2.3)	4.11 (2.3)
Day 8	5.95 (2.0)	4.11 (2.1)	4.24 (1.9)	4.05 (2.2)
First 3 Days[1]	6.08 (1.9)	5.45 (1.7)	5.03 (1.6)	5.16 (1.8)
Week 1	6.00 (1.9)	4.72 (1.8)	4.76 (1.6)	4.70 (2.0)

[1]First 3 days = day 2 + day 3 + day 4

Table 45: Least Square Mean Pain Score by Dose (BOCF)

	Placebo N=84	PGB 300/600[1] N=89		PGB 300[2] N=30		PGB 600[2] N=59	
	mean (sd)	mean (sd)	P value	mean (sd)	P value	mean (sd)	P value
Day 2	6.00 (0.1)	5.62 (0.1)	0.0592	5.52 (0.2)	0.1080	5.69 (0.2)	0.2033
Day 3	5.91 (0.2)	5.26 (0.2)	0.0039	4.63 (0.3)	<0.0001	5.56 (0.2)	0.1572
Day 4	6.07 (0.2)	4.67 (0.2)	<0.0001	4.08 (0.3)	<0.0001	5.00 (0.2)	<0.0001
Day 5	5.90 (0.2)	4.65 (0.2)	<0.0001	4.62 (0.3)	0.0013	4.79 (0.2)	0.0003
Day 6	5.77 (0.2)	4.31 (0.2)	<0.0001	4.32 (0.4)	0.0011	4.37 (0.3)	<0.0001
Day 7	5.79 (0.2)	4.15 (0.2)	<0.0001	3.97 (0.4)	<0.0001	4.24 (0.3)	<0.0001
Day 8	5.92 (0.2)	4.15 (0.2)	<0.0001	3.89 (0.3)	<0.0001	4.28 (0.2)	<0.0001
First 3 days	**6.00 (0.1)**	**5.18 (0.1)**	**<0.0001**	**4.82 (0.2)**	**<0.0001**	**5.41 (0.2)**	**0.0048**
Week 1	5.93 (0.1)	4.79 (0.2)	<0.0001	4.69 (0.3)	<0.0001	4.92 (0.2)	<0.0001

[1] Analysis include treatment, center, and creatinine clearance strata as fixed effects, with baseline mean pain score as covariate, and the interaction between baseline pain score and treatment

[2] Analysis include treatment, and center as fixed effects, with baseline mean pain score as covariate, and the interaction between baseline pain score and treatment

[3] First 3 days = day 2 + day 3 + day 4

There is a significant difference in mean pain scores within the first three days of treatment and by week 1 between the pregabalin-treated group(s) and the placebo (Table 45).

6.3 Study 1008-196

Using the available pain scores for the first week, regardless of status of the subjects at the end of the study, daily pain scores and three day pain scores were summarized and presented in Table 46.

Table 46: Mean Pain Score by Dose (BOCF) – Study 196

	Placebo N=93	PGB150 N=87	PGB 300 N=98	PGB 300/600 N=90
Baseline	6.85 (1.5)	6.44 (1.6)	6.72 (1.4)	6.65 (1.4)
Day 2	6.73 (1.8)	5.87 (2.0)	6.01 (2.0)	5.94 (1.9)
Day 3	6.70 (1.9)	5.37 (2.3)	5.58 (2.0)	5.32 (2.1)
Day 4	6.70 (1.8)	4.98 (2.3)	5.47 (2.0)	5.30 (2.2)
Day 5	6.60 (1.9)	5.25 (2.3)	5.51 (2.2)	5.16 (2.1)
Day 6	6.53 (1.9)	5.33 (2.2)	5.29 (2.2)	5.09 (2.4)
Day 7	6.59 (1.9)	5.29 (2.3)	5.17 (2.2)	4.92 (2.4)
Day 8	6.44 (1.9)	5.10 (2.3)	4.90 (2.2)	4.67 (2.4)
First 3 Days[1]	6.71 (1.7)	5.40 (2.0)	5.65 (2.0)	5.52 (1.9)
Week 1	6.62 (1.8)	5.31 (2.0)	5.45 (1.9)	5.27 (1.9)

[1]First 3 days = day 2 + day 3 + day 4

Table 47: Least Square Mean Pain Score by Dose (BOCF) – Study 196

	Placebo N=93	PGB150 N=87		PGB 300 N=98		PGB 300/600 N=90	
	Mean (sd)	mean (sd)	P value[1]	mean (sd)	P value[1]	mean (sd)	P value[1]
Day 2	6.55 (0.1)	6.04 (0.2)	0.0123	5.94(0.1)	0.0064	5.95 (0.1)	0.0064
Day 3	6.49 (0.2)	5.51 (0.2)	0.0001	5.48 (0.2)	0.0001	5.30 (0.2)	0.0001
Day 4	6.49 (0.2)	5.14 (0.2)	0.0001	5.41 (0.2)	0.0001	5.26 (0.2)	0.0001
Day 5	6.37 (0.2)	5.40 (0.2)	0.0001	5.43 (0.2)	0.0001	5.11 (0.2)	0.0001
Day 6	6.35 (0.2)	5.58 (0.2)	0.0016	5.24 (0.2)	0.0002	5.16 (0.2)	0.0002
Day 7	6.42 (0.2)	5.46 (0.2)	0.0002	5.13 (0.2)	0.0002	4.90 (0.2)	0.0002
Day 8	6.24 (0.2)	5.28 (0.2)	0.0004	4.78 (0.2)	0.0002	4.70 (0.2)	0.0002
First 3 days	**6.50 (0.1)**	**5.55 (0.1)**	**0.0001**	**4.57 (0.1)**	**0.0001**	**5.49 (0.1)**	**0.0001**
Week 1	6.41 (0.1)	5.48 (0.2)	0.0001	5.38 (0.1)	0.0001	5.26 (0.1)	0.0001

[1] Adjustment based on Hochberg's procedure for the six pairwise comparisons versus placebo
[3] First 3 days = day 2 + day 3 + day 4

Table 48: Daily Least Square Mean Pain Score by Dose (BOCF) using New Treatment Assignment

Treatment	Least-Squares Mean (SE)	Treatment Comparisons (Pregabalin – Placebo) p-value[1]	p-value[2]
Day 2			
Placebo	6.58 (0.2)		
PGB 150-Low[3]	6.27 (0.3)	0.3124	0.3124
PGB 150-High[4]	5.97 (0.2)	0.0078	0.0306
PGB 300-Low[3]	5.62 (0.2)	<0.0001	0.0005
PGB 300-High[4]	6.09 (0.2)	0.0102	0.0306
PGB 600	6.25 (0.2)	0.1485	0.2790
Day 3			
Placebo	6.53 (0.2)		
PGB 150-Low[3]	5.70 (0.3)	0.0157	0.0157
PGB 150-High[4]	5.48 (0.2)	<0.0001	0.0004
PGB 300-Low[3]	5.02 (0.2)	<0.0001	0.0004
PGB 300-High[4]	5.64 (0.2)	0.0004	0.0008
PGB 600	5.60 (0.2)	0.0003	0.0008
Day 4			
Placebo	6.53 (0.2)		
PGB 150-Low[3]	5.30 (0.3)	0.0001	0.0002
PGB 150-High[4]	5.18 (0.2)	<0.0001	0.0002
PGB 300-Low[3]	5.00 (0.2)	<0.0001	0.0002
PGB 300-High[4]	5.50 (0.2)	<0.0001	0.0002
PGB 600	5.60 (0.2)	0.0003	0.0003
Day 5			
Placebo	6.43 (0.2)		
PGB 150-Low[3]	5.11 (0.3)	0.0001	0.0003
PGB 150-High[4]	5.62 (0.2)	0.0015	0.0015
PGB 300-Low[3]	5.09 (0.2)	<0.0001	0.0003
PGB 300-High[4]	5.62 (0.2)	0.0014	0.0015
PGB 600	5.35 (0.2)	<0.0001	0.0003
Day 6			
Placebo	6.35 (0.2)		
PGB 150-Low[3]	5.49 (0.3)	0.0173	0.0173
PGB 150-High[4]	5.62 (0.2)	0.0069	0.0138
PGB 300-Low[3]	5.11 (0.2)	<0.0001	0.0003
PGB 300-High[4]	5.33 (0.2)	0.0001	0.0003
PGB 600	5.08 (0.2)	<0.0001	0.0003

Table 48 (Continued):

Treatment	Least-Squares Mean (SE)	Treatment Comparisons (Pregabalin – Placebo) p-value[2]	p-value[3]
Day 7			
Placebo	6.42 (0.2)		
PGB 150-Low[3]	5.40 (0.3)	0.0070	0.0070
PGB 150-High[4]	5.49 (0.2)	0.0010	0.0020
PGB 300-Low[3]	4.89 (0.2)	<0.0001	0.0003
PGB 300-High[4]	5.28 (0.2)	<0.0001	0.0003
PGB 600	4.88 (0.2)	<0.0001	0.0003
Day 8			
Placebo	6.27 (0.2)		
PGB 150-Low[3]	5.13 (0.4)	0.0048	0.0048
PGB 150-High[4]	5.40 (0.2)	0.0030	0.0048
PGB 300-Low[3]	4.54 (0.2)	<0.0001	0.0004
PGB 300-High[4]	5.18 (0.2)	0.0002	0.0006
PGB 600	4.58 (0.2)	<0.0001	0.0004
First 3 Days			
Placebo	6.54 (0.1)		
PGB 150-Low[3]	5.72 (0.3)	0.0045	0.0045
PGB 150-High[4]	5.54 (0.2)	<0.0001	0.0003
PGB 300-Low[3]	5.15 (0.2)	<0.0001	0.0003
PGB 300-High[4]	5.72 (0.2)	0.0001	0.0003
PGB 600	5.81 (0.2)	0.0007	0.0014
Week 1			
Placebo	6.44 (0.1)		
PGB 150-Low[3]	5.46 (0.2)	0.0005	0.0005
PGB 150-High[4]	5.54 (0.2)	<0.0001	0.0002
PGB 300-Low[3]	5.06 (0.2)	<0.0001	0.0002
PGB 300-High[4]	5.52 (0.2)	<0.0001	0.0002
PGB 600	5.44 (0.2)	<0.0001	0.0002

[1] unadjusted p-value
[2] Adjustment based on Hochberg's procedure for the six pairwise comparisons versus placebo
[3] Low = creatinine clearance is between 30 and 60 mL/min
[4] Normal = creatinine clearance >60 mL/min

Tables 47 and 48 present the results from the analysis of covariance with daily pain scores, first 3 days pain score, and week 1 pain score as outcome variables. The analyses include treatment and cluster as fixed effects, and baseline mean pain score as covariate. Creatinine clearance strata are included in the model under Table 46. Although there are significant differences in pain reduction within the first three days of treatment and by Week 1, the differences are quantitatively small to warrant a convincing claim except for pregabalin 300mg/d group.

APPENDICES

Appendix I:

1. Non-completers were assigned baseline pain score each week. Completers who have > 4 missing observations in 7 days (in a week) will be assigned a weekly score from last week's average pain score (LOCF); completers who have < 4 missing observations in a week will be assigned the average of the available pain scores.

Table 10: Mean Pain Score by Dose (BOCF) – ITT population

	Placebo N=81	PGB 150 N=81	PGB 300 N=76
Baseline	6.64 (1.6)	6.93 (1.7)	6.98 (1.6)
Week 1	6.39 (1.8)	6.07 (2.0)	6.17 (2.0)
Week 2	6.33 (1.8)	5.80 (2.2)	5.59 (2.2)
Week 3	6.33 (1.9)	5.69 (2.2)	5.69 (2.3)
Week 4	6.30 (1.9)	5.71 (2.2)	5.57 (2.3)
Week 5	6.16 (2.0)	5.59 (2.4)	5.42 (2.3)
Week 6	6.18 (2.1)	5.58 (2.3)	5.33 (2.4)
Week 7	6.09 (2.1)	5.50 (2.4)	5.36 (2.4)
Endpoint	6.15 (2.1)	5.31 (2.5)	5.34 (2.6)

Table 11: Least Square Mean Pain Score by Dose (BOCF) – ITT population

	Placebo N=81	PGB 150 N=81		PGB 300 N=76	
	mean (SD)	mean (SD)	P value	mean (SD)	P value
Week 1	6.6 (0.1)	6.0 (0.1)	0.0034	6.1 (0.1)	0.0053
Week 2	6.5 (0.2)	5.7 (0.2)	0.0005	5.5 (0.2)	0.0002
Week 3	6.5 (0.2)	5.6 (0.2)	0.0001	5.6 (0.2)	0.0001
Week 4	6.5 (0.2)	5.6 (0.2)	0.0002	5.4 (0.2)	0.0002
Week 5	6.3 (0.2)	5.5 (0.2)	0.0016	5.3 (0.2)	0.0004
Week 6	6.4 (0.2)	5.5 (0.2)	0.0017	5.2 (0.2)	0.0002
Week 7	6.3 (0.2)	5.4 (0.2)	0.0037	5.3 (0.2)	0.0014
Endpoint	6.3 (0.2)	5.2 (0.2)	0.0004	5.2 (0.2)	0.0004

p-value: using Hochberg's test of difference from control (placebo)

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2. Non-completers were assigned baseline pain score each week. Missing observations will be assigned last week's average pain score (LOCF) for completers, and the pain scores for that week will be averaged to get the mean pain score for the week

Table 10: Mean Pain Score by Dose (BOCF) – ITT population

	Placebo N=81	PGB 150 N=81	PGB 300 N=76
Baseline	6.64 (1.6)	6.93 (1.7)	6.98 (1.6)
Week 1	6.40 (1.7)	6.08 (2.0)	6.19 (2.0)
Week 2	6.33 (1.8)	5.80 (2.1)	5.59 (2.2)
Week 3	6.33 (1.9)	5.69 (2.2)	5.70 (2.2)
Week 4	6.30 (1.9)	5.72 (2.2)	5.57 (2.3)
Week 5	6.16 (2.0)	5.59 (2.4)	5.43 (2.3)
Week 6	6.18 (2.1)	5.58 (2.3)	5.33 (2.4)
Week 7	6.09 (2.1)	5.50 (2.4)	5.36 (2.4)
Endpoint	6.15 (2.1)	5.31 (2.5)	5.34 (2.6)

Table 11: Least Square Mean Pain Score by Dose (BOCF) – ITT population

	Placebo N=81	PGB 150 N=81		PGB 300 N=76	
	mean (SD)	mean (SD)	P value	mean (SD)	P value
Week 1	6.6 (0.1)	6.0 (0.1)	0.0034	6.1 (0.1)	0.0064
Week 2	6.5 (0.2)	5.7 (0.2)	0.0005	5.5 (0.2)	0.0002
Week 3	6.5 (0.2)	5.6 (0.2)	0.0001	5.6 (0.2)	0.0001
Week 4	6.5 (0.2)	5.6 (0.2)	0.0002	5.4 (0.2)	0.0002
Week 5	6.3 (0.2)	5.5 (0.2)	0.0014	5.3 (0.2)	0.0004
Week 6	6.4 (0.2)	5.5 (0.2)	0.0017	5.2 (0.2)	0.0002
Week 7	6.3 (0.2)	5.4 (0.2)	0.0037	5.2 (0.2)	0.0016
Week 8	6.3 (0.2)	5.2 (0.2)	0.0005	5.2 (0.2)	0.0005
Endpoint	6.3 (0.2)	5.2 (0.2)	0.0004	5.2 (0.2)	0.0004

p-value: using Hochberg's test of difference from control (placebo)

3. Average pain scores were calculated for non-completers until the week they dropped out when baseline pain scores were then assigned.

Table 10: Mean Pain Score by Dose (BOCF) – ITT population

	Placebo N=81	PGB 150 N=81	PGB 300 N=76
Baseline	6.64 (1.6)	6.93 (1.7)	6.98 (1.6)
Week 1	6.37 (1.8)	5.99 (2.1)	5.77 (2.0)
Week 2	6.27 (1.9)	5.76 (2.2)	5.22 (2.2)
Week 3	6.30 (1.9)	5.65 (2.2)	5.53 (2.2)
Week 4	6.30 (1.9)	5.69 (2.2)	5.46 (2.2)
Week 5	6.12 (2.0)	5.57 (2.4)	5.36 (2.3)
Week 6	6.22 (2.1)	5.58 (2.3)	5.27 (2.4)
Week 7	6.09 (2.1)	5.47 (2.3)	5.33 (2.4)
Week 8	6.14 (2.2)	5.28 (2.5)	5.32 (2.6)
Endpoint[1]	6.15 (2.1)	5.31 (2.5)	5.34 (2.6)

[1] using the last 7 daily scores

Table 11: Least Square Mean Pain Score by Dose (BOCF) - ITT population

	Placebo N=81	PGB 150 N=81		PGB 300 N=76	
	mean (SD)	mean (SD)	P value	mean (SD)	P value
Week 1	6.6 (0.1)	5.9 (0.1)	0.0014	5.6 (0.1)	0.0002
Week 2	6.5 (0.2)	5.7 (0.2)	0.0015	5.1 (0.2)	0.0002
Week 3	6.5 (0.2)	5.6 (0.2)	0.0001	5.4 (0.2)	0.0001
Week 4	6.5 (0.2)	5.6 (0.2)	0.0003	5.3 (0.2)	0.0002
Week 5	6.3 (0.2)	5.5 (0.2)	0.0027	5.2 (0.2)	0.0004
Week 6	6.4 (0.2)	5.5 (0.2)	0.0013	5.2 (0.2)	0.0002
Week 7	6.2 (0.2)	5.4 (0.2)	0.0041	5.2 (0.2)	0.0012
Week 8	6.3 (0.2)	5.2 (0.2)	0.0005	5.2 (0.2)	0.0005
Endpoint	6.3 (0.2)	5.2 (0.2)	0.0004	5.2 (0.2)	0.0004

p-value: using Hochberg's test of difference from control (placebo)

Appears This Way
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Appendix II: Re-Analysis of Study 045

The following are re-analyses of Study 045 with new treatment assignments taking into account patient's creatinine clearance at baseline. These analyses were done upon the request of Dr. Winchell and Dr. Kashoki.

The results following Tables 1A-1B and Figure 1A indicated that only patients with low creatinine clearance taking pregabalin 150 mg/d and patients with normal creatinine clearance taking pregabalin 300 mg/d seem to show significant difference with the placebo. The change from baseline is significantly higher in these subgroups compared to the other subgroups and the placebo. Based on the responder analysis with 50% pain reduction, higher percentage of subjects with low creatinine clearance were responding to the pregabalin 150 mg/d, and higher percentage of subjects with normal creatinine clearance were responding to the pregabalin 300 mg/d. Note however that these analyses are post-hoc, and that the actual study is not designed to analyze such treatment groupings. Therefore, sample size required in each group may not be adequate to detect real treatment difference.

Table 1A: Least Square Mean Pain Score by Dose (BOCF) – ITT population

	Placebo N=81	PGB 150-Low N=42		PGB 150-Normal N=39		PGB 300-Low N=45		PGB 300-Normal N=31	
	Mean (SD)	mean (SD)	P value[1]	Mean (SD)	P value[1]	mean (SD)	P value[1]	Mean (SD)	P value[1]
Week 1	6.6 (0.1)	5.7 (0.2)	0.0008	6.3 (0.2)	0.1797	6.2 (0.2)	0.1606	5.8 (0.2)	0.0078
Week 2	6.5 (0.2)	5.3 (0.2)	0.0003	6.2 (0.2)	0.1867	5.8 (0.2)	0.0098	5.0 (0.3)	0.0003
Week 3	6.5 (0.2)	5.3 (0.2)	0.0004	5.9 (0.2)	0.0253	5.7 (0.2)	0.0034	5.4 (0.3)	0.0012
Week 4	6.5 (0.2)	5.4 (0.2)	0.0003	5.9 (0.2)	0.0293	5.7 (0.2)	0.0102	5.0 (0.3)	0.0003
Week 5	6.3 (0.2)	5.3 (0.3)	0.0051	5.7 (0.3)	0.0378	5.6 (0.3)	0.0378	4.8 (0.3)	0.0004
Week 6	6.4 (0.2)	5.2 (0.3)	0.0018	5.8 (0.3)	0.0799	5.6 (0.3)	0.0450	4.6 (0.3)	0.0004
Week 7	6.2 (0.2)	5.0 (0.3)	0.0024	5.8 (0.3)	0.1678	5.6 (0.3)	0.1284	4.7 (0.3)	0.0004
Week 8[2]	6.3 (0.2)	4.9 (0.3)	0.0006	5.5 (0.3)	0.0716	5.7 (0.3)	0.0716	4.5 (0.4)	0.0004
Endpoint[3]	6.3 (0.2)	4.9 (0.3)	0.0003	5.5 (0.3)	0.0587	5.7 (0.3)	0.0587	4.6 (0.3)	0.0003

[1] using Hochberg's test of difference from control (placebo)
[2] Week 8= baseline mean pain score for non-completers, and average of day 51 to day 57 pain scores for completers
[3] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose

Table 1B: Change in Mean Pain Scores: Results of Analysis of Covariance

	Placebo	PGB150-Low	PGB150-Normal	PGB300-Low	PGB300-Normal
Baseline[1]	6.64 (1.6)	7.02 (1.7)	6.84 (1.6)	6.96 (1.7)	7.00 (1.6)
Endpoint[2]	6.15 (2.1)	5.14 (2.5)	5.48 (2.4)	5.83 (2.4)	4.62 (2.6)
Change[3]	0.50 (1.5)	1.88 (1.9)	1.36 (2.1)	1.13 (1.7)	2.38 (2.8)
lsmeans	0.52 (0.2)	1.94 (0.3)	1.32 (0.3)	1.20 (0.3)	2.28 (0.3)
p-value[4]		0.0003	0.0587	0.0587	0.0003
Week 8[5]	6.14 (2.2)	5.07 (2.5)	5.49 (2.5)	5.83 (2.4)	4.57 (2.7)
Change[6]	0.51 (1.5)	1.89 (1.9)	1.35 (2.1)	1.13 (1.7)	2.44 (2.9)
lsmeans	0.54 (0.2)	1.97 (0.3)	1.32 (0.3)	1.19 (0.3)	2.33 (0.4)
p-value[4]		0.0006	0.0716	0.0716	0.0004

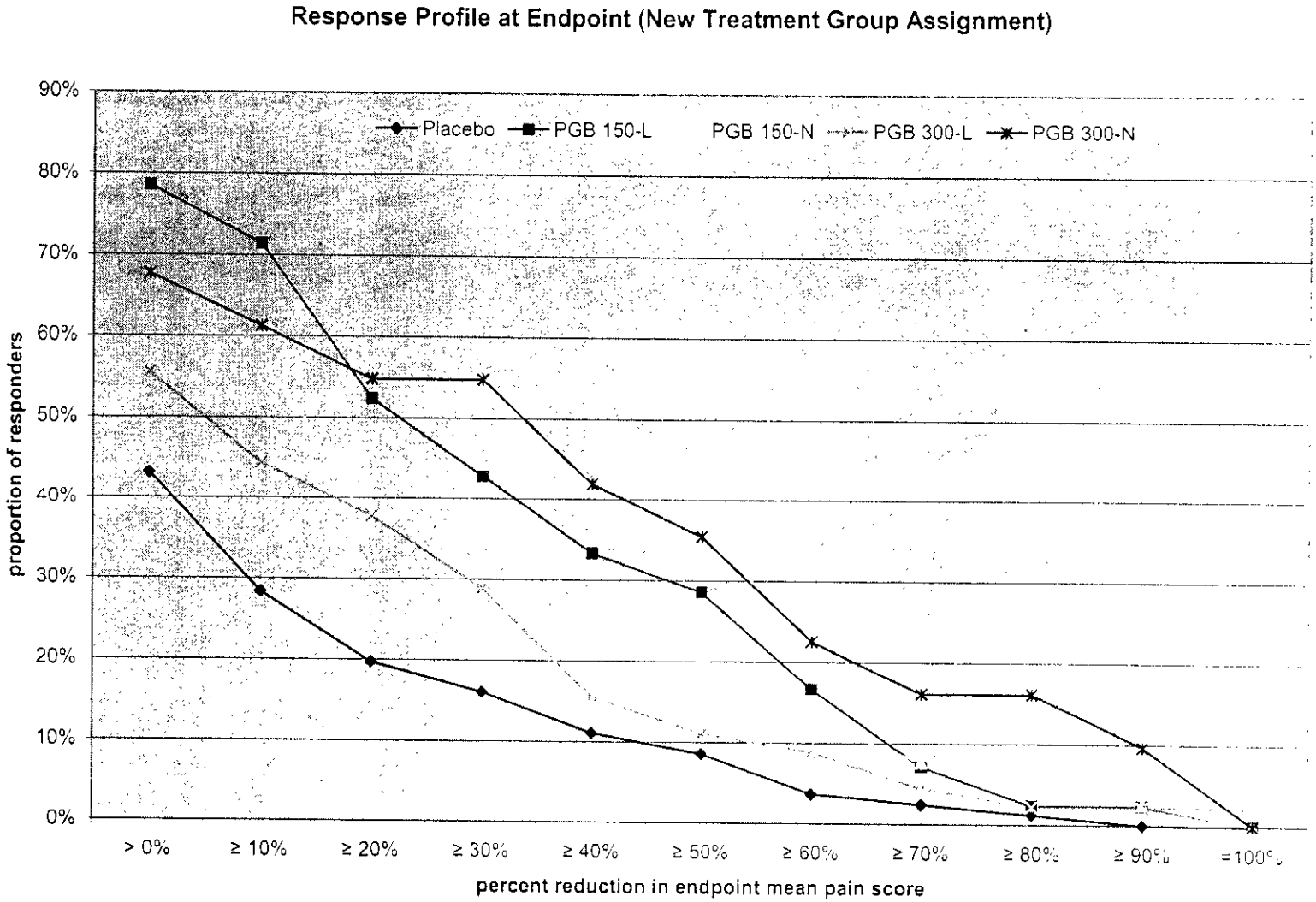
[1] Baseline = Last 7 available scores before taking study medication, up to and including Day 1
[2] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose
[3] Change= Baseline – Endpoint
[4] using Hochberg's test of difference from control (placebo)
[5] Week 8= baseline mean pain score for non-completers, and average of day 51 to day 57 pain scores for completers
[6] Change= Baseline – Week 8

Table 1C: Percentage change in Endpoint mean pain score by dose using new treatment assignment based on creatinine clearance (BOCF) – ITT population

	TOTAL		**PLACEBO**		**PGB 150[1]**		**PGB 150[2]**		**PGB 300[1]**		**PGB 300[2]**	
	Total	**%**	**Total**	**%**	**Total**	**%**	**Total**	**%**	**Total**	**%**	**Total**	**%**
Any increase	39	16%	19	23%	3	7%	8	21%	4	9%	5	16%
None	59	25%	27	33%	6	14%	5	13%	16	36%	5	16%
> 0 % decrease	140	59%	35	43%	33	79%	26	67%	25	56%	21	68%
≥ 10%	115	48%	23	28%	30	71%	23	59%	20	44%	19	61%
≥ 20%	86	36%	16	20%	22	52%	14	36%	17	38%	17	55%
≥ 30%	72	30%	13	16%	18	43%	11	28%	13	29%	17	55%
≥ 40%	53	22%	9	11%	14	33%	10	26%	7	16%	13	42%
≥ 50%	**43**	**18%**	**7**	**9%**	**12**	**29%**	**8**	**21%**	**5**	**11%**	**11**	**35%**
≥ 60%	26	11%	3	4%	7	17%	5	13%	4	9%	7	23%
≥ 70%	15	6%	2	2%	3	7%	3	8%	2	4%	5	16%
≥ 80%	10	4%	1	1%	1	2%	2	5%	1	2%	5	16%
≥ 90%	6	3%	0	0%	1	2%	1	3%	1	2%	3	10%
=100%	1	0%	0	0%	0	0%	0	0%	1	2%	0	0%

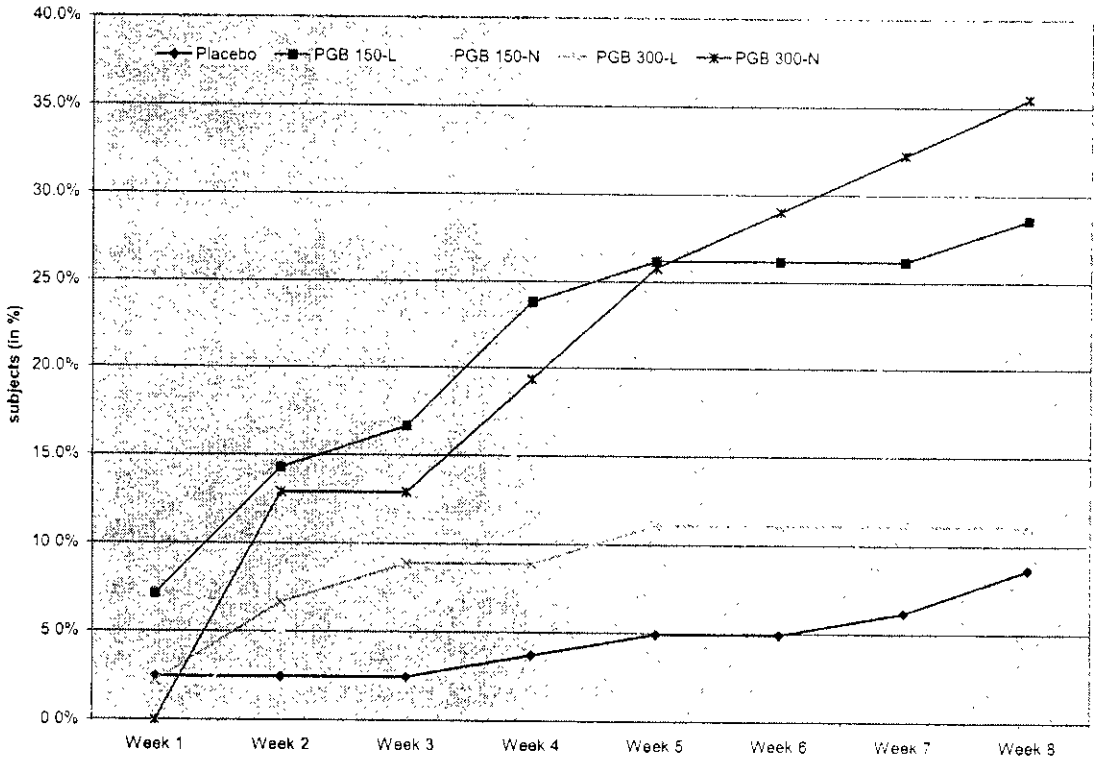
[1]Low = creatinine clearance is between 30 and 60 mL/min
[2]Normal = creatinine clearance >60 mL/min

Figure 1A:


Response Profile at Endpoint (New Treatment Group Assignment)
Placebo
PGB 150-L
PGB 150-N
PGB 300-L
PGB 300-N
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
proportion of responders
> 0%
≥ 10%
≥ 20%
≥ 30%
≥ 40%
≥ 50%
≥ 60%
≥ 70%
≥ 80%
≥ 90%
=100%
percent reduction in endpoint mean pain score

There were a total of 43 subjects (completer) who had 50% mean pain reduction at the end of the study. Figure 1B displays the distribution of these patients from the beginning of the study (week 1) to the end of the study (week 8). The graph shows an increasing trend of responders, particularly on patients with low creatinine clearance taking pregabalin 150, and patients with normal creatinine clearance taking pregabalin 300. This suggests that patient with low creatinine clearance taking pregabalin 150 mg/d who did not respond at week 1 has a potential to respond until week 5, and patient with normal creatinine clearance taking pregabalin 300 mg/d has a chance to respond until or over week 8. Meanwhile, patients in the other subgroups did not show any trend.

Figure 1B: Proportion of Responders by Week



Appendix III:

Upon the request of Dr. Winchell and Dr. Kashoki, statistical tests were conducted on the percentage change in endpoint/week 8/week 13 mean pain score by dose using Cochran-Mantel-Haenszel test. It is important to remind the reader that the purpose of presenting the responder rates for each percentage change (by deciles) in pain reduction is for exploratory purpose. In other words, the responder rates were calculated in order to determine any possible trends in each dose groups, as well as to explore treatment difference. Therefore, any conclusion drawn from the statistical tests should be taken with caution.

Study 045: Response profile with P-values

Table 13: Percentage change in endpoint mean pain score by dose (BOCF) – ITT population

	TOTAL		**PLACEBO**		**PGB150**				**PGB300**			
	Total	**%**	**Total**	**%**	**Total**	**%**	**p-value[1]**	**p-value[2]**	**Total**	**%**	**p-value[1]**	**p-value[2]**
Any increase	39	16%	19	23%	11	14%	0.0935	0.0935	9	12%	0.0420	0.0840
None	59	25%	27	33%	11	14%	0.0042	0.0084	21	28%	0.4258	0.4258
> 0 % decrease	140	59%	35	43%	59	73%	0.0002	0.0004	46	61%	0.0242	0.0242
≥ 10%	115	48%	23	28%	53	65%	<0.0001	0.0002	39	51%	0.0035	0.0035
≥ 20%	86	36%	16	20%	36	44%	0.0007	0.0007	34	45%	0.0007	0.0007
≥ 30%	72	30%	13	16%	29	36%	0.0027	0.0027	30	39%	0.0013	0.0026
≥ 40%	53	22%	9	11%	24	30%	0.0035	0.0070	20	26%	0.0213	0.0213
≥ 50%	**43**	**18%**	7	**9%**	**20**	**25%**	**0.0044**	**0.0088**	**16**	**21%**	**0.0325**	**0.0325**
≥ 60%	26	11%	3	4%	12	15%	0.0073	0.0146	11	14%	0.0198	0.0198
≥ 70%	15	6%	2	2%	6	7%	0.1044	0.1044	7	9%	0.0580	0.1044
≥ 80%	10	4%	1	1%	3	4%	0.2371	0.2371	6	8%	0.0321	0.0642
≥ 90%	6	3%	0	0%	2	2%	0.1435	0.1435	4	5%	0.0340	0.0680
=100%	1	0%	0	0%	0	0%	-		1	1%	0.3173	

[1] p-values are based on the results of the Cochran-Mantel Haenzel procedure, adjusting for center (Unadjusted)
[1] p-values are based on the results of the Cochran-Mantel Haenzel procedure, adjusting for center (Adjusted based on Hochberg's procedure)

Table 14: Percentage change in Week 8 mean pain score by dose (BOCF) – ITT population

	TOTAL		PLACEBO		PGB150				PGB300			
	Total	%	Total	%	Total	%	p-value[1]	p-value[2]	Total	%	p-value[1]	p-value[2]
Any increase	39	16%	20	25%	10	12%	0.0373	0.0373	9	12%	0.0267	0.0373
None	60	25%	26	32%	12	15%	0.0126	0.0252	22	29%	0.6486	0.6486
> 0 % decrease	139	58%	35	43%	59	73%	0.0002	0.0004	45	59%	0.0353	0.0353
≥ 10%	113	47%	26	32%	49	60%	0.0003	0.0006	38	50%	0.0278	0.0278
≥ 20%	88	37%	17	21%	37	46%	0.0008	0.0015	34	45%	0.0015	0.0015
≥ 30%	75	32%	15	19%	30	37%	0.0066	0.0066	30	39%	0.0051	0.0066
≥ 40%	56	24%	10	12%	25	31%	0.0047	0.0094	21	28%	0.0255	0.0255
≥ 50%	**45**	**19%**	**9**	**11%**	**21**	**26%**	**0.0127**	**0.0254**	**15**	**20%**	**0.1512**	**0.1512**
≥ 60%	29	12%	4	5%	14	17%	0.0079	0.0158	11	14%	0.0501	0.0501
≥ 70%	18	8%	3	4%	7	9%	0.1625	0.1625	8	11%	0.0826	0.1625
≥ 80%	12	5%	2	2%	4	5%	0.3713	0.3713	6	8%	0.1048	0.2096
≥ 90%	8	3%	1	1%	3	4%	0.3381	0.3381	4	5%	0.1577	0.3154
=100%	2	1%	0	0%	0	0%	-		2	3%	0.1977	

[1] p-values are based on the results of the Cochran-Mantel Haenzel procedure, adjusting for center (Unadjusted)
[2] p-values are based on the results of the Cochran-Mantel Haenzel procedure, adjusting for center (Adjusted based on Hochberg's procedure)

Study 127: Response profile with P-values

Table 24: Percentage change in endpoint mean pain score by dose (BOCF) – ITT population

	TOTAL		PLACEBO		PGB300				PGB600			
	Total	%	Total	%	Total	%	p-value[1]	p-value[2]	Total	%	p-value[1]	p-value[2]
Any increase	22	12.7	16	19.1	3	10.0	0.2398	0.2398	3	5.1	0.0112	0.0224
None	52	30.1	21	25.0	13	43.3	0.1132	0.2264	18	30.5	0.5662	0.5662
> 0 % decrease	99	57.3	47	56.0	14	46.7	0.5310	0.5310	38	64.4	0.2320	0.4640
≥ 10%	86	49.7	36	42.9	14	46.7	0.5448	0.5448	36	61.0	0.0464	0.0928
≥ 20%	75	43.4	27	32.1	14	46.7	0.0853	0.0853	34	57.6	0.0057	0.0114
≥ 30%	58	33.5	20	23.8	12	40.0	0.0230	0.0302	26	44.1	0.0302	0.0302
≥ 40%	54	31.2	20	23.8	10	33.3	0.1231	0.1231	24	40.7	0.0852	0.1231
≥ 50%	**46**	**26.6**	**17**	**20.2**	**9**	**30.0**	**0.1556**	**0.1556**	**20**	**33.9**	**0.1262**	**0.1556**
≥ 60%	35	20.2	12	14.3	8	26.7	0.1004	0.1737	15	25.4	0.1737	0.1737
≥ 70%	28	16.2	11	13.1	5	16.7	0.4341	0.4341	12	20.3	0.3332	0.4341
≥ 80%	14	8.1	8	9.5	2	6.7	0.8295	0.8295	4	6.8	0.4788	0.8295
≥ 90%	10	5.8	5	6.0	1	3.3	0.8997	0.8997	4	6.8	0.7722	0.8997
=100%	6	3.5	3	3.6	1	3.3	0.8196	0.8774	2	3.4	0.8774	0.8774

[1] p-values are based on the results of the Cochran-Mantel Haenzel procedure, adjusting for center (Unadjusted)
[2] p-values are based on the results of the Cochran-Mantel Haenzel procedure, adjusting for center (Adjusted based on Hochberg's procedure)

Table 25: Percentage change in Week 8 mean pain score by dose (BOCF) – ITT population

	TOTAL		PLACEBO		PGB300				PGB600			
	Total	%	Total	%	Total	%	p-value[1]	p-value[2]	Total	%	p-value[1]	p-value[2]
Any increase	19	11%	14	17%	2	7%	0.1269	0.1269	3	5%	0.0170	0.0340
None	49	28%	18	21%	13	43%	0.0354	0.0708	18	31%	0.2633	0.2633
> 0 % decrease	105	61%	52	62%	15	50%	0.3493	0.5930	38	64%	0.5930	0.5930
≥ 10%	94	54%	43	51%	14	47%	0.8472	0.8472	37	63%	0.1717	0.3434
≥ 20%	78	45%	29	35%	14	47%	0.1445	0.1445	35	59%	0.0053	0.0106
≥ 30%	65	38%	24	29%	12	40%	0.1018	0.1018	29	49%	0.0214	0.0428
≥ 40%	58	34%	23	27%	10	33%	0.2742	0.2742	25	42%	0.0970	0.1940
≥ 50%	**51**	**29%**	**20**	**24%**	**10**	**33%**	**0.1330**	**0.1819**	**21**	**36%**	**0.1819**	**0.1819**
≥ 60%	43	25%	17	20%	9	30%	0.1297	0.2594	17	29%	0.2773	0.2773
≥ 70%	35	20%	15	18%	7	23%	0.3294	0.5746	13	22%	0.5746	0.5746
≥ 80%	22	13%	11	13%	5	17%	0.3826	0.7046	6	10%	0.7046	0.7046
≥ 90%	19	11%	10	12%	3	10%	0.9139	0.9139	6	10%	0.8922	0.9139
=100%	7	4%	4	5%	1	3%	0.8196	0.9021	2	3%	0.9021	0.9021

[1] p-values are based on the results of the Cochran-Mantel Haenzel procedure, adjusting for center (Unadjusted)
[2] p-values are based on the results of the Cochran-Mantel Haenzel procedure, adjusting for center (Adjusted based on Hochberg's procedure)

Study 196: Response profile with P-values

Table 39: Percentage change in Week 8 mean pain score by dose using new treatment assignment based on creatinine clearance (BOCF) – ITT population

Treatment	Number Assessed	Number of Responders, (%)	Treatment Comparisons (Pregabalin – Placebo) p-value[2]	p-value[3]
Any Increase				
Total	368	38 (10)		
Placebo	93	18 (19)		
PGB 150-Low[4]	26	2 (8)	0.1611	0.1851
PGB 150-High[5]	61	5 (8)	0.0331	0.0993
PGB 300-Low[4]	59	2 (3)	0.0027	0.0135
PGB 300-High[5]	65	8 (12)	0.1851	0.1851
PGB 600	64	3 (5)	0.0070	0.0280
None				
Total	368	140 (38)		
Placebo	93	39 (42)		
PGB 150-Low[4]	26	13 (50)	0.8597	0.8597
PGB 150-High[5]	61	17 (28)	0.0722	0.3610
PGB 300-Low[4]	59	26 (44)	0.7337	0.8597
PGB 300-High[5]	65	23 (35)	0.6716	0.8597
PGB 600	64	22 (34)	0.2532	0.8597
> 0 % decrease				
Total	368	190 (52)		
Placebo	93	36 (39)		
PGB 150-Low[4]	26	11 (42)	0.3429	0.3429
PGB 150-High[5]	61	39 (64)	0.0015	0.0075
PGB 300-Low[4]	59	31 (53)	0.0704	0.2112
PGB 300-High[5]	65	34 (52)	0.1614	0.3228
PGB 600	64	39 (61)	0.0042	0.0168
≥ 10%				
Total	368	165 (45)		
Placebo	93	27 (29)		
PGB 150-Low[4]	26	8 (31)	0.5879	0.5879
PGB 150-High[5]	61	36 (59)	0.0002	0.0010
PGB 300-Low[4]	59	27 (46)	0.0238	0.0658
PGB 300-High[5]	65	31 (48)	0.0329	0.0658
PGB 600	64	36 (56)	0.0007	0.0028
≥ 20%				
Total	368	137 (37)		
Placebo	93	22 (24)		
PGB 150-Low[4]	26	8 (31)	0.2912	0.2912
PGB 150-High[5]	61	31 (51)	0.0006	0.0024
PGB 300-Low[4]	59	21 (36)	0.1046	0.2912
PGB 300-High[5]	65	22 (34)	0.1941	0.2912
PGB 600	64	33 (52)	0.0003	0.0015

Table 39 (Continued):

Treatment	Number Assessed	Number of Responders, (%)	Treatment Comparisons (Pregabalin – Placebo) p-value[2]	p-value[3]
≥ 30%				
Total	368	109 (30)		
Placebo	93	18 (19)		
PGB 150-Low[4]	26	5 (19)	0.6963	0.6963
PGB 150-High[5]	61	26 (43)	0.0019	0.0095
PGB 300-Low[4]	59	15 (25)	0.3537	0.6963
PGB 300-High[5]	65	21 (32)	0.0854	0.2562
PGB 600	64	24 (38)	0.0106	0.0424
≥ 40%				
Total	368	83 (23)		
Placebo	93	8 (9)		
PGB 150-Low[4]	26	5 (19)	0.0602	0.0602
PGB 150-High[5]	61	18 (30)	0.0012	0.0048
PGB 300-Low[4]	59	13 (22)	0.0153	0.0306
PGB 300-High[5]	65	17 (26)	0.0042	0.0126
PGB 600	64	22 (34)	<0.0001	0.0005
≥ 50%				
Total	368	65 (18)		
Placebo	93	6 (6)		
PGB 150-Low[4]	26	2 (8)	0.5623	0.5623
PGB 150-High[5]	61	13 (21)	0.0093	0.0279
PGB 300-Low[4]	59	10 (17)	0.0180	0.0360
PGB 300-High[5]	65	15 (23)	0.0027	0.0108
PGB 600	64	19 (30)	<0.0001	0.0005
≥ 60%				
Total	368	48 (13)		
Placebo	93	3 (3)		
PGB 150-Low[4]	26	2 (8)	0.2263	0.2263
PGB 150-High[5]	61	10 (16)	0.0052	0.0156
PGB 300-Low[4]	59	7 (12)	0.0187	0.0374
PGB 300-High[5]	65	12 (18)	0.0012	0.0048
PGB 600	64	14 (22)	0.0001	0.0005
≥ 70%				
Total	368	32 (9)		
Placebo	93	3 (3)		
PGB 150-Low[4]	26	2 (8)	0.2263	0.3548
PGB 150-High[5]	61	6 (10)	0.1406	0.3548
PGB 300-Low[4]	59	3 (5)	0.3548	0.3548
PGB 300-High[5]	65	7 (11)	0.0453	0.1812
PGB 600	64	11 (17)	0.0014	0.0070

Table 39 (Continued):

Treatment	Number Assessed	Number of Responders, (%)	Treatment Comparisons (Pregabalin – Placebo) p-value[2]	p-value[3]
≥ 80%				
Total	368	17 (5)		
Placebo	93	3 (3)		
PGB 150-Low[4]	26	1 (4)	0.7038	0.9241
PGB 150-High[5]	61	2 (3)	0.9204	0.9241
PGB 300-Low[4]	59	1 (2)	0.7659	0.9241
PGB 300-High[5]	65	2 (3)	0.9241	0.9241
PGB 600	64	8 (13)	0.0172	0.0860
≥ 90%				
Total	368	6 (2)		
Placebo	93	1 (1)		
PGB 150-Low[4]	26	1 (4)	0.4975	0.4975
PGB 150-High[5]	61	0 (0)	0.4497	0.4975
PGB 300-Low[4]	59	0 (0)	0.3545	0.4975
PGB 300-High[5]	65	0 (0)	0.3980	0.4975
PGB 600	64	4 (6)	0.0417	0.2085
= 100%				
Total	368	2 (1)		
Placebo	93	1 (1)		
PGB 150-Low[4]	26	0 (0)	0.5930	0.6182
PGB 150-High[5]	61	0 (0)	0.4497	0.6182
PGB 300-Low[4]	59	0 (0)	0.3545	0.6182
PGB 300-High[5]	65	0 (0)	0.3980	0.6182
PGB 600	64	1 (2)	0.6182	0.6182

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Table 40: Percentage change in endpoint mean pain score by dose using new treatment assignment based on creatinine clearance (BOCF) – ITT population

Treatment	Number Assessed	Number of Responders, (%)	Treatment Comparisons (Pregabalin – Placebo) p-value[2]	p-value[3]
Any Increase				
Total	368	48 (13)		
Placebo	93	21 (23)		
PGB 150-Low[4]	26	2 (8)	0.1068	0.1857
PGB 150-High[5]	61	9 (15)	0.1857	0.1857
PGB 300-Low[4]	59	2 (3)	0.0014	0.0070
PGB 300-High[5]	65	8 (12)	0.0737	0.1857
PGB 600	64	6 (9)	0.0300	0.1200
None				
Total	368	137 (37)		
Placebo	93	36 (39)		
PGB 150-Low[4]	26	14 (54)	0.3658	0.8168
PGB 150-High[5]	61	16 (26)	0.1020	0.5100
PGB 300-Low[4]	59	27 (46)	0.4084	0.8168
PGB 300-High[5]	65	24 (37)	0.9185	0.9185
PGB 600	64	20 (31)	0.2278	0.8168
> 0 % decrease				
Total	368	183 (50)		
Placebo	93	36 (39)		
PGB 150-Low[4]	26	10 (38)	0.6106	0.6106
PGB 150-High[5]	61	36 (59)	0.0117	0.0468
PGB 300-Low[4]	59	30 (51)	0.1313	0.3716
PGB 300-High[5]	65	33 (45)	0.1858	0.3716
PGB 600	64	38 (55)	0.0056	0.0280
≥ 10%				
Total	368	155 (42)		
Placebo	93	25 (27)		
PGB 150-Low[4]	26	8 (31)	0.5271	0.5271
PGB 150-High[5]	61	31 (51)	0.0031	0.0124
PGB 300-Low[4]	59	27 (46)	0.0223	0.0669
PGB 300-High[5]	65	29 (45)	0.0342	0.0684
PGB 600	64	35 (55)	0.0002	0.0010
≥ 20%				
Total	368	128 (35)		
Placebo	93	19 (20)		
PGB 150-Low[4]	26	6 (23)	0.5274	0.5274
PGB 150-High[5]	61	30 (49)	0.0001	0.0005
PGB 300-Low[4]	59	21 (36)	0.0360	0.1080
PGB 300-High[5]	65	22 (34)	0.0653	0.1306
PGB 600	64	30 (47)	0.0003	0.0012

Table 40 (Continued):

Treatment	Number Assessed	Number of Responders, (%)	Treatment Comparisons (Pregabalin – Placebo) p-value[2]	p-value[3]
≥ 30%				
Total	368	107 (29)		
Placebo	93	15 (16)		
PGB 150-Low[4]	26	5 (19)	0.4408	0.4408
PGB 150-High[5]	61	25 (41)	0.0005	0.0020
PGB 300-Low[4]	59	14 (24)	0.1490	0.2980
PGB 300-High[5]	65	21 (32)	0.0180	0.0540
PGB 600	64	27 (42)	0.0003	0.0015
≥ 40%				
Total	368	87 (24)		
Placebo	93	8 (9)		
PGB 150-Low[4]	26	5 (19)	0.0384	0.0384
PGB 150-High[5]	61	19 (31)	0.0002	0.0008
PGB 300-Low[4]	59	13 (22)	0.0089	0.0178
PGB 300-High[5]	65	18 (28)	0.0011	0.0033
PGB 600	64	24 (38)	<0.0001	0.0005
≥ 50%				
Total	368	72 (20)		
Placebo	93	6 (6)		
PGB 150-Low[4]	26	5 (19)	0.0216	0.0216
PGB 150-High[5]	61	17 (28)	0.0002	0.0008
PGB 300-Low[4]	59	11 (19)	0.0089	0.0200
PGB 300-High[5]	65	13 (20)	0.0100	0.0200
PGB 600	64	20 (31)	<0.0001	0.0005
≥ 60%				
Total	368	50 (14)		
Placebo	93	6 (6)		
PGB 150-Low[4]	26	1 (4)	0.9021	0.9021
PGB 150-High[5]	61	11 (18)	0.0250	0.1000
PGB 300-Low[4]	59	6 (10)	0.3014	0.6028
PGB 300-High[5]	65	11 (17)	0.0344	0.1032
PGB 600	64	15 (23)	0.0010	0.0050
≥ 70%				
Total	368	38 (10)		
Placebo	93	5 (5)		
PGB 150-Low[4]	26	1 (4)	0.8933	0.8933
PGB 150-High[5]	61	11 (18)	0.1604	0.4168
PGB 300-Low[4]	59	6 (10)	0.1690	0.4168
PGB 300-High[5]	65	11 (17)	0.2084	0.4168
PGB 600	64	15 (23)	0.0036	0.0180

Table 40 (Continued):

Treatment	Number Assessed	Number of Responders, (%)	Treatment Comparisons (Pregabalin – Placebo) p-value[2]	p-value[3]
≥ 80%				
Total	368	23 (6)		
Placebo	93	4 (4)		
PGB 150-Low[4]	26	1 (4)	0.4658	0.9316
PGB 150-High[5]	61	7 (11)	0.9922	0.9922
PGB 300-Low[4]	59	6 (10)	0.1928	0.7712
PGB 300-High[5]	65	11 (17)	0.2885	0.8655
PGB 600	64	15 (23)	0.0154	0.0770
≥ 90%				
Total	368	11 (3)		
Placebo	93	3 (3)		
PGB 150-Low[4]	26	0 (0)	0.6547	0.9871
PGB 150-High[5]	61	2 (3)	0.9871	0.9871
PGB 300-Low[4]	59	2 (3)	0.6345	0.9871
PGB 300-High[5]	65	0 (0)	0.1370	0.6850
PGB 600	64	4 (6)	0.3889	0.9871
= 100%				
Total	368	8 (2)		
Placebo	93	2 (2)		
PGB 150-Low[4]	26	0 (0)	0.6547	0.7911
PGB 150-High[5]	61	2 (3)	0.7911	0.7911
PGB 300-Low[4]	59	1 (2)	0.7870	0.7911
PGB 300-High[5]	65	0 (0)	0.2457	0.7911
PGB 600	64	3 (5)	0.4432	0.7911

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/s/

Joan Buenconsejo
8/6/04 12:32:26 PM
BIOMETRICS

S. Edward Nevius
8/6/04 03:00:01 PM
BIOMETRICS
Concur with review.

NDA 21-723, pregabalin

Additional information pertaining to this section can be found in the action package for NDA 21-446.