DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA - EFFICACY

Brand Name:	**Lyrica**
Generic Name:	**pregabalin**
Sponsor:	**Pfizer**
Indication:	**Epilepsy, Adjunctive use**
NDA Number:	**21-724**
Original Receipt Date:	**October 1, 2003**
Clinical Reviewer:	**Howard D. Chazin, M.D.**
Review Author:	**Howard D. Chazin, M.D.**
Review Completed:	**August 11, 2004**

1 Executive Summary/Conclusions

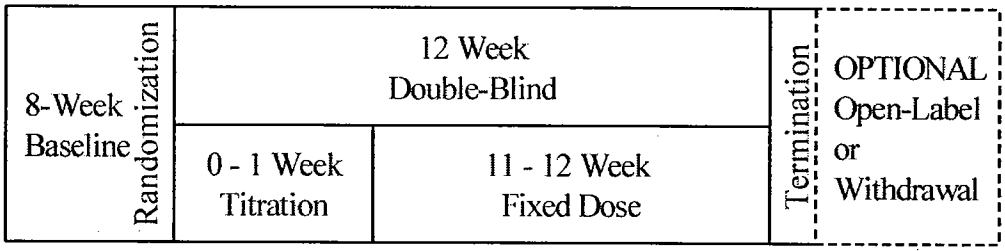
1.1 Recommendation on Approvability

Due to the strong efficacy results, this reviewer would recommend approval of this drug for use as adjunctive therapy for epilepsy. However, this review should be only one part of a total review of the drug and does not attend to the drug safety issues or other issues raised by other reviewers.

1.1.1 Introduction

This reviewer was responsible primarily for the efficacy review of pregabalin for use as adjunctive treatment in epilepsy. The results of three large adjunctive add-on epilepsy trials (Studies 009, 011 and 034) were used to support the efficacy evaluation. Each epilepsy study comprised three phases illustrated in Sponsor Figure 47.

Figure 47. Overall Study Design for 3 Add-On Epilepsy Studies



The **8-week baseline phase** allowed for patients to stay on their baseline seizure medication. Patients recorded in their seizure diaries the number of baseline seizures.

During the **12-week double-blind phase**, patients were randomly assigned to add on therapy either with pregabalin or placebo. In Studies 009 and 011, pregabalin doses were titrated to full dose over 1 week. In Study 034, pregabalin doses were not titrated and patients received the full dose on Day 1. Existing antiepileptic (AED) therapy was kept constant, and was only allowed to be adjusted for intolerable CNS adverse events. Seizures were recorded in a daily diary.

Patients who withdrew early or completed the double-blind phase had the option of either entering the follow-on, open-label study or discontinuing treatment during a withdrawal phase.

Generally, to ensure a refractory period, the following **inclusion criteria** were common to all pivotal studies.

- A history of partial seizures (as defined by the International League Against Epilepsy Classification of Seizures) along with an EEG within the preceding 2 years consistent with the diagnosis of focal onset epilepsy.
- A minimum of three partial seizures during the one month prior to screening entry for baseline.
- A baseline seizure frequency of not less than six partial seizures during an eight-week baseline with no seizure free period for four weeks or more.
- Currently taking at least one but no more than three antiepileptic drugs and dosing within a clinically acceptable therapeutic range and within the range of tolerability for the patient.
- History of being refractory to at least 2 marketed AEDs at maximum tolerated doses.
- In addition, patients were not to have a treatable cause of seizures, absence seizures, Lennox-Gastaut Syndrome or a progressive neurological or systemic disorder. **Adolescents aged 12 to 17 years were included in Study 034. Patients less than 12 years of age were excluded from all three trials; therefore, no efficacy claims are being sought by the sponsor outside of this age range.**
- Patients were also required to have normal creatinine clearance at baseline (>60ml/min).

Patients were excluded if they had no seizures, a treatable cause of seizures, Lennox-Gastaut Syndrome, or status epilepticus within the previous year.

Efficacy of pregabalin was established by reduction in frequency of all partial seizures during the double-blind period compared with the baseline period. For each patient, the baseline period was defined as Days -56 to -1. The double-blind period was defined as starting on Day 1 and ending on the last day the patient took study medication during the double-blind treatment period. The observed seizure rate during baseline and double-blind was standardized for a 28-day period. Because the amount of diary data and duration of time in the double-blind period of the study varied from patient to patient, the 28-day seizure rate was defined as follows:

$$28\text{-day rate} = \frac{\#\text{ of partial seizures in period}}{[\#\text{ of days in period} - \#\text{ of missing diary days in period}]} \times 28$$

Period in the above formula was either the baseline phase or double-blind phase of the study.

The **primary efficacy parameter**, response ratio (RRatio or symmetrized percent change) compares baseline seizure frequency (B) with treatment seizure frequency (T). The RRatio (or symmetrized percent change) is calculated by dividing the difference between 28-day seizure rates during treatment and baseline by the sum of baseline and double-blind seizures.

$$\mathbf{RRatio = [(T - B)/(T + B)] \times 100.}$$

The RRatio is between 100 and -100. Negative values indicate reduction in seizure rate and positive values indicate increase in seizure rate during treatment. An RRatio of -33 is equivalent to a 50% reduction in seizures. Analysis was performed using an analysis of variance (ANOVA) model with treatment (as main effect), center (clusters), and rank RRatio as the dependent variable.

1.1.2 Study Summaries

Study 009 was a 12-week randomized, double-blind, parallel-group, placebo-controlled multicenter study evaluating the efficacy and safety of 2 regimens of 600 mg/day pregabalin as adjunctive therapy in patients with partial seizures. Men and women at least 18 years of age with partial seizures not adequately controlled while on 1-3 standard

antiepileptic drugs were eligible to enroll. Following an 8-week baseline period, **312** patients received placebo or either pregabalin 600 mg/day given twice a day (BID) or pregabalin 600 mg/day given 3 times a day (TID). Patients maintained their current AED therapy throughout the study.

The 3 treatment groups were well-matched on demographic parameters, including age, sex, and race. All of the patients who entered the double-blind treatment phase had medically refractory partial seizures. A total of 378 patients entered the baseline phase, of these, 65 did not qualify or withdrew, so that 313 were randomized and 312 went on to receive study drug. The majority of the randomized patients (76%) completed the 12-week study. During the study, 76 patients (24%) withdrew, more in the placebo group due to lack of efficacy, while the rate for adverse event withdrawals was higher for the pregabalin groups. Specifically, 27 patients (26%) in the pregabalin BID group, 21 patients (19%) in the pregabalin TID group, and 7 patients (7%) in the placebo group withdrew due to adverse events. Completion rate was slightly higher in the placebo group (83%) compared to the pregabalin groups (77% for TID and 68% for BID). 237 patients (76%) completed the 12-week study and 260 patients entered the open-label extension Study 1008-010.

Results from the planned primary analysis (RRatio) with the primary ITT population demonstrate that pregabalin 600 mg/day administered TID or BID resulted in highly significant reductions in seizure frequency compared with placebo (ANOVA, rank transformed analysis adjusted for cluster, all p <0.0001). This is illustrated in Sponsor Table 12 reproduced below.

Table 12. Summary of RRatio Analysis (All Partial Seizures): ITT Population

Treatment Comparisons (Group 1/Group 2)	Treatment Differences[a]			p-Value[b]	Generaliz-ability[c]
	N[d]	Means (SE)	95% CI		
PGB 600 mg/day TID/PBO	111/98	-36.7 (5.0)	[-46.4, -27.0]	P ≤0.0001*	
PGB 600 mg/day BID/PBO	103/98	-29.0 (5.0)	[-38.9, -19.0]	P ≤0.0001*	
PGB 600 mg/day TID/PGB 600 mg/day BID	111/103	-7.7 (4.9)	[-17.4, 1.9]	P = 0.1092	P = 0.9387

PGB = Pregabalin; PBO = Placebo.

* = Statistically significant based on Hochberg's procedure (p ≤0.049).

[a] Based on treatment means for the raw RRatio

[b] Hochberg procedure applied to the ranked RRatio

[c] Treatment-by-cluster interaction for the ranked RRatio

[d] N for Group 1/N for Group 2

Study 011 was a 12-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter study evaluating the safety, efficacy, and dose-response characteristics of pregabalin administered three times a day (TID) as add-on treatment in patients with

partial seizures. Men and women at least 18 years of age with partial seizures not adequately controlled while on 1-3 standard antiepileptic drugs were eligible to enroll. Following screening and an 8-week baseline period, 288 patients were randomized to receive placebo, pregabalin 150 mg/day, or pregabalin 600 mg/day. Study medication was titrated over 1 week; **287** patients received study medication.

Of the 344 patients who entered the baseline phase of the study, 288 patients were randomized to treatment and 287 went on to receive study drug (145 men, 142 women). The 3 treatment groups were well matched on all demographic parameters. Ninety-two patients received 600 mg/day pregabalin, 99 received 150 mg/day pregabalin, and 96 received placebo. A total of 241 patients completed the study. Forty-seven patients withdrew from the double-blind phase of the study, 33 of these withdrew due to adverse events.

Results for the primary efficacy parameter, (RRatio) with the primary ITT population, demonstrated the efficacy of pregabalin at doses of 600 and 150 mg/day. Statistically significant differences favoring both pregabalin treatment groups compared to the placebo group were seen in the analysis of RRatio for all partial seizures (during the double-blind phase) at the endpoint of the study compared to baseline. ($p<0.0001$ and $p=0.0007$ respectively, ANOVA, rank transformed analysis adjusted for cluster). This is summarized in Sponsor Table 14 below.

Table 14. Summary of RRatio Analysis for All Partial Seizures: ITT Population

Treatment Comparisons	Treatment Differences[a]			p-value
	N[b]	Mean (SE)	95% CI	
PGB 600 mg/day TID vs Placebo	92/96	-32.3 (4.2)	[-40.6, -24.0]	p <0.0001*
PGB 150 mg/day TID vs Placebo	99/96	-12.4 (4.1)	[-20.5, -4.3]	p = 0.0007*
PGB 600 mg/day TID vs 150 mg/day TID	92/99	-19.9 (4.2)	[-28.1, -11.7]	p <0.0001†
Generalizability[c]	p = 0.7028			
Linear Trend[d]	p <0.0001†			

* Statistically significant based on the Ruberg procedure ($p \leq 0.05$).
† Statistically significant ($p \leq 0.05$).
[a] Based on means for the untransformed RRatio data
[b] N in Group 1/N in Group 2
[c] Treatment-by-cluster interaction for the model-ranked RRatio
[d] Linear contrast

Study 034 was a 12-week, double-blind, parallel-group, placebo-controlled study evaluating the efficacy and safety of 4 dosages of pregabalin as add-on treatment in patients with partial seizures. Patients at least 12 years of age with partial seizures not adequately controlled while on 1-3 standard antiepileptic drugs were eligible to enroll.

Following an 8-week baseline period, a total of **453** patients were randomized to either placebo, or to 1 of 4 pregabalin dose groups: 50, 150, 300, or 600 mg/day administered BID.

A total of 455 patients were randomized to treatment, and 453 received treatment (ITT) population. Of the 453 patients in the ITT population, 100 were randomized to the placebo group, 88 to the 50 mg/day pregabalin group, 86 to the 150 mg/day pregabalin group, 90 to the 300 mg/day pregabalin group, and 89 to the 600 mg/day pregabalin group. Patients were primarily white (85%) and at screening had a mean age of 38 years (range, 12 through 75 years), with a mean age of 14 years at diagnosis of epilepsy. The majority of the randomized patients (83%) completed the study. However, there was a dose-related increase in the incidence of withdrawals due to adverse events in the 600 mg/day (24%) and 300 mg/day (14%) pregabalin groups relative to the placebo group (5%).

Based on the RRatio, all pregabalin treatment groups, except for the 50 mg/day group, showed statistically significantly greater reductions in seizures compared to the placebo group (based on the Ruberg step down procedure for controlling the overall type I error rate at 0.049). The 150 mg/day group was a minimum effective dose. This is summarized in Sponsor Table 12 below.

Table 12. Summary of RRatio Analysis (All Partial Seizures): ITT Population

Treatment Comparisons	Treatment Differences[a]			Probability
	N[b]	Mean (SE)	95% CI	
Pregabalin 600 mg/day BID/Placebo	89/100	-33.5 (4.8)	[-42.9, -24.1]	P ≤0.0001*
Pregabalin 300 mg/day (BID)/Placebo	90/100	-24.0 (4.8)	[-33.3, -14.6]	P ≤0.0001*
Pregabalin 150 mg/day (BID)/Placebo	86/100	-16.6 (4.8)	[-26.1, -7.2]	P ≤0.0001*
Pregabalin 50 mg/day (BID)/Placebo	88/100	-2.3 (4.8)	[-11.7, 7.1]	P = 0.4232
Pregabalin 600 mg/day BID/50 mg/day BID	89/88	-31.2 (4.9)	[-40.9, -21.5]	P ≤0.0001**
Pregabalin 300 mg/day BID/50 mg/day BID	90/88	-21.6 (4.9)	[-31.3, -12.0]	P ≤0.0001**
Pregabalin 150 mg/day BID/50 mg/day BID	86/88	-14.3 (5.0)	[-24.0, -4.5]	P = 0.0013**
Pregabalin 600 mg/day BID/150 mg/day BID	89/86	-16.9 (4.9)	[-26.6, -7.2]	P = 0.0176**
Pregabalin 300 mg/day BID/150 mg/day BID	90/86	-7.3 (4.9)	[-17.0, 2.4]	P = 0.3189
Pregabalin 600 mg/day BID/300 mg/day BID	89/90	-9.6 (4.9)	[-19.2, 0.1]	P = 0.1616
Generalizability[c]		P = 0.1656		
Linear Dose Response With, Without Placebo[d]		P ≤0.0001**, P ≤0.0001**		
Quadratic Dose Response With, Without Placebo[e]		P = 0.0213**, P = 0.0741		

* Statistically significant based on the Ruberg procedure (p ≤0.049)
** Statistically significant (p ≤0.049)
[a] Based on LSMEANS for the untransformed RRatio data
[b] N in Group 1/N in Group 2
[c] Treatment-by-cluster interaction for the model ranked Rratio
[d] Linear contrast
[e] Quadratic contrast

1.1.3 Pooled Efficacy Results

A total of 1056 patients were randomized in the 3 double-blind studies. One patient randomized to placebo and three patients randomized to pregabalin did not take study medication, reducing the intent to treat (ITT) population to 1052, 758 treated with pregabalin and 294 with placebo.

Across the 3 studies, 76% to 84% of all patients completed double-blind treatment and 81% to 87% of all patients chose to enter the corresponding open-label study. The incidence of withdrawals tended to increase with dose, particularly at 300 and 600 mg/day, where withdrawal rates ranged from 21% to 32%. The percentage of patients withdrawing in the 150 mg/day dose groups (given in 2 or 3 divided doses) and 50-mg/day dose group given in 2 divided doses were comparable to the percentages withdrawing in placebo groups. In any of the treatment groups, including the placebo groups, the majority of withdrawals were **due to adverse events**. Adverse event withdrawals increased with increasing doses of pregabalin. Ten to 18% of all patients withdrew due to adverse events across the 3 studies. The percentage of patients withdrawing due to lack of efficacy was 5% in each placebo group and 0% to 5% for the pregabalin treatment groups.

RRatio results for all 3 studies are presented in **Sponsor Table 39** below. The p-values reflect the rank transformed analysis of the RRatio, adjusted for center, while the treatment difference estimates are based on the unranked RRatio data. All pregabalin treatment groups, with the exception of the 50-mg/day group, showed statistically significantly greater reductions in seizure frequency compared to the corresponding placebo group. Results were consistent among the 3 studies in doses common across studies (e.g., 150 and 600 mg/day). The minimum effective dose was 150 mg/day, demonstrating significant difference from placebo both in Study 034, where it was given BID and in Study 011, where it was given in TID.

Per the sponsor, Pregabalin demonstrated robust and consistent efficacy at doses of 150, 300, and 600 mg/day in all 3 studies. (Reviewer note: There are some limitations to the sponsor's opinion regarding these results, which need to be interpreted with caution. There appear to be no significant statistical difference in efficacy between the BID and TID doses at 150 and 600mg. The 300mg dose was not tested at TID dosing, only at BID dosing. Also, regarding the 150mg dose group, there seems to be much more robust results in Study 034 compared to Study 011 when comparing the mean RR ratios – 20.5 versus –11.5 respectively. The studies were designed to only demonstrate that the 600mg dose was superior to placebo. The 300mg dose was only explored in one trial and the results from the 150mg dose group are difficult to reconcile, as they were more robust in only one of the two studies in which they were tested.)

Table 39. Summary of RRatio (All Partial Seizures) Results of Analysis of Variance - ITT Population

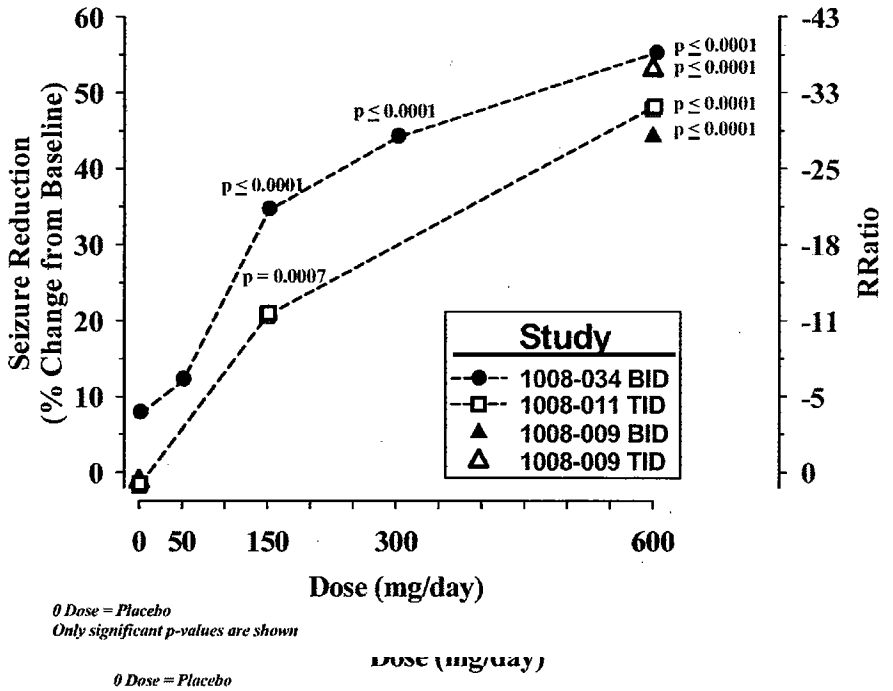
Study/Treatment (Total Daily Dose and Regimen)	N	Mean	SD	Median	Treatment Difference Between Pregabalin and Placebo		
					Mean (SE)	p Value	95% CI
Study 009							
Placebo	98	0.6	28.8	-0.4			
PGB 600 mg/day BID	103	-28.4	36.7	-21.7	-29.0 (5.0)	≤0.0001*	-38.9, -19.0
PGB 600 mg/day TID	111	-36.1	40	-31.7	-36.7 (5.0)	≤0.0001*	-46.4, -27.0
Study 011							
Placebo	96	0.9	26	0.7			
PGB 150 mg/day TID	99	-11.5	22.9	-9	-12.4 (4.1)	0.0007*	-20.5, -4.3
PGB 600 mg/day TID	92	-31.4	36.3	-27.1	-32.3 (4.2)	≤0.0001*	-40.6, -24.0
Study 034							
Placebo	100	-3.8	25.6	0			
PGB 50mg/day BID	88	-6.2	23.7	-4.5	-2.3 (4.8)	0.4232	-11.7, 7.1
PGB 150mg/day BID	86	-20.5	29.6	-21	-16.6 (4.8)	≤0.0001*	-26.1, -7.2
PGB 300mg/day BID	90	-27.8	36.5	-22.5	-24.0 (4.8)	≤0.0001*	-33.3, -14.6
PGB 600mg/day BID	89	-37.4	44.4	-34.1	-33.5 (4.8)	≤0.0001*	-42.9, -24.1

ITT = Intent-to-treat; SD = Standard deviation; SE = standard error; CI = confidence interval; PGB = Pregabalin.

* Statistically significant based on Hochberg's (Study 009) or the Ruberg (Studies 011 and 034) procedure ($\alpha = 0.049$ for Studies 009 and 034, $\alpha = 0.05$ for Study 011).

APPEARS THIS WAY
ON ORIGINAL

Figure 48. Seizure Reduction and Mean RRatio by Dose (All Partial Seizures) for Studies 009, 011, and 034



Dose (mg/day)
0 Dose = Placebo
Only significant p-values are shown

1.1.4 Additional trials

Study 007 (monotherapy)

The objectives of this study were to evaluate the efficacy and safety of pregabalin at 600 mg/day as compared with gabapentin at 300 mg/day (active control) as short term monotherapy in hospitalized patients with complex partial (CP) seizures, with or without secondary generalization. Patients enrolled were those who had their concomitant

antiepileptic drugs (AEDs) discontinued as part of an inpatient hospitalization for clinical seizure monitoring.

Study Design: Patients were screened to enter an **8-day**, randomized, double-blind, parallel-group, low-dose active controlled multicenter study. Following a prestudy period of variable length, randomization was to either 300 mg/day (TID) gabapentin or 600 mg/day (TID) pregabalin. Patients were maintained on randomized dosages for 8 days or until they experienced an exit event (end of 8 days treatment, 1 secondarily-generalized tonic-clonic [SGTC] seizure if negative history; 4 CP and/or SGTC seizures; status epilepticus; prolongation or intensification of seizures; or other lack of efficacy).

During the prestudy period, previous AED therapy (monitoring therapy) was discontinued. This time was highly variable as it comprised the time from entry into the hospital's epilepsy monitoring unit until the patient met entry criteria, was randomized to double-blind therapy and took the first dose of study medication. Patients entered the termination period after exiting or withdrawing from double blind. In termination, patients either tapered off of study medication over 3 days and resumed therapy with standard AEDs or continued and initiated treatment with pregabalin monotherapy or with pregabalin plus up to 2 AEDs in the open-label follow-up study (008).

At the end of the 8-day study, subjects had the option of entering an open-label study (008). However, any patient who experienced a treatment-related serious adverse event was not allowed to enter the open label study.
A total of 93 patients, 51 (55%) men and 42 (45%) women, were randomized to treatment, 42 patients to pregabalin and 51 patients to gabapentin (Sponsor Table 4). Patients were primarily white (87%) and at screening had a mean age of 36 years (range 19 through 65 years), with a mean age of 12 years at diagnosis of epilepsy. The mean weight of the patients randomized to the pregabalin group was slightly (8%) higher than that of the patients randomized to the gabapentin group at prestudy.

All 93 patients enrolled received at least 1 dose of study medication. Fifty-five percent of the patients in the pregabalin group and 22% of the patients in the gabapentin group received all 24 double-blind doses (completed the study). Most patients exited due to study exit criteria. No patient withdrew because of an adverse event. With the exception of 2 pregabalin patients and 8 gabapentin patients who withdrew due to other/administrative reasons, all patients either completed or withdrew due to exit events. This is illustrated in Sponsor Table 10.

should reflect the need to adjust the dose in the likelihood of renal insufficiency in this patient population.

2 Introduction and Background

2.1 Product Information

Pregabalin [CI-1008, (S)-3-(aminomethyl)-5-methylhexanoic acid], is an analogue of gamma-aminobutyric acid (GABA), which is being investigated as an anticonvulsant for the treatment of patients with partial seizures. The mechanism of pregabalin appears different from agents that alter GABA receptors or uptake carriers, Na + channel blockers, opiates, or nonsteroidal anti-inflammatory drugs. Pregabalin is a derivative of GABA, but is not active at several GABA receptors nor does it appear to mimic GABA physiologically.

2.2 State of Armamentarium For Indication (of adjunctive use in epilepsy)

Per FDA COMIS, the following antiepileptic medications are approved for the treatment of epilepsy. Specifics regarding each drug are summarized in the following table.

Drug Name	Sponsor	Indication
DILANTIN (PHENYTOIN)	PFIZER	Partial seizures, Primary generalized tonic clonic seizures.
PHENOBARBITOL	PARKE DAVIS	Primary generalized tonic clonic seizures.
TEGRETOL, TEGRETOLXR (CARBAMAZEPINE)	NOVARTIS	Partial seizures, Primary generalized tonic clonic seizures.
CARBATROL(CARBAMAZEPINE)	SHIRE PHARM	Partial seizures, Primary generalized tonic clonic seizures.
DEPAKOTE(DIVALPROEX SODIUM) ER 500MG TAB	ABBOTT	Epilepsy, monotherapy and adjunctive therapy for partial seizures in isolation or in combination with other seizures.
CEREBYX (FOSPHENYTOIN)	PARKE DAVIS	TREATMENT OF EPILEPSY
FELBATOL (FELBAMATE) CHEWABLE TABS 600MG	MEDPOINTE PHARM HLC	Monotherapy and adjunctive therapy for partial seizures with and without secondary generalization and for monotherapy for Lennox Gastaut Syndrome.
NEURONTIN (GABAPENTIN) CAPSULES	PARKE DAVIS/ PFIZER	Adjunctive therapy in the treatment of partial seizures.
LAMICTAL (LAMOTRIGINE)		Adjunctive treatment of partial seizures, primary generalized tonic clonic seizures, typical and atypical absence, atonic and myoclonic seizures, Lennox Gastaut Syndrome. Also approved for titration to monotherapy.
GABATRIL (TIAGABINE)		Adjunctive therapy for partial seizures.
TOPAMAX (TOPIRAMATE)		Adjunctive treatment of partial seizures,

		primary generalized tonic clonic seizures, atonic, tonic, tonic-clonic seizures, Lennox Gastaut Syndrome.
ZONEGRAN (ZONISAMIDE) 100 MG CAPSULES	DAINIPPON	Adjunctive therapy for partial seizures.
TRILEPTAL (OXCARBAZEPINE) 150/300/600MG	NOVARTIS	Monotherapy or adjunctive therapy for partial seizures in adults and children.
KEPPRA(LEVETIRACETAM)	UCB	Adjunctive therapy for partial seizures with and without secondary generalization in adults.

2.3 Availability of Proposed Product in the U.S.

The proposed product is a new molecular entity and is currently not available in the United States.

2.4 Important Issues with Pharmacologically Related Products

The closest pharmacologically related product is Neurontin ® (gabapentin). Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not modify GABA A or GABA B radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation.

2.5 Pre-submission Regulatory Activity

Key information regarding pre-submission regulatory activity (with regards to the clinical program only) is as follows:

- Sponsor representatives had 4 meetings/ teleconferences with the Division of Neuropharmacologic Drug Products (The Division) to discuss the add-on epilepsy program. The outcome of these meetings between the sponsor and the Division was to obtain: (1) consensus on the Phase 3 clinical development, and (2) to identify any additional preclinical and/ or clinical information necessary to support NDA approval of pregabalin for adjunctive treatment of patients with partial seizures, with and

- In the June 17, 1999 End-of-Phase 2 meeting with the Division, the requirements for both [redacted] and adjunctive therapy for epilepsy were discussed. For the

- The epilepsy clinical plan was presented in the June 7, 2000 Pre-NDA meeting and confirmed as being acceptable.

2.6.1 Carcinogenicity Studies

Sponsor representatives met or had teleconferences with the Divisions of Anesthetics, Critical Care, and Addiction Drug Products (DACCADP), Anti- inflammatory, Analgesic and Ophthalmologic Drug Products (DAAODP), and Neuropharmacological Drug Products (DNDP or The Division) 8 times to discuss the carcinogenicity findings in mice and its relevance to the continued development of pregabalin for the indications of epilepsy, pain,

In October 1999, preliminary findings of an increased incidence of hemangiosarcoma in B6C3F1 mice treated with pregabalin were first identified and reported to FDA. In June 2000, the final results of the mouse carcinogenicity study, confirming the initial finding, were provided along with the negative results of a rat carcinogenicity study to FDA. Following review of these documents and the discussions of January 26 and 29, 2001 and February 2 and 8, 2001, the DACCADP placed a partial clinical hold on pregabalin studies in neuropathic pain. For epilepsy and , agreements were reached in a February 13, 2001 meeting with the Pfizer and DNDP regarding an acceptable patient population that could continue on pregabalin treatment. In summary, the FDA requested that no new patients start pregabalin treatment unless they met new entry criteria as refractory to available treatments. Similarly, patients who were already enrolled in open-label studies were to be assessed to determine whether they met the new criteria for refractory and for response to pregabalin treatment. The sponsor felt that the animal findings were species specific and did not apply to humans. (Please see further discussion of this in section 3.2.1 Carcinogenicity.)

On August 11, 2003, a teleconference was held between FDA and Pfizer to discuss Pfizer's proposed NDA timeline and to obtain clarity as to FDA's planned steps for reviewing the NDA. Pfizer and FDA then reconfirmed the acceptability of the proposed October 30, 2003 submission date for the pregabalin NDA and that current partial clinical hold. FDA explained that the mouse carcinogenicity finding would be considered a separate scientific issue for the NDA review and would not be considered a refusal to file issue.

2.6.2 Pediatric final rule

At the EOP2 meeting on June 17, 1999, the Division granted the following deferral and partial waiver for pediatric studies in epilepsy:

- A deferral for the submission of safety and efficacy in infants and children until after submission of the adult epilepsy NDA; and

- A waiver for collection of safety, efficacy, and pharmacokinetic data in neonates (0- 1 month of age).

As was also discussed at the EOP2 meeting safety and efficacy data from adolescents (12– 16 years of age)

2.6.3 Regulatory Briefing (March 19, 2004)

A Regulatory Briefing regarding possible safety issues related to pregabalin was held on March 19, 2004. The panel did not find the preclinical findings to be strong enough to hold any decisions regarding approvability. However, findings related to pregabalin's abuse potential and other potential safety issues were discussed at the meeting.

2.6.4 Abuse Potential Meeting (April 13, 2004)

A meeting was held between the Sponsor and the Controlled Substances Staff (CSS) for pregabalin to be considered for scheduling under the Controlled Substances Act (CSA). There were reports of euphoria in the safety database signaling a strong abuse potential. These effects were seen in 5 human populations (3 patient populations, a drug abusing population and healthy subjects.) Pregabalin subjective responses were similar to those of diazepam (a Schedule IV drug in the CSA) in a human abuse potential study (098) where subjects reported that pregabalin induced a "good drug effect", "drug liking," and production of a "high". CSS is preparing an Eight Factor Analysis for DEA review for scheduling.

3 Significant Findings from Other Review Disciplines

3.1 Chemistry

I spoke with the chemist, Tom Broadbent, who had only minor concerns regarding the final dose formulations.

3.2 Animal Pharmacology/Toxicology

The main issues related to pregabalin toxicology is the incidence of mice hemangiosarcoma and dermatopathy seen in the tails of rats and monkeys. A summary

of these problems is reproduced in part from materials present by HFD-170 at the Regulatory Briefing on March 19, 2004.

3.2.1 Carcinogenicity

In the first mouse carcinogenicity study, groups of 65 B6C3F1 mice/ sex were given 200, 1000, or 5000 mg/ kg in the diet daily for 104 weeks. A dose- related increased incidence of hemangiosarcoma occurred in both sexes at 1000 and 5000 mg/ kg. Hemangiosarcoma occurred in multiple tissue/ organ sites, although they were most frequently observed in the liver, spleen, and bone marrow and correlated with clinical signs of internal palpable masses and gross pathologic findings of liver masses and enlarged spleens. Hemangiosarcoma was considered the cause of death in 1, 3, 13, and 13 males, and in 1, 3, 12, and 15 females in the controls and at 200, 1000, and 5000 mg/ kg, respectively. The first hemangiosarcoma was diagnosed in a control female found dead at Week 49. The first hemangiosarcoma in a drug- treated group occurred in a male at 1000 mg/ kg during Week 50. Hemangiosarcomas were primarily late in onset, with mean tumor latency across all groups of 88 to 102 weeks in males and 76 to 96 weeks in females.

To assess the carcinogenic potential of pregabalin in another mouse strain groups of 65 CD- 1 mice/ sex were given 200, 1000, or 5000 mg/ kg in the diet daily for 104 weeks. Doses were the same as used previously in B6C3F1 mice. Of 27 tumor types in males and 45 tumor types in females, only hemangiosarcoma in males showed a statistically significant positive- dose trend in the Peto test. The number of tumor- bearing males was 2, 5, 6, and 14 at 0, 200, 1000, and 5000 mg/ kg, respectively. There was a statistically significant difference at 5000 mg/ kg when compared to untreated controls ($p < 0.005$). In females, the numbers of animals with hemangiosarcoma were 6, 9, 10, and 13 at 0, 200, 1000, and 5000 mg/ kg, respectively. There was a slight increase in tumor incidence with dose but the dose trend was not statistically significant ($p = 0.0058$). Hemangiosarcomas occurred in multiple tissues of both males and females but were found most frequently in liver, spleen, and bone marrow. In females, hemangiosarcoma occurred most frequently in uterus at all doses. The first hemangiosarcoma was diagnosed in a female at 5000 mg/ kg in Week 46 and the first in a control female at Week 47. Hemangiosarcomas were primarily late in onset with mean tumor latency across all groups of 90 to 104 weeks in males and 80 to 100 weeks in females. There were no differences between control and drug- treated animals in tumor onset or latency.

3.2.2 Dermatopathy

Skin lesions characterized clinically by a spectrum of lesions ranging from erythema to necrosis, and histologically by hyperkeratosis, acanthosis, fibrosis, and/ or necrosis of the tail, were observed in rats given = 50 mg/ kg in oral repeated- dose studies, with associated $AUC_{(0-24)} = 241$ µg· hr/ mL. Lesions typically appeared within the first 2 weeks of treatment at higher doses and resolved in most affected animals by Week 7 in the 13-week study and by Week 4 in the 52- week study. Similar skin lesions were

observed in monkeys in oral repeated- dose studies, and were located primarily on the tail in most animals. In the chronic monkey study, lesions were observed at = 25 mg/ kg, with plasma pregabalin AUC(0- 24) values = 219 μg· hr/ mL. As in rats, lesions in affected animals in the chronic monkey study generally resolved prior to study termination. Subcutaneous tail temperature, used as an indirect measure of tail blood flow in the chronic monkey study, showed no consistent differences between control and high- dose animals, or between affected and unaffected animals within the same group. Pregabalin at 5% and 7.5% did not induce contact sensitization (allergic dermatitis) in rats in the local lymph node assay.

The etiology of the skin lesions remains unknown. No tail dermatopathy was observed in mice given repeated oral doses of pregabalin up to 13-g/ kg up to 13 weeks. Missing tail tips were observed in mice given up to 5000 mg/ kg (AUC $_{(0-24)}$ of 3150 μg· hr/ mL) in the B6C3F1 but not the CD- 1 carcinogenicity study, however, the relationship of this lesion to dermatopathy in rats and monkeys is unknown.

3.3 Clinical Safety Team

A separate clinical safety team evaluated the submission for this indication as well as for Gerald Boehm was the primary safety reviewer for the epilepsy indication. The safety team was particularly concerned regarding the potential for rhabdomyolysis seen as increased serum creatinine phosphokinase (CPK). Per Dr. Boehm's report, "The laboratory data suggest that there is a mean increase in CPK for the pregabalin group and an excess of outliers."

3.3.1 CPK elevation (3)

- **009-008016** This 31 year old male had a history of refractory seizures and Sturge Weber syndrome. On study day 84, while taking pregabalin 600mg/day TID, he had an elevated CPK of 4722U/L (isoenzymes 100% MM) during routine clinical lab work. This lab result was not associated with an AE of myalgia. Two days later his CPK was 1031U/L. Other study CPKs were: Day 14=150U/L, Day 28=187U/L, Day 56= 193U/L. On day 91 the subject's CPK was 244U/L. The lab abnormality was attributed to doing yard work in hot weather. Concurrent medications were lamotrigine and verapamil. He continued into the open label extension where he was exposed for 707 days and experienced no additional elevated CPK results.
- **009-008015** This 26 year old male with refractory seizures experienced elevated CPK of 7,893 U/L (100% MM) on day 142 of pregabalin treatment (86 days of double blind, 56 days of open label treatment). At the same time his AST was 111 U/L, potassium 3.9mEq/L and creatinine was 1.0mg/dL. He was taking pregabalin 450mg/day at the time of the event. Follow up CPK four days later was 1,805U/L and seven days after that it was 203U/L. During the preceding double blind study, his CPKs ranged from 137 to 239 U/L. This subject had no recorded AEs of myalgia. Concomitant medications were carbamazepine and valproate. The abnormality was attributed to a strenuous soccer game on study day 55.
- **009-034006** This 48 year old female experienced an increase in CPK to 5,262U/L (100% MM) after 310 days of pregabalin (92 days in a controlled trial and 218 days in the open label extension). At the same time her AST was 165U/L, potassium was 4.2mEq/L and Creatinine was 1.1mg/dL. Fourteen days later, a repeat CPK was 292U/L. She continued in the trial with no additional elevated CPK

results. Concomitant medications were topiramate and lamotrigine. The event was attributed to strenuous exercise. This subject had no recorded AEs of myalgia.

3.3.2 Myopathy (2)

- **080 112001** This 30 year old male with a history of social phobia, mitral valve prolapse, experienced rhabdomyolysis. This subject had a screening CPK of 94U/L, AST of 24U/L and ALT of 22 U/L. After 16 days of pregabalin, he had his labs drawn and his CPK was 30,700 U/L, his AST was 507 U/L and ALT was 142 U/L and the potassium at that time was reportedly normal. His labs were rechecked the next day and his CPK was 44,700 U/L, his AST was 787 U/L and ALT was 170 U/L and his potassium was now 8.4mEq/L. The subject did experience myalgias, which he attributed to work outs. His only concomitant medication was propranolol. He was admitted to a hospital and treated with IV hydration and urine alkalinization. He was discharged two days later without sequelae. By study day 32, all labs had returned to normal.
- **149 430001** This 31 year old female with a history of diabetes mellitus, neuropathy, nephrotic syndrome, gastroparesis, retinopathy, recurrent UTIs, and hypertension developed acute renal failure, rhabdomyolysis, and pneumonia. The study drug was stopped on study day 59 for the adverse events of pneumonia, rhabdomyolysis, acute renal failure, and fever. The narrative reported that this subject was admitted to a hospital on study day 60 with acute renal failure, fever, lethargy, shortness of breath, cough, dehydration, and painful swelling and weakness in her legs. The patient profile submitted by Pfizer included lab values from study day 59 and at that time her CPK was 79 U/L and her creatinine was 2.7mg/dL (baseline creatinine 1.4 mg/dL). While hospitalized she was diagnosed with pneumonia and myopathy. On study day 60, her CPK rose to 4504 U/L, and her creatinine was 5.6mg/dL. She was treated with antibiotics, insulin, heparin, and intravenous fluids. Her creatinine improved to 2 mg/dL and creatinine kinase to 124 U/L. and she was discharged on study day 72.

In addition to the concern for increased CPK, the safety data (from HFD 170) showed that nervous system abnormalities were the most common adverse effects. Another issue of concern raised by the HFD-170 was the potential for visual disturbances including, "signs and symptoms of visual impairment, including the development of visual field defect, loss of visual acuity on formal testing, and complaints of blurred vision." Preliminary draft labeling for pregabalin provided to HFD-170 included discussion regarding potential warnings and precautions. The following are reproduced from the draft labeling for the peripheral diabetic neuropathy indication.

WARNINGS:
Ophthalmological Effects:

1 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 4

4 Data Sources, Review Methods, and Data Integrity

4.1 Sources of Clinical Data

The submission was primarily electronic. This reviewer focused on the efficacy data for partial seizures. [redacted] The main data were derived from Sponsor Studies 009, 011 and 034. Additional studies available included Study [redacted] (Reviewer note: This study was reviewed separately in Appendix 11 at the end of this report.)

4.2 Tables of Clinical Studies – Double blind phase

Table 34. Overview of Epilepsy Clinical Studies – ITT Population

Study No.	Placebo	All Pregabalin	Pregabalin Group Total Daily Dose (mg/day) and Regimen						All Patients
			50 BID	150 BID	150 TID	300 BID	600 BID	600 TID	
009	98	214					103	111	312
011	96	191			99			92	287
034	100	353	88	86		90	89		453
Total Patients	294	758	88	86	99	90	192	203	1052

ITT = Intent to treat

4.3 Review Methods

This reviewer evaluated the sponsor's submitted Integrated Review of Efficacy, which included pooled data from the three double blind clinical studies listed above. This reviewer also evaluated each trial separately looking at all primary, secondary and ad hoc efficacy results. In addition, I reviewed the monotherapy trial.

The safety review for this submission was the responsibility of the safety team. In addition, several other reviews [redacted] were being performed in other parts of HFD-120 for the use of pregabalin [redacted] and in HFD-170 for the use of pregabalin in pain syndromes related to diabetes [redacted]

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) did audit several locations for this NDA. Sites were selected for DSI by locating the largest enrollment sites on a master list provided by the sponsor. As of the date of this report, one clinical investigator from study 009 was evaluated. 14 subjects were enrolled in the protocol. The audit did reveal that there was some missing adverse event data. However per the report, the "data appear acceptable".

4.5 Compliance with Good Clinical Practices

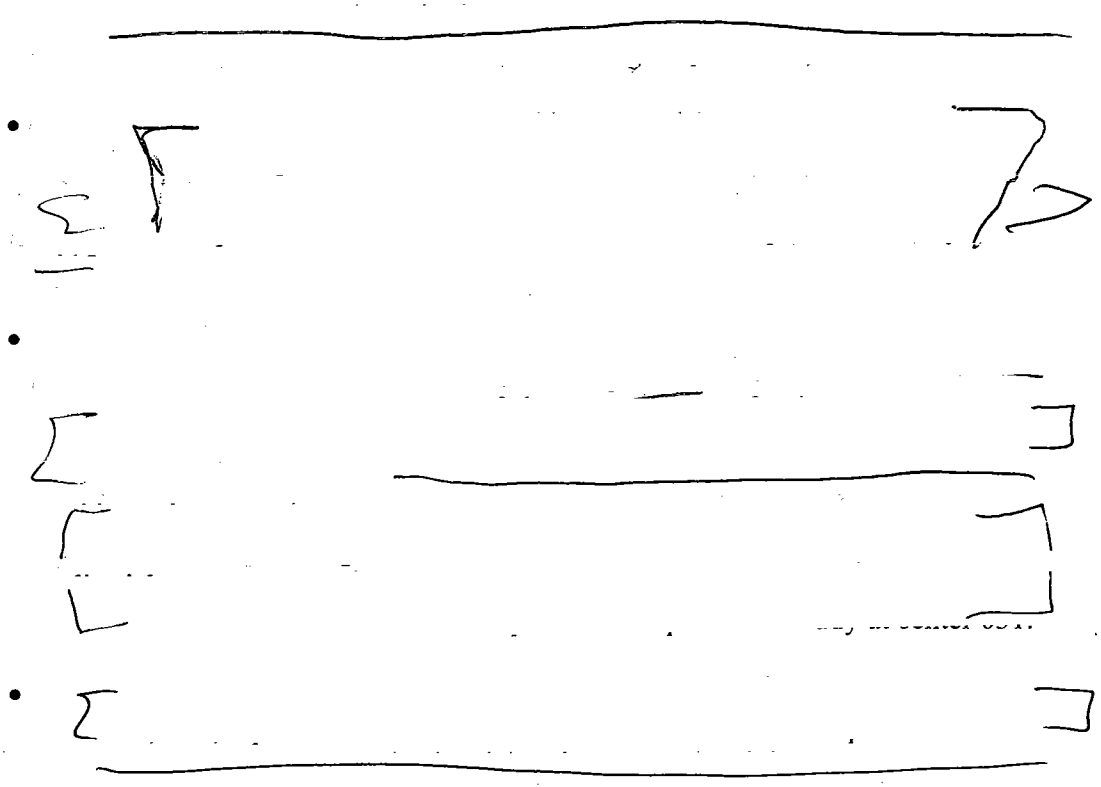
The sponsor complied with good clinical practices with regards to informed consent. Protocol variations and reasons for exclusions of patients from the study are summarized in each study report in the appendix of this review.

4.6 Financial Disclosures

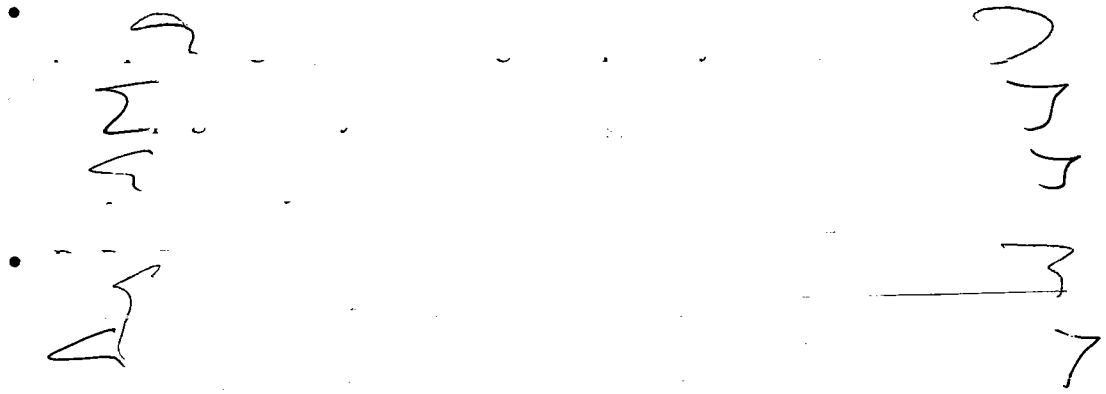
I reviewed financial disclosures related to the three main epilepsy protocols 009, 011 and 034. The financial disclosure information was pooled information from over 20 studies performed by 3300 investigators and subinvestigators. Most of these studies were initiated prior to the merger between Warner Lambert and Pfizer. The sponsors relate that they "acted with due diligence" regarding obtaining complete financial disclosure information from all the investigators involved in the studies. They sent out Financial Disclosure Questionnaires (FDQ) forms, followed by a follow-up letter, informal contacts and a second follow up letter if needed. They further state that they were unable to obtain information from 187 investigators and 55 responses from investigators were incomplete. A total of 25 investigators reported "significant" financial interests. Details regarding the key investigators involved in the studies pertinent to the epilepsy clinical program are as follows:

Protocol 009 was a double-blind, placebo-controlled multicenter study with a total of 46 study sites. The total number of patients entered into study 1008-009 was 313 and a total of 237 patients completed the study. The sponsor has noted financial interests affecting a total of 32 patients randomized and 23 patients who completed the study, approximately 10% of the total patients in this study. Per the sponsor:

- [redacted]



Protocol 011 was a double-blind, placebo-controlled multicenter study with a total of 94 study sites. The total number of patients entered into study was 288 and a total of 241 patients completed the study. The sponsor has noted financial interests among a total of 12 patients randomized and 5 patients who completed the study, approximately less than 5% of the total patients in this study. Per the sponsor:



Protocol 034 was a double-blind, placebo-controlled multicenter study with a total of 84 study sites. The total number of patients entered into study 034 was 455 and a total of 378 patients completed the study. The sponsor has noted financial interests among a total of

19 patients randomized and 18 patients who completed the study, approximately less than 5% of the total patients in this study. Per the sponsor:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

In summary, the sponsor related due diligence in obtaining financial disclosure information from its investigators. All studies were multicenter in nature and no one investigator enrolled more than 5% of patients in their respective trials. (Reviewer note: This reviewer is still concerned for the unknown investigator information, but overall doubts that financial rewards to these investigators impacted the results of the study.)

5 Clinical Pharmacology

5.1 Pharmacokinetics/Pharmacodynamics

5.1.1 Study 009 – Daily doses of 600mg given BID or TID

One-hundred seventy-two patients from this study were included in the pharmacokinetic analysis. A total of 476 plasma samples from patients randomized to pregabalin and considered to be at steady-state (patient continued for at least 48 hours without a missed dose or dosage adjustment) and collected within 18 hours from the last dose taken were included in the analysis. The mean (range) plasma pregabalin concentrations associated

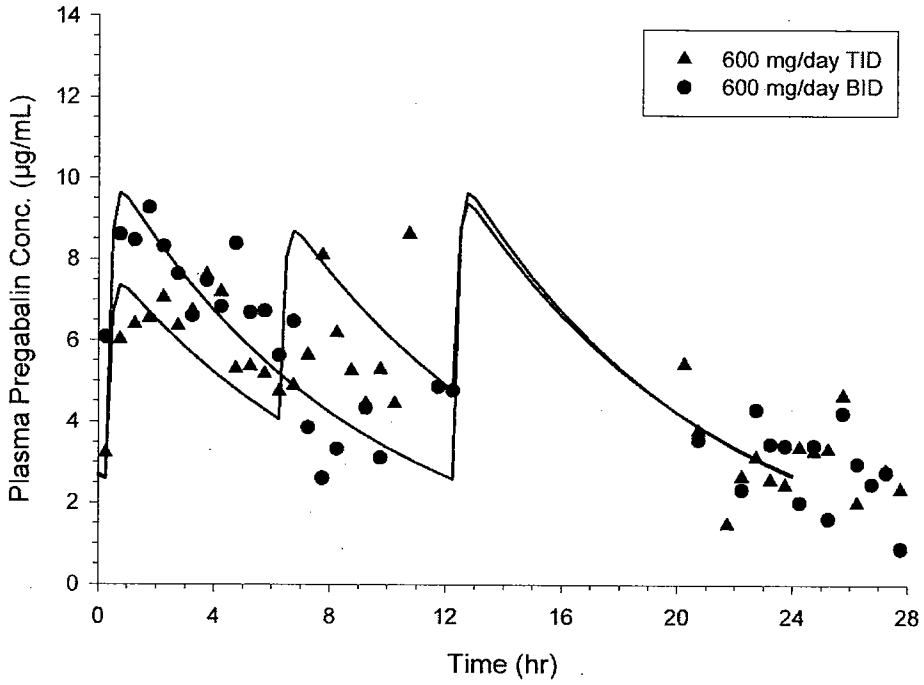


Figure 4. Observed Mean Steady-State Plasma Pregabalin Concentrations and Model Predicted Steady-State Plasma Pregabalin Concentration-Time Profiles Following 600-mg/day of BID (●), and TID (▲) Administration

with a daily dose of 600 mg/day were 6.84 µ g/mL (0.32-14.80 µ g/mL) for BID and 5.82 µ g/mL (0.38-18.2 µ g/mL) for TID.

The observed mean and model predicted steady-state plasma pregabalin concentration-time profiles for BID and TID dosing are illustrated in Figure 4. The BID and TID regimens achieved similar peak and trough plasma pregabalin concentrations and similar overall daily pregabalin exposure. Model predicted concentration-time profiles closely represent the observed mean steady-state plasma pregabalin concentrations for both regimens.

5.1.2 Study 011 – Daily doses of 150mg or 600mg given TID

One hundred eight patients from this study were included in the pharmacokinetic analysis. A total of 300 plasma samples from patients who were randomized to pregabalin and considered to be at steady-state (patient continued for at least 48 hours without a missed dose or dosage adjustment) and collected within 18 hours from the last dose taken were included in the analysis. The mean (range) plasma pregabalin concentrations associated with a daily dose of 150 and 600 mg/day administered TID were 1.27 µ g/mL (0.29 to 2.84 µ g/mL) and 4.88 µ g/mL (0.87 to 14.2 µ g/mL), respectively. The observed mean and model-predicted steady-state plasma pregabalin concentration-time profiles for 150 and 600 mg/day dosing are illustrated in Figure 4. Model-predicted concentration-time profiles closely represent the observed mean steady-state plasma pregabalin concentrations for both regimens.

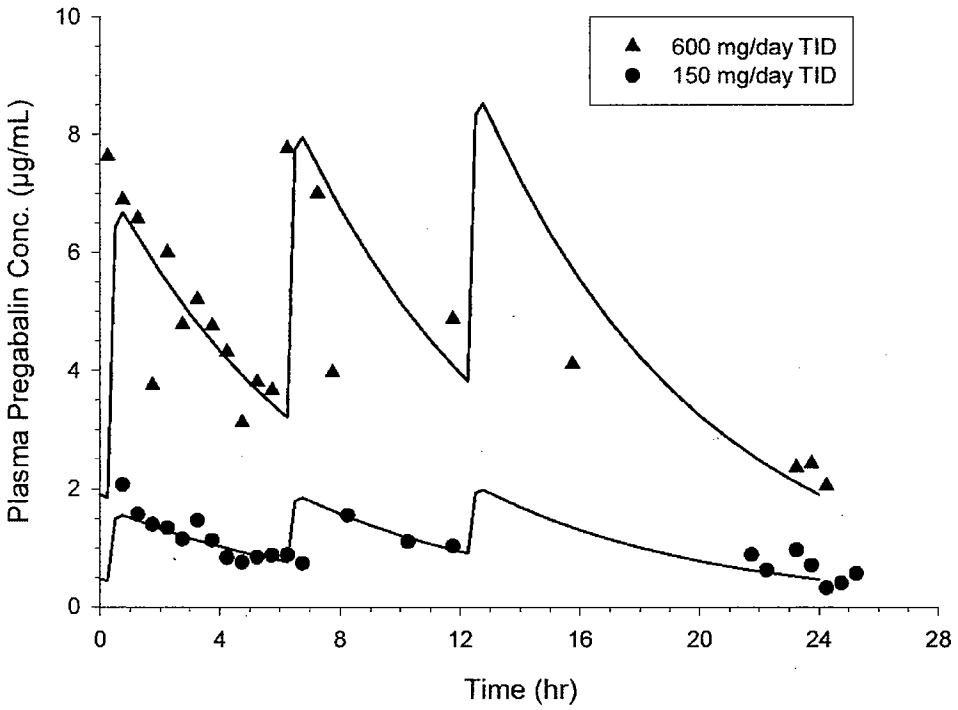


Figure 4. Observed Mean Steady-State Plasma Pregabalin Concentrations and Model-Predicted Steady-State Plasma Pregabalin Concentration-Time Profiles Following 150 mg/day (●) and 600 mg/day (▲) Pregabalin Administered TID

5.1.3 Study 034 – Daily doses of 50, 150, 300 or 600mg given BID

Three hundred and eleven patients from this study were included in the pharmacokinetic analysis. A total of 558 plasma samples from patients randomized to pregabalin and considered to be at steady-state (patient continued for at least 48 hours without a missed dose or dosage adjustment) and collected within 18 hours from the last dose taken were included in the analysis. The plasma pregabalin concentrations associated with a daily dose of 50, 150, 300, and 600 mg/day averaged (range) 0.569 (0.06-5.02), 1.63 (0.31-5.71), 2.84 (0.06-11.2), and 5.47 (0.18-12.5) µ g/mL, respectively.

The observed mean and model predicted steady-state plasma pregabalin concentration-time profiles for each dose group following BID dosing are illustrated in Figure 4. Model predicted concentration-time profiles closely represent the observed mean steady-state plasma pregabalin concentrations for all dose groups.

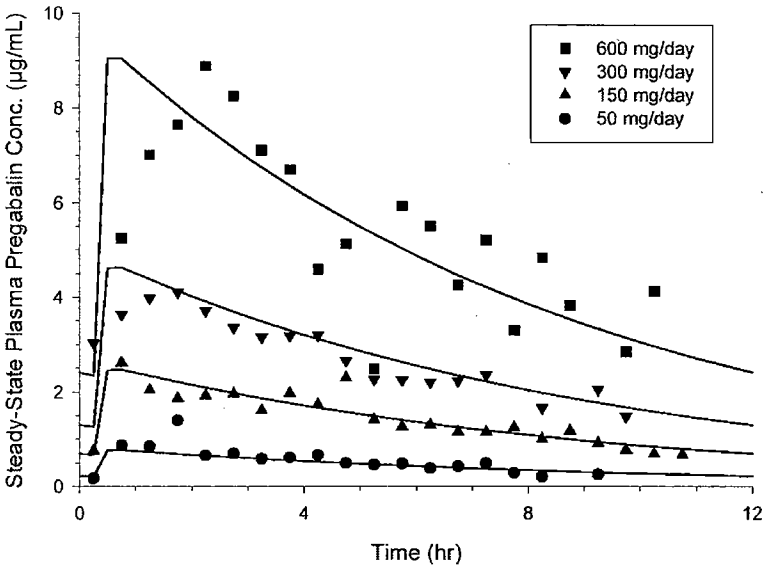


Figure 4. Observed Mean Steady-State Plasma Pregabalin Concentrations and Model Predicted Steady-State Plasma Pregabalin Concentration-Time Profiles for Each Dose Group Following BID Administration of 50 (●), 150 (▲), 300 (▼), and 600 mg/day (■) Pregabalin

5.2 Exposure-Response Relationships

This reviewer discussed with the clinical pharmacology reviewer (Veneeta Tandoon, PhD) whether there was any substantial difference between the BID and TID dosing schedules. Except for safety issues, there were no significant pharmacokinetic or pharmacodynamic differences. Overall, per this reviewer, when dosing an antiepileptic medication, it would be better to give the dose BID rather than TID. BID dosing would improve compliance and allow for ease of especially when added onto a primary antiepileptic.

Some efficacy results suggest that a BID dose is preferred. However, this reviewer believes that there is not enough information to compare doses and dosing schedules to derive any meaningful results. For example, in study 009, 600mg BID and TID were compared and except for a slightly lower Cmin, the mean values were essentially the same. The only other dose that we can compare TID with BID dosing is 150mg and those results were almost identical. The 300mg dose was only given as BID dosing in study 032. Dose and exposure responses related to efficacy are discussed further in the Integrated Review of Efficacy section below.

6 Integrated Review of Efficacy

6.1 Data Sources

The submission was predominantly electronic. The results were presented as a summary in the Summary of Clinical Efficacy. Efficacy results were also discussed separately in each study report. The primary data for efficacy were included in three double blind "pivotal" studies (009, 011 and 034). All three studies were randomized, double-blind, fixed-dose, placebo-controlled studies. Each consisted of three phases: an eight week baseline phase, a 12-week double-blind treatment phase (where a one-week titration phase was used in Studies 009 and 011), and a withdrawal phase (one week) for subjects choosing to exit the study rather than continue into a long term, open label study. Per the sponsor, the withdrawal phase in these studies was, "consistent with clinical practice in prescribing anticonvulsant therapy." The major differences in the studies involved whether or not there was a one week titration phase within the 12 week double blind phase and the inclusion of patients ages 12-17 within Study 034 only.

Patients in these studies were randomized to the following fixed doses of pregabalin, or placebo, on completing the baseline phase and meeting the inclusion criteria for the study:

- Study 009 – 600mg/day as BID or TID regimen; placebo
- Study 011 – 150 or 600mg/day as TID regimen; placebo
- Study 034 – 50, 150, 300 or 600mg/day as BID regimen; placebo

Table 1: Summary of pregabalin doses taken in studies

Study	Pregabalin total daily dose						Placebo	
	50 mg	150 mg		300 mg	600 mg			
	Regimens							
	25 mg BID	50 mg TID	75 mg BID	150 mg BID	200 mg TID	300 mg BID	TID	BID
-09					X	X	X	
-11		X			X		X	
-34	X		X	X		X		X

[redacted] (045) with only 3 enrollees, and ongoing open label extension studies (008, 010 and 012) where patients received pregabalin as adjunctive therapy. These additional studies are discussed separately in the appendix at the end of this report and are not included in the pooled efficacy discussion.

6.2 Summary of Overall Exposure in the three pivotal studies

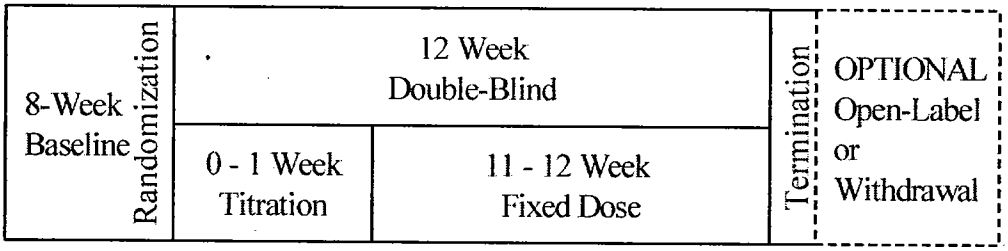
The patient population in these studies was found to be equally divided between males and females, and was mainly white, with a mean age of 37-40 years and a normal creatinine clearance. Across the three studies, the median baseline seizure rate was 10-12 seizures within the 28-day baseline assessment period (placebo 9-11 seizures), with mean baseline seizure rates for pregabalin patients of 21-22 seizures (placebo 22-25 seizures) within the 28-day baseline assessment period. Across the studies, 47-55% of the patients were taking two concurrent AEDs (placebo 44-51%) and 18-29% were taking three AEDs (placebo 16-31%).

6.3 Efficacy Review of Studies

6.3.1 Study Design

Each pivotal study comprised three phases illustrated in Sponsor Figure 47

Figure 47. Overall Study Design for 3 Add-On Epilepsy Studies



The **8-week baseline phase** allowed for patients to stay on their baseline seizure medication. Patients recorded in their seizure diaries the number of baseline seizures.

During the **12-week double-blind phase**, patients were randomly assigned to add on therapy either with pregabalin or placebo. In Studies 009 and 011, pregabalin doses were titrated to full dose over 1 week. In Study 034, pregabalin doses were not titrated and patients received the full dose on Day 1. Existing AED therapy was kept constant, and was only allowed to be adjusted for intolerable CNS adverse events. Seizures were recorded in a daily diary.

Patients who withdrew early or completed the double-blind phase had the option of either entering the follow-on, open-label study or discontinuing treatment during a withdrawal phase.

Generally, to ensure a refractory period, the following **inclusion criteria** were common to all pivotal studies.

- A history of partial seizures (as defined by the International League Against Epilepsy Classification of Seizures) along with an EEG within the preceding 2 years consistent with the diagnosis of focal onset epilepsy.
- A minimum of three partial seizures during the one month prior to screening entry for baseline.
- A baseline seizure frequency of not less than six partial seizures during an eight-week baseline with no seizure free period for four weeks or more.
- Currently taking at least one but no more than three antiepileptic drugs and dosing within a clinically acceptable therapeutic range and within the range of tolerability for the patient.
- History of being refractory to at least 2 marketed AEDs at maximum tolerated doses.
- In addition, patients were not to have a treatable cause of seizures, absence seizures, Lennox-Gastaut Syndrome or a progressive neurological or systemic disorder. **Adolescents aged 12 to 17 years were included in Study 034. Patients less than 12 years of age were excluded from all three trials; therefore, no efficacy claims are being sought by the sponsor outside of this age range.**
- Patients were also required to have normal creatinine clearance at baseline (>60ml/min).

Patients were excluded if they had no seizures, a treatable cause of seizures, Lennox-Gastaut Syndrome, or status epilepticus within the previous year.

6.3.2 Study summaries

The following are **study summaries** from each of the three clinical studies

Study 009 was a 12-week randomized, double-blind, parallel-group, placebo-controlled multicenter study evaluating the efficacy and safety of 2 regimens of 600 mg/day pregabalin as adjunctive therapy in patients with partial seizures. Men and women at least 18 years of age with partial seizures not adequately controlled while on 1-3 standard antiepileptic drugs were eligible to enroll. Following an 8-week baseline period, 313 patients were randomized to receive placebo, **312** patients received drug either pregabalin 600 mg/day given twice a day (BID) or pregabalin 600 mg/day given 3 times a day (TID). Patients maintained their current AED therapy throughout the study.

Study 011 was a 12-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter study evaluating the safety, efficacy, and dose-response characteristics of pregabalin administered three times a day (TID) as add-on treatment in patients with partial seizures. Men and women at least 18 years of age with partial seizures not adequately controlled while on 1-3 standard antiepliileptic drugs were eligible to enroll. Following screening and an 8-week baseline period, 288 patients were randomized to

receive placebo, pregabalin 150 mg/day, or pregabalin 600 mg/day. Study medication was titrated over 1 week; **287** patients received study medication.

Study 034 was a 12-week, double-blind, parallel-group, placebo-controlled study evaluating the efficacy and safety of 4 dosages of pregabalin as add-on treatment in patients with partial seizures. Patients at least 12 years of age with partial seizures not adequately controlled while on 1-3 standard antiepileptic drugs were eligible to enroll. Following an 8-week baseline period, a total of **453** patients were randomized to either placebo, or to 1 of 4 pregabalin dose groups: 50, 150, 300, or 600 mg/day administered BID.

6.3.3 Open Label Extension Studies

A discussion of results from ongoing open-label extension studies (Studies 008, 010, 012, and 035) where patients received pregabalin as adjunctive therapy are presented in **Section 6.13 Persistence of Efficacy and/or Tolerance Effects.**

6.4 General Discussion of Endpoints

6.4.1 Primary Endpoint

The primary efficacy parameter in all three pregabalin double-blind adjunctive studies was the difference in frequency of partial seizures during the double blind treatment period compared with the baseline period, each standardized for a 28-day period.

The primary statistic used was the **Response Ratio** (RRatio or symmetrized percent change) which is a comparison of baseline 28-day seizure rate (B) with treatment 28-day seizure rate (T) according to the formula:

$$\mathbf{RRatio = [(T-B)/(T+B)] \times 100}$$

A negative value for the RRatio indicates that treatment was associated with a reduction in seizures. The RRatio can also be considered as a direct monotonic transformation of percent change from baseline using the following calculation:

$$\mathbf{RRatio = [100 \times percent\ change]/[percent\ change + 200]}$$

Values for RRatio always fall between -100 and +100 with negative values indicating improvement. An RRatio of -33 is equivalent to a 50% reduction in seizures from baseline to treatment period, zero reflects no change from baseline, and a RRatio of +33 is a doubling (100% increase) of the seizure rate compared with baseline.

Per the sponsor, although the most usual approach in clinical trials is to define the primary efficacy parameter as a responder rate, typically 50% response, the RRatio measure is considered to be useful especially in analyses by seizure type, when baseline seizure rates may be zero and both percent change and responder rate are not useable and undefined. (Reviewer note: This reviewer recognizes that this endpoint was used similarly in the Neurontin ® (gabapentin) efficacy studies for its indication as adjunctive treatment of epilepsy.)

For ease of clinical interpretation, treatment group estimates of seizure reduction on the percent change scale were obtained by back transforming the mean RRatio; i.e.,

Percent change = [(200*RRatio)/(100-RRatio)].

6.4.2 Secondary and Additional Endpoints

Secondary endpoints examined in all studies included:

- **Responder rate** defined as the proportion of patients who had a ≥50% reduction in partial seizure rate during the treatment as compared to baseline.
- **Median percent change** in seizure frequency during treatment compared with baseline.
- By **seizure-type analysis of RRatio, responder rate** (50% reduction defined using -33 RRatio to include patients with 0 baseline seizures), **and percent change** assessed for each partial seizure type.
- **Seizure free analyses** including the length of seizure free intervals and the number and percent of seizure free days.

Additional planned parameters examined in individual studies included:

- Change in frequency of secondarily generalized tonic-clonic (SGTC) seizures (Study 011),
- Dose response relationship (Studies 011 and 034).

Table 35. Summary of Planned Efficacy Analyses for Epilepsy Studies

	Statistical Method	Comparison/Time	Population
Primary Efficacy			
RRatio	Ranked ANOVA model with treatment and center as main effects	All pairwise/double-blind treatment through Week 12 of treatment/termination	ITT and Evaluable
Secondary Efficacy			
Responder Rate	CMH chi-square adjusting for center	All pairwise/double-blind treatment through Week 12 of treatment/termination	ITT and Evaluable
Median Percent Change in Seizure Frequency	Descriptive statistics by treatment, 95% Confidence Intervals	All pairwise/double-blind treatment through Week 12 of treatment/termination	ITT and Evaluable
By Seizure-Type RRatio Responder Rate Median Percent Change	Descriptive statistics by treatment	NA/double-blind treatment through Week 12 of treatment/termination	ITT and Evaluable
Seizure-Freedom[a]	Descriptive statistics by treatment	NA/double-blind treatment through Week 12 of treatment/termination	ITT and Evaluable
Dose Response[c]			
RRatio	Main effects unranked ANOVA model	NA	ITT and Evaluable
Responder Rate	CMH	NA	ITT and Evaluable

ANOVA = Analysis of Variance; ITT = Intent-to-treat; NA = not applicable; . CMH = Cochran-Mantel-Haenszel; PGB = Pregabalin.

[a] Length of seizure-free intervals and number and percent of seizure-free days were examined.

[b]

[c] Studies 1008–011 and 034 only. RRatio (ANOVA) analysis tested both linear and quadratic models and Responder Rate (CMH) tested linear model.

6.4.3 Primary and Secondary Statistical Analyses

The primary and secondary analyses were performed using data from the intent-to-treat (ITT) population. The **ITT population** consisted of all randomized patients who took at least 1 dose of study medication. A secondary patient population, the **evaluable population**, comprised all patients who were randomized to study medication, received at least 28 days of study medication, and had a minimum of 28 days of seizure diary data within both the baseline phase and the double-blind phase.

RRatio was analyzed by an ANOVA model with treatment and center as main effects, and rank of the RRatio as the dependent variable. The difference in unadjusted means on unranked raw RRatio data were summarized for each pairwise comparison of treatment

groups overall, and by center. A 95% confidence interval for each difference in means was also computed. Generalizability of the ANOVA models was examined. Consistency of treatment effects across centers was explored by adding a treatment-by-center (interaction term) to the ANOVA model. To examine generalizability, the interaction term was tested at a significance level of 0.15.

Study 009 was considered positive if the RRatio for all partial seizures statistically significantly favored either pregabalin regimen (BID or TID) versus placebo in the primary analysis. For **Studies 011 and 034**, the study was positive if the RRatio for all partial seizures statistically significantly favored the pregabalin 600 mg/day group compared to placebo in the primary analysis.

Power - A sample size of 80 patients per group randomized (ITT population) for each study was estimated to provide 80% power to detect a mean RRatio treatment difference of 12 points between placebo and pregabalin. The 12-point treatment difference estimation was based on results from previous non-pregabalin add-on trials.

Data from centers with fewer than 18 patients were pooled geographically in the analyses prior to breaking the blind; these pooled centers were referred to as **clusters** in the inferential analysis plan. (This is best illustrated in the individual study reports in the appendices)

All statistical testing was done using SAS procedures. All testing was 2-sided. In Studies 009 and 034, a planned interim analysis was conducted for administrative and planning purposes. Haybittle and Peto methods were used as an adjustment of $\alpha = 0.001$ for the interim and $\alpha = 0.049$ for the final analyses ($\alpha = 0.05$ overall). In Study 011, there was no interim analysis and $\alpha = 0.05$ was used for the study analyses.

Study 009 used the *Hochberg procedure* to control the type I error for comparisons between pregabalin and placebo. Studies 011 and 034 controlled between-group comparisons using the *Ruberg step-down procedure* starting with the 600-mg/day dose versus placebo. If nonsignificant, all doses were declared not statistically significant from placebo. If the first pairwise comparison was significant, then the procedure was repeated until either a nonsignificant result was obtained or the last pregabalin versus placebo comparison was made.

6.5 Pooled Efficacy Results - Patient Characteristics

A summary of patient characteristics by study is displayed in Sponsor Table 37 below.

Table 37. Summary of Patient Characteristics by Study: ITT Population

Characteristic	Study					
	009		011		034	
	Placebo N = 98	All Pregabalin N = 214	Placebo N = 96	All Pregabalin N = 191	Placebo N = 100	All Pregabalin N = 353
Gender, N (%)						
Male	50 (51.0)	106 (49.5)	54 (56.3)	91 (47.6)	52 (52.0)	166 (47.0)
Female	48 (49.0)	108 (50.5)	42 (43.8)	100 (52.4)	48 (48.0)	187 (53.0)
Race, N (%)						
White, Non-Hispanic	87 (88.8)	179 (83.6)	89 (92.7)	177 (92.7)	84 (84.0)	301 (85.3)
Black, Non-Hispanic	4 (4.1)	9 (4.2)	1 (1.0)	4 (2.1)	7 (7.0)	24 (6.8)
Hispanic (White or Black)	3 (3.1)	20 (9.3)	2 (2.1)	3 (1.6)	7 (7.0)	19 (5.4)
Asian or Pacific Islander	0 (0.0)	4 (1.9)	1 (1.0)	3 (1.6)	1 (1.0)	6 (1.7)
American Indian or Alaskan Native	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Other	4 (4.1)	1 (0.5)	3 (3.1)	4 (2.1)	1 (1.0)	2 (0.6)
Age (Years)	N = 98	N = 214	N = 96	N = 191	N = 100	N = 353
Mean (SD)	39.6 (11.8)	38.8 (11.9)	38.1 (12.4)	36.5 (10.9)	39.5 (12.6)	38.0 (11.7)
Median	38.5	38	37.5	35	40	38
Range	17-82	18-75	17-73	18-70	16-73	12-75
Estimated Creatinine Clearance at Baseline (mL/min)	N = 98	N = 211	N = 95	N = 187	N = 100	N = 352
Mean (SD)	104.53 (31.17)	107.32 (31.34)	105.72 (27.05)	112.59 (33.57)	111 (32.4)	109 (31.0)
Median	101.7	103	104	108	108	102.8
Range	39.3-200.1	45.8-220.2	50-191	47-297	42.5-224.5	53-245.5
28-Day Seizure Rate at Baseline						
N	98	214	96	191	100	353
Mean (SD)	25.1 (37.8)	21.4(40.1)	23.5 (41.1)	22.8 (34.0)	22.3 (42.1)	22.0 (36.3)
Median	11.0	10.0	9.3	12.0	9.5	9.5
Range	2.5-245	2-435.8	1.5-327.5	2-219.0	2.7-311	1-356
Concurrent AEDs[a], N (%)						
1 AED	30 (30..6)	61 (28.5)	23 (24.0)	30 (15.7)	26 (26.0)	109 (30.9)
2 AEDs	50 (51.0)	100 (46.7)	42 (43.8)	105 (55.0)	48 (48.0)	178 (50.4)
3 AEDs	16 (16.3)	48 (22.4)	30 (31.3)	55 (28.8)	24 (24.0)	65 (18.4)
4 AEDs	0 (0.0)	3 (1.4)	1 (1.0)	1 (0.5)	2 (2.0)	1 (0.3)

ITT = Intent-to-treat; SD = Standard deviation; AEDs = Antiepileptic drugs.
[a] Four patients (2 placebo, 2 pregabalin) in Study 009 were not taking any AED at study initiation.

6.6 Pooled Efficacy Results - Patient disposition

A total of 1056 patients were randomized in the 3 double blind studies. One patient randomized to placebo and three patients randomized to pregabalin did not take study medication, to the ITT population is 1052, 758 treated with pregabalin and 294 with placebo.

Table 38. Summary of Patient Disposition

	Placebo	Pregabalin Dose (mg/day) and Regimen						
		50 BID	150 BID	150 TID	300 BID	600 BID	600 TID	All Patients
009								
Randomized	98					104	111	313
ITT Population	98					103	111	312
Evaluable Population	91					85	91	265
Withdrawals	17 (17.3)					33 (31.7)	26 (23.4)	76 (24.3)
Lack of Efficacy	5 (5.1)					1 (1.0)	2 (1.8)	8 (2.6)
Adverse Event	7 (7.1)					27 (26.0)	21 (18.9)	55 (17.6)
Lack of Compliance	2 (2.0)					2 (1.9)	3 (2.7)	7 (2.2)
Other/Administrative	3 (3.1)					3 (2.9)	0 (0.0)	6 (1.9)
Completed Study	81 (82.7)					71 (68.3)	85 (76.6)	237 (75.7)
Entered Open-Label Study	88 (89.8)					78 (75.0)	94 (84.7)	260 (83.1)
011								
Randomized	97			99			92	288
ITT Population	96			99			92	287
Evaluable Population	88			91			77	256
Withdrawals	13 (13.4)			11 (11.1)			23 (25.0)	47 (16.3)
Status Epilepticus	0 (0.0)			1 (1.0)			1 (1.1)	2 (0.7)
Lack of Efficacy	5 (5.2)			0 (0.0)			1 (1.1)	6 (2.1)
Adverse Event	6 (6.2)			10 (10.1)			17 (18.5)	33 (11.5)
Lack of Compliance	2 (2.1)			0 (0.0)			1 (1.1)	3 (1.0)
Other/Administrative	0 (0.0)			0 (0.0)			3 (3.3)	3 (1.0)
Completed Study	84 (86.6)			88 (88.9)			69 (75.0)	241 (83.7)
Entered Open-Label Study	81 (83.5)			82 (82.8)			69 (75.0)	232 (80.6)
034								
Randomized	100	88	88		90	89		455
ITT Population	100	88	86		90	89		453
Evaluable Population	97	81	82		77	69		406
Withdrawals	13 (13.0)	10 (11.4)	7 (8.0)		19 (21.1)	28 (31.5)		77 (16.9)
Lack of Efficacy	5 (5.0)	1 (1.1)	1 (1.1)		2 (2.2)	4 (4.5)		13 (2.9)
Adverse Event	5 (5.0)	6 (6.8)	1 (1.1)		13 (14.4)	21 (23.6)		46 (10.1)
Lack of Compliance	0 (0.0)	0 (0.0)	1 (1.1)		1 (1.1)	2 (2.2)		4 (0.9)
Other/Administrative	3 (3.0)	3 (3.4)	4 (4.5)		3 (3.3)	1 (1.1)		14 (3.1)
Completed Study	87 (87.0)	78 (88.6)	81 (92.0)		71 (78.9)	61 (68.5)		378 (83.1)
Entered Open-Label Study	87 (87.0)	78 (88.6)	81 (92.0)		75 (83.3)	73 (82.0)		394 (86.6)

Patient disposition is presented in Table 38 above. Across the 3 studies, 76% to 84% of all patients completed double-blind treatment and 81% to 87% of all patients chose to enter the corresponding open-label study. The incidence of withdrawals tended to increase with dose, particularly at 300 and 600 mg/day, where withdrawal rates ranged from 21% to 32%. The percentage of patients withdrawing in the 150 mg/day dose groups (given in 2 or 3 divided doses) and 50 mg/day dose group given in 2 divided doses were comparable to the percentages withdrawing in placebo groups. In any of the treatment groups, including the placebo groups, the majority of withdrawals were **due to adverse events**. Adverse event withdrawals increased with increasing doses of pregabalin. Ten to 18% of all patients withdrew due to adverse events across the 3 studies. The percentage of patients withdrawing due to lack of efficacy was 5% in each placebo group and 0% to 5% for the pregabalin treatment groups.

6.7 Efficacy Conclusions/Primary Outcome Measures

Table 36. Description of Clinical Efficacy Studies - Adjuvant Therapy in Partial Seizures

Study ID No. of Study Centers[a] Location	Study Start Study Status Enrollment Total (ITT)/Goal	Design Control Type	Study and Control Drugs, Total Daily Dose, Route and Regimen	No. of Patients by Arm ITT/Completed	Duration	Gender M/F Mean Age (Range)	Efficacy Results - Primary Parameter Treatment Group (mg/day)	N	RRatio*Treatment Difference Mean (SE)	p Value
009	Jun 98	Randomized, double-blind,	Placebo	98/81	Twelve weeks double-blind	156/156	Placebo	98		
35 US 6 Canada	Completed Sept 99	placebo	PGB 600 mg/day PO BID	103/71	including 1-week titration	39.1 (17-82)	PGB 600 BID	103	-29.0 (5.0)	≤0.0001
	312/240		PGB 600 mg/day PO TID	111/85			PGB 600 TID	111	-36.7 (5.0)	≤0.0001
011	Apr 98	Randomized, double-blind,	Placebo	96/84	Twelve weeks double-blind	145/142	Placebo	96		
45 International	Completed Nov 99	placebo	PGB 150 mg/day PO TID	99/88	including 1-week titration	37.6 (17-73)	PGB 150 TID	99	-12.4 (4.1)	0.0007
	287/240		PGB 600 mg/day PO TID	92/69			PGB 600 TID	92	-32.3 (4.2)	≤0.0001
034	Nov 98	Randomized, double-blind,	Placebo	100/87	Twelve weeks double blind,	218/235	Placebo	100		
69 US 5 Canada	Completed Sept 99	placebo	PGB 50 mg/day PO BID	88/78	no titration	38.4 (12-75)	PGB 50 BID	88	-2.3 (4.8)	0.4232
			PGB 150 mg/day PO BID	86/81			PGB 150 BID	86	-16.6 (4.8)	≤0.0001
	453/400			90/71			PGB 300 BID	90	-24.0 (4.8)	≤0.0001
			PGB 300 mg/day PO BID	89/61			PGB 600 BID	89	-33.5 (4.8)	≤0.0001
			PGB 600 mg/day PO BID							

ITT = Intent-to-treat; SE = Standard error; PGB = Pregabalin.
[a] Number of centers that received study drug and enrolled patients.

6.7.1 Study 009 Efficacy Results - See Appendix 1 for complete discussion

- **312** patients received study medication with 240 patients completing the study. Both pregabalin regimens produced highly significant ($p < 0.0001$) reductions in seizure frequency compared with placebo. Mean RRatios were 0.6, -36.1 and –28.4 for placebo, pregabalin 600mg TID and pregabalin 600mg BID, respectively. Analysis of secondary parameters was consistent with the primary analysis; both regimens of pregabalin were statistically superior to placebo in responder rate and percent change in seizure rate. The BID and TID regimens achieved similar peak and trough plasma pregabalin concentrations and similar overall daily exposure.

6.7.2 Study 011 Efficacy Results: - See Appendix 2 for complete discussion

- **287** patients received study medication with 240 patents completing the study. Statistically significant differences favoring both pregabalin treatment groups were seen in the analysis of RRatio compared to placebo. Mean RRatios were 0.9, -11.5, and –31.4 for placebo, pregabalin 150 mg/day and pregabalin 600 mg/day, respectively. The proportion of responders in the 600 mg/day pregabalin group was statistically significantly higher than placebo

Table 39. Summary of RRatio (All Partial Seizures) Results of Analysis of Variance - ITT Population

Study/Treatment (Total Daily Dose and Regimen)	N	Mean	SD	Median	Treatment Difference Between Pregabalin and Placebo		
					Mean (SE)	p Value	95% CI
Study 009							
Placebo	98	0.6	28.8	-0.4			
PGB 600 mg/day BID	103	-28.4	36.7	-21.7	-29.0 (5.0)	≤0.0001*	-38.9, -19.0
PGB 600 mg/day TID	111	-36.1	40	-31.7	-36.7 (5.0)	≤0.0001*	-46.4, -27.0
Study 011							
Placebo	96	0.9	26	0.7			
PGB 150 mg/day TID	99	-11.5	22.9	-9	-12.4 (4.1)	0.0007*	-20.5, -4.3
PGB 600 mg/day TID	92	-31.4	36.3	-27.1	-32.3 (4.2)	≤0.0001*	-40.6, -24.0
Study 034							
Placebo	100	-3.8	25.6	0			
PGB 50mg/day BID	88	-6.2	23.7	-4.5	-2.3 (4.8)	0.4232	-11.7, 7.1
PGB 150mg/day BID	86	-20.5	29.6	-21	-16.6 (4.8)	≤0.0001*	-26.1, -7.2
PGB 300mg/day BID	90	-27.8	36.5	-22.5	-24.0 (4.8)	≤0.0001*	-33.3, -14.6
PGB 600mg/day BID	89	-37.4	44.4	-34.1	-33.5 (4.8)	≤0.0001*	-42.9, -24.1

ITT = Intent-to-treat; SD = Standard deviation; SE = standard error; CI = confidence interval; PGB = Pregabalin.

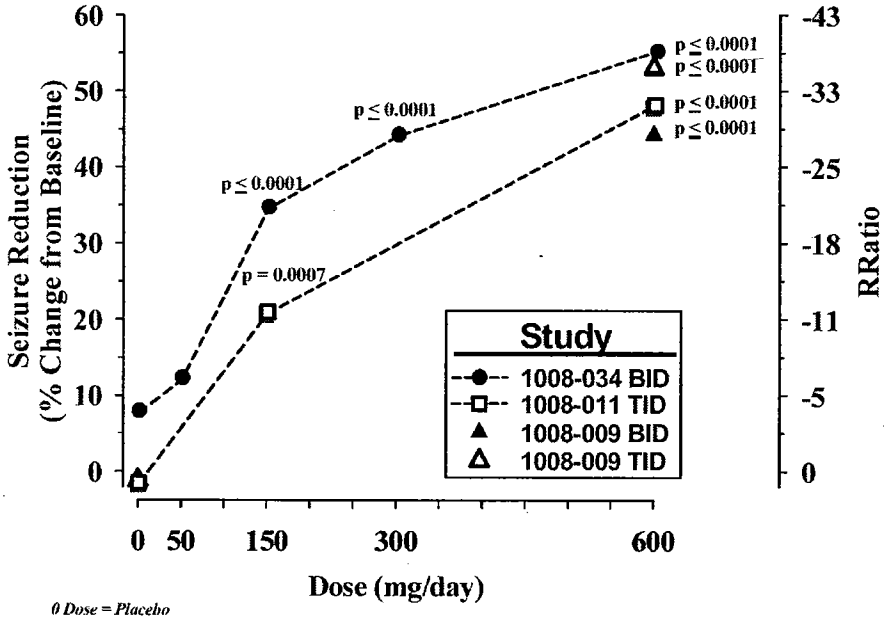
* Statistically significant based on Hochberg's (Study 009) or the Ruberg (Studies 011 and 034) procedure ($\alpha = 0.049$ for Studies 009 and 034, $\alpha = 0.05$ for Study 011).

6.7.5 Additional Efficacy results

(See also results of individual study reports in the Appendix (Section 7) at the end of this report).

Mean RRatio is plotted by treatment group, dose, and study in Sponsor Figure 48 below; associated p Values are presented and data points from the dose response studies are indicated by the dotted lines. For comparison, the percent change scale, relative to the RRatio (percent change = [200 × RRatio]/ [100-RRatio]) is also provided. Statistical analyses were not performed on the percent change data.

Figure 48. Seizure Reduction and Mean RRatio by Dose (All Partial Seizures) for Studies 009, 011, and 034



6.7.5.1 Secondary Efficacy Parameter - Evaluable population – ANOVA analysis

In order to assess the robustness of the primary parameter, the ANOVA analysis was performed on the evaluable population (all patients who were randomized to study medication, received at least 28 days of study medication, and had a minimum of 28 days of seizure diary data within both the baseline phase and the double-blind phase). The findings of this analysis support the primary analysis on the ITT population. (See Sponsor Table 40 below).

(Reviewer note: This reviewer compares Table 40 with Table 39. Since the ITT population is larger than the evaluable population, one would expect the results to be even more robust in the evaluable group as it excludes all patients who could not tolerate the drug or dropped out for other reasons. By examining only the evaluable population, it would bias the results in favor of those who stayed in the study. There would be less variability in this population. The results of the evaluable population do show slightly smaller means and standard deviations in all dose groups as expected. To the sponsor's credit, they chose the ITT population over the evaluable population for the primary analysis, which included dropouts.)

Table 40. Summary of RRatio (All Partial Seizures) Results of Analysis of Variance – Evaluable Population

Study/Treatment (Total Daily Dose and Regimen)	Treatment Difference			
	N	Mean	SD	p Value
Study 009				
Placebo	91	-1.8	26.6	
PGB 600 mg/day BID	83	-27.7	31.5	≤0.0001*
PGB 600 mg/day TID	91	-33.1	35.6	≤0.0001*
Study 011				
Placebo	88	-1.0	25.2	
PGB 150 mg/day TID	91	-11.5	21.1	0.0013*
PGB 600 mg/day TID	77	-30.0	33.1	≤0.0001*
Study 034				
Placebo	97	-4.1	25.9	
PGB 50 mg/day BID	81	-7.2	21.4	0.4824
PGB 150 mg/day BID	82	-20.1	28.2	≤0.0001*
PGB 300 mg/day BID	77	-24.0	31.4	≤0.0001*
PGB 600 mg/day BID	69	-29.9	37.2	≤0.0001*

SD=Standard Deviation; PGB = Pregabalin.
* Statistically significant from placebo based on Hochberg's (Study 009) or the Ruberg (Studies 011 and 034) procedure ($\alpha = 0.049$ for Studies 009 and 034, $\alpha = 0.05$ for Study 011).

6.7.5.2 Secondary Efficacy Parameter – Responder Rate

A patient was classified as a "responder" if they experienced at least a 50% reduction in seizure frequency compared to baseline seizure frequency. Across all 3 studies, results of the analysis of responder rate for all partial seizures showed highly significant differences between pregabalin 150 to 600 mg/day and placebo, with responder rates ranging from 43% to 51% in the 600 mg/day treatment groups (illustrated in **Sponsor Table 41** below). **Sponsor Figure 49** presents these data graphically with dotted lines indicating data from the dose response studies. The responder rate analyses were consistent with the primary analysis with the exception of the 150 mg/day dose group from Study 011 which approached, but did not meet, statistical significance (p = 0.087). (Reviewer note: This implies to this reviewer that the 150mg dose, although showing efficacy, should be the starting dose and not the goal dose for patients with refractory epilepsy. Also there are subtle result differences in the 150mg dosing regimens favoring the BID dosing regimen over the TID dosing regimen.)

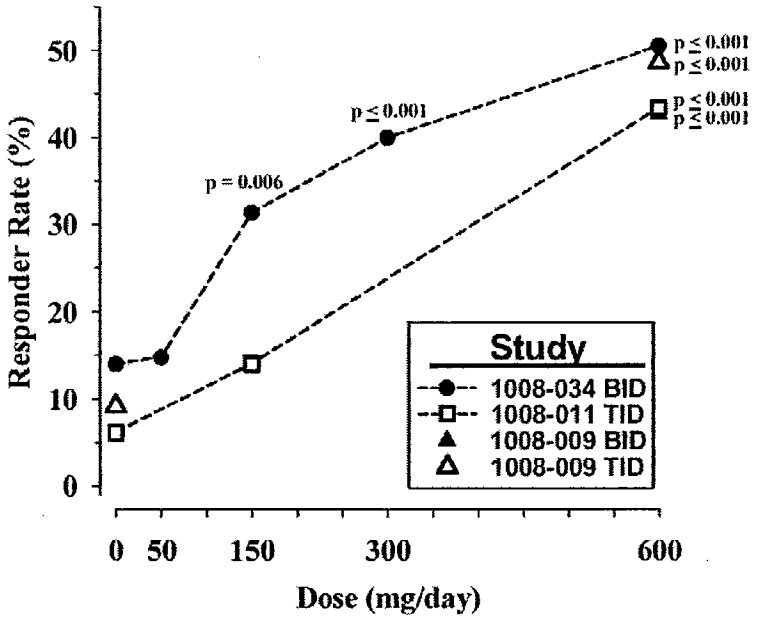
Table 41. Summary of Responder Rate (All Partial Seizures) - ITT Population

Study/Treatment (Total Daily Dose and Regimen)			Treatment Difference Between Pregabalin and Placebo			
	N	Responder (%)	%	SE	p Value	95% CI
Study 009						
Placebo	98	9 (9.2)				
PGB 600 mg/day BID	103	44 (42.7)	33.5	5.7	≤0.001*	22.4, 44.7
PGB 600 mg/day TID	111	54 (48.7)	39.5	5.6	≤0.001*	28.5, 50.4
Study 011						
Placebo	96	6 (6.2)				
PGB 150 mg/day TID	99	14 (14.1)	7.9	4.3	0.087	-0.5, 16.3
PGB 600 mg/day TID	92	40 (43.5)	37.2	5.7	≤0.001*	26.0, 48.5
Study 034						
Placebo	100	14 (14.0)				
PGB 50 mg/day BID	88	13 (14.8)	0.8	5.1	0.840	-9.3, 10.8
PGB 150mg/day BID	86	27 (31.4)	17.4	6.1	0.006*	5.5, 29.3
PGB 300mg/day BID	90	36 (40.0)	26.0	6.2	≤0.001*	13.8, 38.2
PGB 600mg/day BID	89	45 (50.6)	36.6	6.3	≤0.001*	24.1, 49.0

ITT = Intent-to-treat; SE = Standard error; CI = confidence interval;
PGB = Pregabalin.

* Statistically significant based on Hochberg's (Study 009) or the Ruberg (Studies 011 and 034) procedure ($\alpha = 0.049$ for Studies 009 and 034, $\alpha = 0.05$ for Study 011).

Figure 49. Responder Rate (All Partial Seizures) by Dose for Studies 009, 011, and 034



0 Dose = Placebo
Only significant p-values are shown

6.7.5.3 Secondary Efficacy Parameter - Percent change from Baseline

Percent change in baseline was defined as the percent change in 28-day seizure frequency during treatment compared with baseline. This is illustrated in **Sponsor Table 42** and in the following cumulative distribution plots of percent change for studies 009, 011 and 034.

APPEARS THIS WAY
ON ORIGINAL

Table 42. Summary of Median Percent Change From Baseline in Seizure Frequency (All Partial Seizures) - ITT Population

Study Treatment (Total Daily Dose and Regimen)	N	Median Percent Change	Treatment Difference[a]	
			Median	95%CI
Study 009				
Placebo	98	-0.8		
PGB 600 mg/day BID	103	-35.6	-41.6	-55.8, -27.6
PGB 600 mg/day TID	111	-48.1	-51.8	-64.4, -38.6
Study 011				
Placebo	96	1.3		
PGB 150 mg/day TID	99	-16.5	-21.6	-33.2, -9.5
PGB 600 mg/day TID	92	-42.6	-48.9	-62.1, -35.8
Study 034				
Placebo	100	0		
PGB 50 mg/day BID	88	-8.6	-5.2	-15.8, 6.7
PGB 150 mg/day BID	86	-34.8	-25.9	-38.3, -13.9
PGB 300 mg/day BID	90	-36.7	-33.0	-46.0, -20.4
PGB 600 mg/day BID	89	-50.9	-43.9	-57.8, -31.1

ITT = Intent-to-treat; CI = Confidence interval; PGB = Pregabalin.
[a] Between pregabalin and placebo.

6.7.5.4 Cumulative Distribution Plots

Figure 50. Cumulative Distribution Plot - Study 009

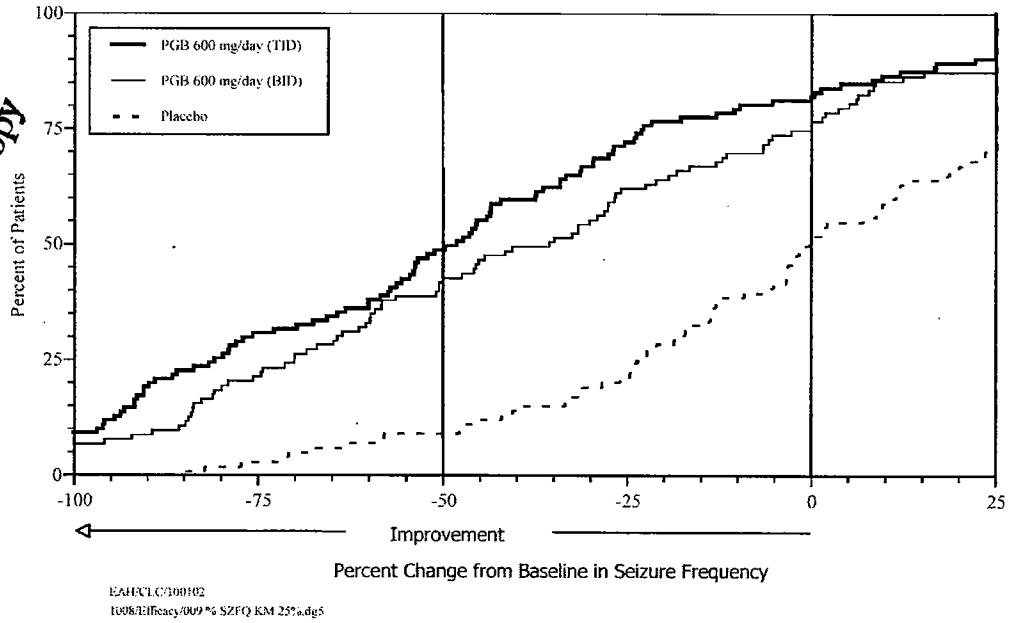
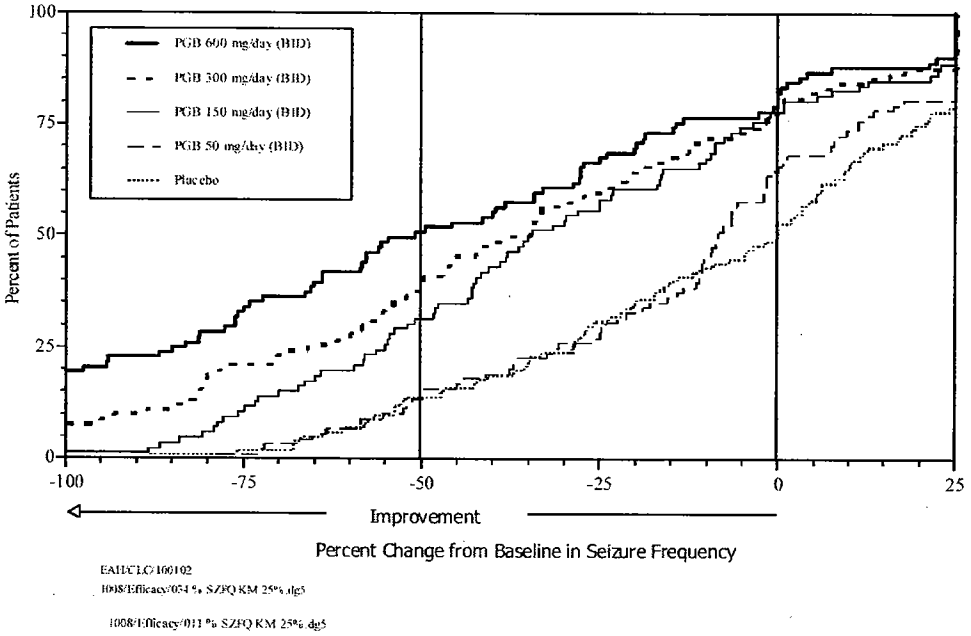


Figure 52. Cumulative Distribution Plot - Study 034



EA11/CLC/160102
1008/Efficacy/034 % SZFQ KM 25% dg5

1008/Efficacy/011 % SZFQ KM 25% dg5

6.7.5.5 Secondary Efficacy Parameter - Cumulative distribution plots of percent change

Results of Studies 009, 011, and 034 are displayed in Figure 50, Figure 51, and Figure 52, above respectively. This presentation allows comparison of treatment groups using any specified level of percent change to dichotomize patients into responders/nonresponders. For example, the percent of patients who attained at least a 25% reduction in seizures can be found by locating -25% on the X-axis and then reading up the Y-axis on the graph for each treatment group. In the figures, the Y-axis displays the percentage of patients who attained a percent change in seizure frequency less than or equal to that displayed on the X-axis. As seen in the figures, pregabalin treatment groups of 150 to 600 mg/day maintained consistent superiority in seizure reduction compared to placebo. These figures also illustrate the pregabalin dose-response relationship by the consistent separation and ordering of the treatment groups. The separation from placebo in the 150 to 600 mg/day dose groups was evident even for patients who experienced an *increase* in seizure frequency during the study.

6.7.5.6 Secondary Efficacy Parameter - Greater than 25% increase in seizures

The percentage of patients with a clinically meaningful increase in seizure frequency was examined. In accordance with the European Union (EU) guidance, potential exacerbation of seizures should be assessed by examining seizure frequency increases of > 25%. A larger proportion of placebo patients experienced a > 25% seizure increase than pregabalin- treated patients (**Sponsor Table 43**). (Reviewer note: This reviewer questions why anywhere from 10-16% of patients in any treated group would have an increase in seizure rate. Is pregabalin acting in some patients as a promoter of seizures? This finding might possibly dilute the 28-day seizure rates and RRatios in the primary analysis. This finding in all treated groups is concerning and does not seem to be dose dependent.)

Table 43. Proportion of Patients With ≥25% Increase in Seizure Frequency (All Partial Seizures): ITT Population

Study	Treatment Group	n/N	%
009	Placebo	29/98	30
	PGB 600 mg/day BID	13/103	13
	PGB 600 mg/day TID	11/110	11
011	Placebo	32/96	33
	PGB 150 mg/day BID	16/99	16
	PGB 600 mg/day TID	4/92	4
034	Placebo	21/100	21
	PGB 50 mg/day BID	17/88	19
	PGB 150 mg/day BID	10/86	12
	PGB 300 mg/day BID	11/90	12
	PGB 600 mg/day BID	9/89	10

ITT = Intent-to-treat; PGB = Pregabalin.

6.7.5.7 Secondary Efficacy Parameter – Seizure type analysis RRatio, responder rate, and percent change for each partial seizure type (simple partial, complex partial, and [redacted] were assessed in each study.)

Results for each of these seizure types as well as results for simple and complex combined and all partial seizures are presented in Sponsor Tables 44, 45 and 46. In addition, I asked the statistical reviewer, Tristan Massey, to provide data relating seizure type with dose for the pooled data related to the primary endpoint, RR ratio.

Table 44. Summary of RRatio by Seizure Type: ITT Population

Seizure Type / Study	Placebo	Pregabalin Dose (mg/day) and Regimen					
		50 BID	150 BID	150 TID	300 BID	600 BID	600 TID
Simple Partial Seizures							
009 [Mean, N]	8.4, 56					-10.4, 49	-37.8, 59
011 [Mean, N]	-6.1, 40			-11.4, 32			-26, 30
034 [Mean, N]	2.2, 48	0.3, 44	-10.7, 42		-23.5, 46	-46.5, 45	
Complex Partial Seizures							
009 [Mean, N]	-5.9, 85					-31.1, 94	-35.9, 97
011 [Mean, N]	-3.1, 85			-14.3, 88			-37, 83
034 [Mean, N]	0.5, 90	-5.8, 82	-18, 75		-25.5, 79	-36.7, 80	
Simple and Complex Seizures							
009 [Mean, N]	2.4, 97					-23.4, 98	-33.8, 109
011 [Mean, N]	1.9, 92			-10.6, 96			-30.7, 88
034 [Mean, N]	-0.7, 100	-5.1, 87	-21.4, 84		-28.3, 87	-35.3, 89	
All Partial Seizures							
009 [Mean, N]	0.6, 98					-28.4, 103	-36.1, 111
011 [Mean, N]	0.9, 96			-11.5, 99			-31.4, 92
034 [Mean, N]	-3.8, 100	-6.2, 88	-20.5, 86		-27.8, 90	-37.4, 89	

ITT = Intent-to-treat.

Table 45. Summary of Responder Rate by Seizure Type: ITT Population

Seizure Type / Study	Placebo	Pregabalin Dose (mg/day) and Regimen					
		50 BID	150 BID	150 TID	300 BID	600 BID	600 TID
Simple Partial Seizures							
009 [n (%), N]	13 (23.2), 56					20 (40.8), 49	31 (52.5), 59
011 [n (%), N]	10 (25.0), 40			8 (25.0), 32			14 (46.7), 30
034 [n (%), N]	11 (22.9), 48	9(20.5), 44	15 (35.7), 42		15 (32.6), 46	30 (66.7), 45	
Complex Partial							
009 [n (%), N]	16 (18.8), 85					41 (43.6), 94	49 (50.5), 97
011 [n (%), N]	13 (15.3), 85			19 (21.6), 88			45 (54.2), 83
034 [n (%), N]	15 (16.7), 90	13(15.9), 82	30 (40.0), 75		32 (40.5), 79	42 (52.5), 80	
Simple and Complex Seizures							
009 [n (%), N]	11 (11.3), 97					36 (36.7), 98	51 (46.8), 109
011 [n (%), N]	10 (10.9), 92			15 (15.6), 96			40 (45.5), 88
034 [n (%), N]	14 (14.0), 100	12(13.8), 87	32 (38.1), 84		34 (39.1), 87	46 (51.7), 89	
All Partial Seizures							
009 [n (%), N]	9 (9.2), 98					44 (42.7), 103	54 (48.7), 111
011 [n (%), N]	6 (6.3), 96			14 (14.1), 99			40 (43.5), 92
034 [n (%), N]	14 (14.0), 100	13(14.8), 88	27 (31.4), 86		36 (40.0) 90	45 (50.6), 89	

ITT = Intent-to-treat.

Pregabalin treatment groups of 150 to 600 mg/day were consistently better than placebo in reducing the frequency of simple partial, complex partial, and simple and complex seizures combined as measured by RRatio, responder rate and percent change. Additionally, changes in seizure frequency for simple partial and complex partial seizure types showed trends consistent with those seen for all partial seizures combined in all 3 studies. The few results that vary in magnitude from those seen in the combined data were felt by the sponsor to possibly be due to the small sample sizes in those particular subgroups.

Pregabalin treatment groups of 300 and 600 mg/day were consistently better than placebo in reducing ——— frequency. However, the results for ——— were not statistically significant. The 150-mg/day dose was not as effective for simple partial seizures alone.

Table 46. Summary of Median Percent Change From Baseline in Seizure Frequency by Seizure Type: ITT Population

Seizure Type / Study	Placebo	Pregabalin Dose (mg/day) and Regimen					
		50 BID	150 BID	150 TID	300 BID	600 BID	600 TID
Simple Partial Seizures							
009 [Median, N]	-12.6, 48					-54.5, 40	-74.1, 54
011 [Median, N]	-3.7, 36			-24.2, 29			-53.5, 28
034 [Median, N]	-17.6, 40	-10.9, 38	-35.7, 36		-31.7, 44	-78.9, 42	
Complex Partial							
009 [Median, N]	-3.0, 85					-34.9, 94	-51.1, 97
011 [Median, N]	-4.5, 83			-23.3, 87			-54, 81
034 [Median, N]	0, 86	-11.6, 79	-39.4, 73		-41.8, 76	-55.6, 79	
Simple and Complex Seizures							
009 [Median, N]	-1.1, 95					-29.7, 98	-46.2, 108
011 [Median, N]	4.2, 91			-17.9, 95			-44.5, 87
034 [Median, N]	0, 98	-9.1, 86	-38.1, 83		-34.9, 87	-55.8, 88	
All Partial Seizures							
009 [Median, N]	-0.8, 98					-35.6, 103	-48.1, 111
011 [Median, N]	1.3, 96			-16.5, 99			-42.6, 92
034 [Median, N]	0, 100	-8.6, 88	-34.8, 86		-36.7, 90	-50.9, 89	

Table 1 Study 34: Analysis of RRatio by Seizure Type with statistical significance noted in bold. (Provided by the statistical reviewer and amended by this reviewer.)

			Level of RXGRP				
			PBO	50(BID)	150(BID)	300(BID)	600(BID)
Seizure Type			47.00	43.00	42.00	44.00	45.00
Simple partial seizure	N						
	Mean RRatio		2.21	0.34	-10.65	-24.52	-46.52

only	StdErr		8.63	8.42	9.46	7.42	8.68
	P-value		.	0.92	0.23	**0.04**	**<0.01**
Complex partial seizure only	N		89.00	82.00	75.00	77.00	78.00
	Mean RRatio		0.50	-5.77	-17.97	-26.20	-37.62
	StdErr		4.05	4.18	4.77	5.45	6.00
	P-value		.	0.29	**<0.01**	**<0.01**	**<0.01**
Simple partial and complex partial sz.	N		99.00	86.00	84.00	85.00	87.00
	Mean RRatio		-0.73	-5.12	-21.40	-29.01	-36.15
	StdErr		3.09	2.99	3.85	4.13	5.39
	P-value		.	0.40	**<0.01**	**<0.01**	**<0.01**

6.7.5.8 Secondary Efficacy Parameter - **Epilepsy Seizure-Free Analysis**

Per protocol, seizure freedom was summarized in each study by examining the length of seizure free interval and the number of seizure free days per 28-day interval. No inferential analyses were performed on these data. In each study, pregabalin-treated patients were seizure-free for a longer period of time and experienced more seizure-free days than placebo patients.

6.8 Post Hoc Efficacy Analyses

Based on the robust effect on efficacy seen in other efficacy parameters after the blind was broken, as well as anecdotal reports from investigators during the study, the question of whether pregabalin could enable refractory patients to become seizure free was explored in post-hoc analyses. These analyses used a Fisher's Exact statistical method to examine the number of patients that were seizure free during all or part of the double-blind period.

Several post-hoc analyses were performed using data from Studies 009, 011 and 034. Seizure data from individual studies were further examined to assess seizure freedom and efficacy at weekly increments. Data were pooled to examine results by seizure-type and, specifically ——— data were examined in each individual study and pooled across studies.

Results of the Post Hoc analyses are discussed as follows.

6.8.1 Post Hoc - Seizure Free Analysis –

The number and percent of patients who remained seizure free for the last 28 days of treatment were examined in each study. Pregabalin treated patients tended to achieve seizure freedom with increasing doses in all three studies. However, the only statistically significant results were that significantly more patients in the 600mg/day TID dose groups were seizure free the last 28 days when compared to placebo groups. Per the sponsor, "these results were clinically significant given that the mean duration of epilepsy in these studies was approximately 25 years, that the median baseline seizure rate was approximately 10 seizure per 28 days and patients were taking up to 3 concomitant AEDs.

6.8.2 Post Hoc - By seizure type meta-analysis –

The efficacy measures RRatio, responder rate and percent change were analyzed by seizure type in a pooled analysis combining data from the 3 pivotal studies. As was seen for all partial seizures combined, there is evidence of increasing efficacy with increasing dose for each subtype. At doses of 150mg/day, pregabalin had a significant effect in reducing complex partial seizures and at 600mg/day, pregabalin was statistically superior to placebo in reducing simple partial, complex partial and———— This is illustrated in Sponsor Table 49.

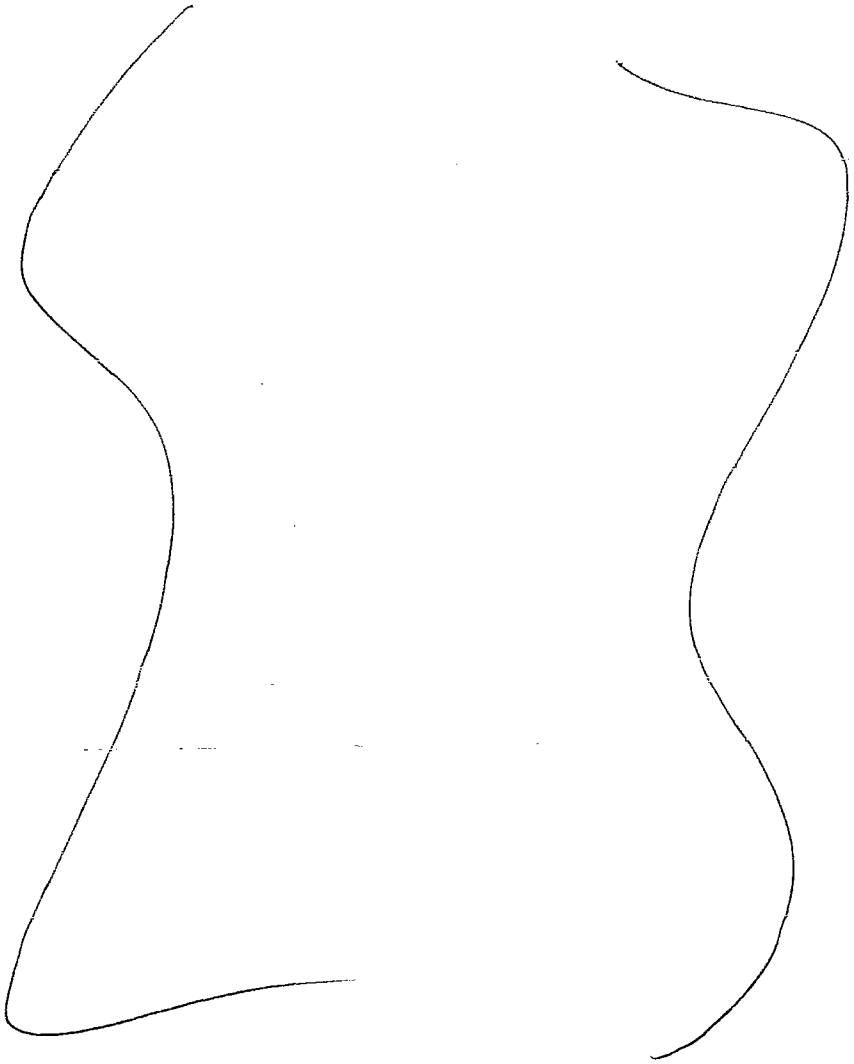
Table 49. Summary of RRatio by Seizure Type – Meta Analysis: ITT Population

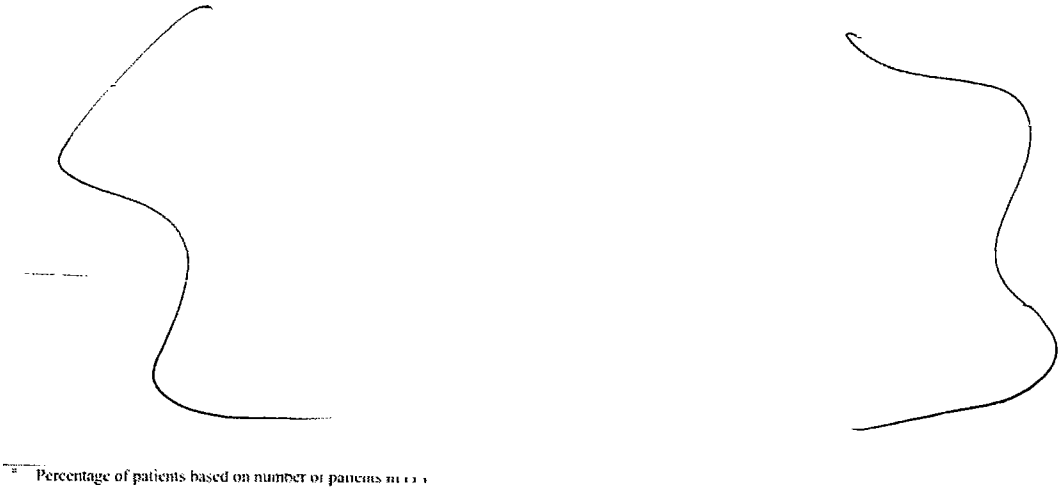
Seizure Type	Placebo	Pregabalin Dose (mg/day) and Regimen					
		50 BID	150 BID	150 TID	300 BID	600 BID	600 TID
Simple Partial, N	144	44	42	32	46	94	89
Mean (SE)	2.3 (5.0)	0.3 (9.0)	-10.7 (9.2)	-11.4 (10.6)	-23.5 (8.8)	-27.7 (6.2)	-33.8 (6.3)
p Value		0.3727	0.7904	0.2165	0.1601	≤0.0001*	≤0.0001*
Complex Partial, N	260	82	75	88	79	174	180
Mean (SE)	-2.8 (2.6)	-5.8 (4.6)	-18.0 (4.8)	-14.3 (4.4)	-25.5 (4.7)	-33.7 (3.2)	-36.4 (3.1)
p Value		0.5189	0.0008*	0.0142*	≤0.0001*	≤0.0001*	≤0.0001*
Simple and Complex Partial, N	289	87	84	96	87	187	197
Mean (SE)	1.2 (2.2)	-5.1 (4.0)	-21.4 (4.1)	-10.6 (3.8)	-28.3 (4.0)	-29.1 (2.7)	-32.5 (2.7)
p Value		0.7754	≤0.0001*	0.007*	≤0.0001*	≤0.0001*	≤0.0001*
All Partial, N	294	88	86	99	90	192	203
Mean (SE)	-0.8 (1.9)	-6.2 (3.5)	-20.5 (3.5)	-11.6 (3.3)	-27.8 (3.4)	-32.5 (2.4)	-34.0 (2.3)
p Value		0.6346	≤0.0001*	0.0004*	≤0.0001*	≤0.0001*	≤0.0001*

SGTC = Secondarily generalized tonic clonic.
* Statistically significant.

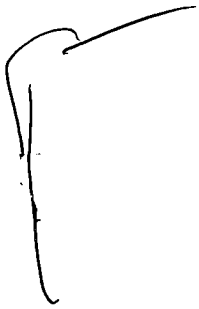
(Reviewer Note: This reviewer notes what the sponsor did not, that for simple partial seizures, only the 600mg daily dose is statistically significant. For complex partial seizures, although 150mg BID is better statistically than TID dosing, the 300mg dose has more meaningful significance and appears to be just as efficacious as 600mg daily. For simple and complex partial combined, the 150mg dose begins to look better. For type seizures, as with complex partial seizure, the effective dosing begins at 600mg/daily. So overall depending on seizure type, dose related efficacy is difficult to interpret)

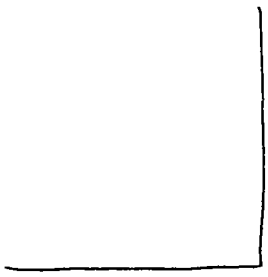
6.8.3 Post Hoc -





Percentage of patients based on number of patients in [illegible]





6.9 Subset analyses - Comparison of Results in subpopulations

Table 52. Summary of RRatio by Subpopulations of Age, Race, Gender, and Menopausal Status: ITT Population

Subpopulation	N	Mean	SD	Median	Minimum	Maximum
AGE[a]						
12 Through 16 Years[b]						
Placebo	1	43.8	--	43.8	44	44
All Effective Pregabalin Doses	9	-16	44.4	-10.3	-100	53
17 Through 64 Years						
Placebo	285	-1.1	27	-0.2	-100	88
All Effective Pregabalin Doses	649	-27.6	36.5	-22.8	-100	99
65 Through 74 Years[a]						
Placebo	7	6.2	14.4	4.1	-10	36
All Effective Pregabalin Doses	10	-51.5	37.4	-51.8	-100	-1
RACE						
White						
Placebo	260	-1.1	26.5	-0.8	-100	75
All Pregabalin	581	-26.7	37	-21.1	-100	99
Black						
Placebo	12	3.4	32.8	7.3	-56	46
All Pregabalin	32	-26.9	31.3	-22.7	-100	50
Hispanic						
Placebo	12	1.5	33.4	1.3	-37	88
All Pregabalin	39	-38.5	35.5	-36.7	-100	39
Other						
Placebo	10	-1.1	24.4	6.4	-47	30
All Pregabalin	18	-36.8	32.9	-33.6	-100	14
GENDER						
Male						
Placebo	156	-1.6	24.1	-0.3	-70	73
All Pregabalin	324	-25.5	33.6	-21.1	-100	96
Female						
Placebo	138	0	29.7	0	-100	88
All Pregabalin	346	-29.7	39.2	-24.8	-100	99
MENOPAUSAL STATUS						
Premenopausal						
Placebo	99	0.2	32.5	0	-100	88
All Pregabalin	261	-27.5	37.9	-21.7	-100	99
Postmenopausal						
Placebo	39	-0.3	21.4	0	-50	60
All Pregabalin	83	-38.2	41.5	-34.3	-100	92

ITT = Intent-to-treat; SD = Standard Deviation.

[a] Age Category ≥75 years is not presented due to the small sample size (N = 2; 1 patient given 150 mg/day and the other given 600 mg/day).

[b] Patient ages were: 12, 12, 13, 13, 15, 15, 15, 15, and 16 years for pregabalin and 16 years for placebo.

Table 53. Summary of RRatio, Dose Administered, and Estimated Creatinine Clearance by Age Category

Age Subpopulation	RRatio	Dose Administered (mg/day)	CLcr (mL/min)
12 Through 16 Years (N = 9)			
Mean (SD)	-16 (44.4)	283 (190.4)	118 (32.7)
Median	-10.3	150	101
Minimum, Maximum	-100, 53	150, 600	82, 164
17 Through 64 Years (N = 649)			
Mean (SD)	-27.6 (36.5)	437 (201.8)	110 (32.1)
Median	-22.8	600	105
Minimum, Maximum	-100, 99	150, 600	46, 297
65 Through 74 Years (N = 10)			
Mean (SD)	-51.5 (37.4)	465 (217.4)	71 (9.6)
Median	-51.8	600	71
Minimum, Maximum	-100, -1	150, 600	53, 82

CLcr = Creatinine clearance; SD = Standard deviation.

6.10 Dose response in Epilepsy

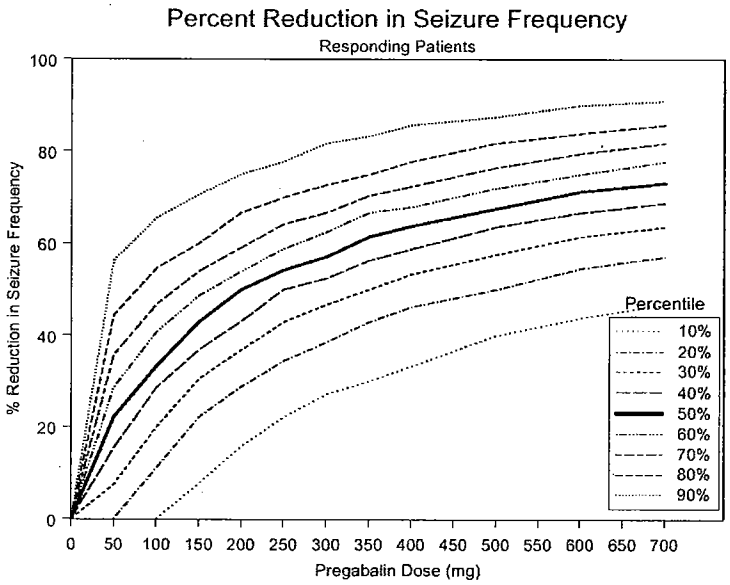
In Studies 011 and 034, where differing doses were administered within each study, dose response analyses were performed. Data from the patients in the pregabalin groups and the placebo group were used to characterize the dose response relationship between pregabalin and partial seizure control as measured by the RRatio and the responder rate. The dose response for the unranked RRatio in terms of linear and quadratic (Study 034 only) contrasts were tested using the main effects ANOVA model and appropriate contrast statements. The dose response of the responder rate using placebo and all pregabalin treatments was tested using a linear association hypothesis with the Cochran-Mantel Haenszel correlation statistic.

A statistically significant dose response (linear trend) in the RRatio and responder rate was shown in the 2 dose response studies (Studies 011 and 034). In Study 034, a statistically significant quadratic trend in these parameters was due to the rapid increase in effect between placebo and 150 mg/day, which then increased linearly for the 300 and 600mg doses. The median percent change also showed a dose response in these 2 studies, although not tested statistically.

6.11 Pharmacokinetic/pharmacodynamic modeling

A dose response relationship was noted regarding reduction of seizure frequency. The model confirmed that age, race and menopausal status had no influence on pregabalin effect. A difference in gender was seen with women experiencing a greater reduction in seizure frequency than men. To this reviewer, this is a significant finding that may indicate that women may respond better than men to this drug. Figure 53 illustrates the expected percent reduction in seizure frequency with increasing dose and may aid in dose selection. For example, a daily dose of 300 mg/day in patients who are likely to respond is expected to result in at least 82%, 57%, and 27% reduction in seizure frequency in 10%, 50%, and 90% of the population, respectively.

Figure 53. Expected Percent Reduction in Seizure Frequency With Increasing Dose



6.12 *Concomitant Antiepileptic Drug Use*

Multiple concomitant antiepileptic drugs were taken by patients at baseline and allowed in the protocol with the exception of Neurontin ®, Felbatol ® and Vigabatrin ®. There was no unique interaction with any particular drug that would have affected the results of the trials.

The use of concomitant AEDs is summarized in each trial by the following 3 tables. (The first Table 8 is from Study 009, Table 11 is from Study 011 and the second Table 8 is from Study 034). Please note that for the combined trials, approximately one half of the patients took at least 2 concomitant antiepileptic medications.

Table 8. Summary of Concurrent Antiepileptic Drugs Taken at Baseline: ITT Population[a]
[Number (%) of Patients]

Antiepileptic Drugs (AEDs)[b]	Placebo N = 98		Pregabalin 600 mg/day (TID) N = 111		Pregabalin 600 mg/day (BID) N = 103		All Patients N = 312	
Carbamazepine	55	(56.1%)	62	(55.9%)	64	(62.1%)	181	(58.0%)
Lamotrigine	32	(32.7%)	36	(32.4%)	34	(33.0%)	102	(32.7%)
Phenytoin Sodium	20	(20.4%)	22	(19.8%)	26	(25.2%)	68	(21.8%)
Topiramate	26	(26.5%)	18	(16.2%)	23	(22.3%)	67	(21.5%)
Phenytoin	5	(5.1%)	10	(9.0%)	11	(10.7%)	26	(8.3%)
Valproate Semisodium	10	(10.2%)	17	(15.3%)	8	(7.8%)	35	(11.2%)
Tiagabine	9	(9.2%)	10	(9.0%)	7	(6.8%)	26	(8.3%)
Clonazepam	3	(3.1%)	5	(4.5%)	6	(5.8%)	14	(4.5%)
Clorazepate Dipotassium	0	(0.0%)	1	(0.9%)	6	(5.8%)	7	(2.2%)
Phenobarbital	4	(4.1%)	5	(4.5%)	6	(5.8%)	15	(4.8%)
Valproic Acid	2	(2.0%)	6	(5.4%)	5	(4.9%)	13	(4.2%)
Clobazam	1	(1.0%)	1	(0.9%)	4	(3.9%)	6	(1.9%)
Primidone	3	(3.1%)	1	(0.9%)	3	(2.9%)	7	(2.2%)
Vagus Nerve Stimulator (Antiepileptics)[c]	1	(1.0%)	5	(4.5%)	2	(1.9%)	8	(2.6%)
Oxazepam	0	(0.0%)	0	(0.0%)	2	(1.9%)	2	(0.6%)
Acetazolamide	3	(3.1%)	2	(1.8%)	1	(1.0%)	6	(1.9%)
Diazepam	0	(0.0%)	0	(0.0%)	1	(1.0%)	1	(0.3%)
Felbamate	0	(0.0%)	0	(0.0%)	1	(1.0%)	1	(0.3%)
Mesuximide	0	(0.0%)	0	(0.0%)	1	(1.0%)	1	(0.3%)
Methylphenobarbital	0	(0.0%)	0	(0.0%)	1	(1.0%)	1	(0.3%)
Phenobarbital Sodium	0	(0.0%)	0	(0.0%)	1	(1.0%)	1	(0.3%)
Alclofenac	1	(1.0%)	0	(0.0%)	0	(0.0%)	1	(0.3%)
Ethotoin	2	(2.0%)	0	(0.0%)	0	(0.0%)	2	(0.6%)
Lorazepam	1	(1.0%)	3	(2.7%)	0	(0.0%)	4	(1.3%)

[a] Data sorted by decreasing frequency in the pregabalin BID group
[b] More than one AED per patient possible
[c] WHO dictionary uses the term "antiepileptics" for vagus nerve stimulator (VNS)

Table 10. Summary of Most Frequent Concurrent Antiepileptic Drugs: ITT Population[a]
[Number (%) Patients]

Antiepileptic Drugs (AEDs)[b]	Placebo N = 96		PGB 150 mg/day N = 99		PGB 600 mg/day N = 92		All Patients N = 287	
Carbamazepine	53	(55.2%)	63	(63.6%)	60	(65.2%)	176	(61.3%)
Lamotrigine	27	(28.1%)	37	(37.4%)	31	(33.7%)	95	(33.1%)
Valproic Acid	11	(11.5%)	5	(5.1%)	18	(19.6%)	34	(11.8%)
Topiramate	21	(21.9%)	17	(17.2%)	16	(17.4%)	54	(18.8%)
Clobazam	19	(19.8%)	16	(16.2%)	14	(15.2%)	49	(17.1%)
Phenobarbital	8	(8.3%)	16	(16.2%)	12	(13.0%)	36	(12.5%)
Phenytoin	19	(19.8%)	12	(12.1%)	10	(10.9%)	41	(14.3%)
Clonazepam	7	(7.3%)	7	(7.1%)	9	(9.8%)	23	(8.0%)
Valproate Sodium	14	(14.6%)	9	(9.1%)	9	(9.8%)	32	(11.1%)
Tiagabine	3	(3.1%)	8	(8.1%)	4	(4.3%)	15	(5.2%)
Diazepam	2	(2.1%)	3	(3.0%)	3	(3.3%)	8	(2.8%)
Primidone	0	(0.0%)	1	(1.0%)	3	(3.3%)	4	(1.4%)
Oxcarbazepine	6	(6.3%)	10	(10.1%)	1	(1.1%)	17	(5.9%)

PGB = Pregabalin.
[a] AEDs taken by ≥3% of patients in any pregabalin group; data are sorted by the pregabalin 600 mg/day group.
[b] Patients may have taken more than one AED.

Table 8. Summary of Concurrent AEDs: ITT Population

Antiepileptic Drugs (AEDs)[a]	Placebo N = 100	Pregabalin 50 mg/day (BID) N = 88	Pregabalin 150 mg/day (BID) N = 86	Pregabalin 300 mg/day (BID) N = 90	Pregabalin 600 mg/day (BID) N = 89	All Patients N = 453
Carbamazepine	48 (48%)	47 (53%)	50 (58%)	44 (49%)	45 (51%)	234 (52%)
Phenytoin Sodium	31 (31%)	23 (26%)	19 (22%)	29 (32%)	27 (30%)	129 (29%)
Lamotrigine	22 (22%)	21 (24%)	17 (20%)	20 (22%)	19 (21%)	99 (22%)
Valproate Semisodium	21 (21%)	15 (17%)	13 (15%)	16 (18%)	19 (21%)	84 (19%)
Topiramate	16 (16%)	16 (18%)	15 (17%)	15 (17%)	16 (18%)	78 (17%)
Tiagabine	6 (6%)	19 (22%)	11 (13%)	10 (11%)	11 (12%)	57 (13%)
Clonazepam	6 (6%)	0 (0%)	3 (4%)	3 (3%)	5 (6%)	17 (4%)
Phenobarbital	12 (12%)	3 (3%)	5 (6%)	8 (9%)	5 (6%)	33 (7%)
Clobazam	4 (4%)	1 (1%)	3 (4%)	3 (3%)	4 (5%)	15 (3%)
Clorazepate Dipotassium	3 (3%)	1 (1%)	4 (5%)	0 (0%)	4 (5%)	12 (3%)
Primidone	5 (5%)	3 (3%)	2 (2%)	3 (3%)	4 (5%)	17 (4%)
Valproic Acid	0 (0%)	1 (1%)	3 (4%)	3 (3%)	3 (3%)	10 (2%)
Alprazolam	0 (0%)	0 (0%)	0 (0%)	1 (1%)	2 (2%)	3 (<1%)
Gabapentin	1 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)	3 (<1%)
Lorazepam	6 (6%)	7 (8%)	3 (4%)	2 (2%)	2 (2%)	20 (4%)
Phenytoin	5 (5%)	6 (7%)	4 (5%)	3 (3%)	2 (2%)	20 (4%)
Acetazolamide	2 (2%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)	4 (<1%)
Diazepam	5 (5%)	1 (1%)	2 (2%)	0 (0%)	1 (1%)	9 (2%)
Felbamate	5 (5%)	0 (0%)	3 (4%)	1 (1%)	1 (1%)	10 (2%)
Pentobarbital Sodium	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (<1%)
Antiepileptics[b]	2 (2%)	1 (1%)	1 (1%)	1 (1%)	0 (0%)	5 (1%)
Ethosuximide	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	2 (<1%)
Mesuximide	1 (1%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	3 (<1%)
Methylphenobarbital	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (<1%)

[a] More than one AED per patient possible
[b] Vagal nerve stimulator device codes to antiepileptics

Tristan Massie, the statistician, provided statistical analyses regarding any PD effects on efficacy and failed to find any in the most commonly used antiepileptics allowed for the trial. This is summarized by his table reproduced below.(Please see his separate reviews in DFS.)

Table 2 NDA 21724 Pregabalin Efficacy by Concomitant AED*

		Pregabalin Dose (mg/day)				
		0	50	150	300	600
AED						
All	N	293	87	185	88	390
	Mean RRatio	-0.83	-6.25	-15.69	-28.43	-33.71
	StdDev	26.91	23.88	26.50	36.63	39.47
	P-value	.	0.461	0.000	0.000	0.000
Carbamazepine	N	156	47	113	43	229
	Mean RRatio	0.02	-6.94	-15.06	-28.08	-34.78
	StdDev	25.63	24.50	25.38	37.12	38.54
	P-value	.	0.451	0.000	0.000	0.000
Lamotrigine	N	80	21	54	19	117
	Mean RRatio	1.39	-7.47	-18.84	-41.00	-33.89
	StdDev	23.97	34.41	29.32	43.08	38.18
	P-value	.	0.215	0.000	0.000	0.000
Phenytoin Sodium/ Phenytoin	N	82	28	36	31	110
	Mean RRatio	-1.71	-4.17	-20.05	-27.09	-32.62
	StdDev	24.69	22.83	26.84	30.39	38.21
	P-value	.	0.960	0.003	0.000	0.000
Topiramate	N	63	16	32	15	73
	Mean RRatio	0.52	-4.78	-18.69	-37.94	-28.99
	StdDev	26.67	20.63	28.99	36.57	42.64
	P-value	.	0.638	0.012	0.005	0.000
Valproate SemiSodium/ Valproate Sodium	N	46	15	22	16	51
	Mean RRatio	-4.85	-18.05	-20.03	-6.28	-38.75
	StdDev	31.42	22.92	23.06	31.94	41.27
	P-value	.	0.064	0.104	0.674	0.000
Tiagabine/ Tiagabine HCl	N	18	19	20	10	32
	Mean RRatio	4.20	-10.68	-9.60	-32.68	-30.95
	StdDev	20.71	20.16	18.34	29.38	41.16

		Pregabalin Dose (mg/day)				
		0	50	150	300	600
	P-value	.	0.324	0.242	0.000	0.000

*Pooled over studies 0009, 0011, 0034 and BID and TID regimens
Note that patients can contribute to the results for more than one AED

6.13 Dosing interval and recommendation

Per the sponsor, the minimally effective dose for partial seizures was 150mg daily given as two divided doses. Based on individual patient responses and tolerability, the dosage could be increased to 300mg daily after 1 week (in divided doses) with a maximum dose of 600mg daily after an additional week of titration. (Reviewer note: this was not done during double blind administration in any of the clinical trials.) Comparable results were seen when the drug was given in either 2 or 3 divided doses. However, in patients with a history of renal insufficiency, creatinine clearance should be determined prior to dosing and daily dosages reduced accordingly. If pregabalin is to be discontinued, it is recommended to taper the dose gradually over 1 week. (Reviewer note: this consideration for dosing seems reasonable, and considering the short half-life of the drug, the titration could be done every few days if necessary. The drug does have a wide range of dose related efficacy across the seizure types as already discussed. Unfortunately, a dose between 300 and 600mg was not tested to see if a lower efficacious dose might be available that would reduce side effects. We can only consider the doses tested in the clinical trials.)

6.14 Persistence of effect or tolerance

There are no controlled studies that specifically assessed persistence of efficacy and/or tolerance to treatment in patients with epilepsy. However, a total of 4 open-label add-on studies were conducted in order to evaluate long-term safety and efficacy of pregabalin in patients with partial seizures.

Patients from Study 007, a proof of concept, randomized, double-blind, low dose active-controlled in-patient, monotherapy study and patients from the 3 double-blind placebo controlled studies 009, 011, and 034 were eligible to enter open-label studies (Studies 008, 010, 012, and 035, respectively). Additionally, de novo patients were allowed entry into Studies 010, 012, and 035.

The principal criterion to establish efficacy of pregabalin was the reduction in frequency of all partial seizures during the open-label treatment period compared with the seizure frequency during the baseline period of the preceding double-blind study. Efficacy was evaluated using the percent change in 28-day seizure rates in treatment compared to the baseline. Additionally, responder rate, defined as the proportion of patients who had a

>50% reduction in seizure rate during treatment as compared to baseline of the preceding double-blind study was assessed.

All data were summarized descriptively. The efficacy parameters of responder rate and percent change were summarized using data from the evaluable population (ITT patients who entered open-label from the preceding double-blind study with at least 1 day of open-label and at least 1 day of baseline seizure diary data). Efficacy was also summarized using subsets of these populations who had remained in the study for 6 months (6-Month Cohort), for 1 year (1-Year Cohort), and for 2 years (2-Year Cohort).

The protocols of the Studies 008, 010, and 035 were modified, at the request of the FDA, to limit continuing participation in the studies, at centers in the US, to those patients who were refractory to other AEDs and who were responding to pregabalin. Patients must have also reconsented to continue in the studies. The requalification procedure excluded patients who did not continue to have a >30% reduction in seizure frequency compared to the baseline frequency. Because this created a bias in favor of pregabalin, seizure data collected after requalification were not included in the analyses of responder rate and percent change.

As of February 14, 2003, a total of 1480 patients had participated in the open-label studies. One thousand one hundred forty-three patients were treated for at least 24 weeks, 879 patients for at least 1 year, 512 patients for at least 2 years and 248 patients for at least 3 years. Of the 1480 patients in the ITT population, 881 (60%) met the criteria for the evaluable population. Patients in Study 008 and de novo patients in any study were not included in the evaluable population because of inadequate or missing baseline data. Overall, the evaluable population was predominantly white (87%) with a mean age at study entry of 38 years; there were a similar number of male and female patients. The mean duration of epilepsy was 25 years for the evaluable population and approximately half of these patients were taking 2 AEDs at Day 1 of the open-label studies. In the ongoing uncontrolled studies, a responder rate of 37% and a median percent reduction from baseline seizures of 38% were seen for the evaluable population during the initial 84-day (12-week) open-label period. For the cohort of patients followed for 2 years, the responder rate and the median percent change at subsequent intervals were maintained over time (Table 55 and Table 56).

Table 55. Summary of Responder Rate[a]: Evaluable Population and 2 Year Cohort[b] of Evaluable Population: Open Label Studies 010, -012, and -035

Period (Study Days)	Evaluable Population N = 881		2-Year Cohort N = 220	
	N	Responders (%)	N	Responders (%)
OL 1 (1-84)	881	329 (37.3)	220	114 (51.8)
OL 2 (85-168)	785	322 (41.0)	220	109 (49.5)
OL 3 (169-252)	687	302 (44.0)	220	109 (49.5)
OL 4 (253-336)	610	291 (47.7)	220	120 (54.5)
OL 5 (337-420)	550	272 (49.5)	220	115 (52.3)
OL 6 (421-504)	507	268 (52.9)	220	128 (58.2)
OL 7 (505-588)	481	258 (53.6)	220	128 (58.2)
OL 8 (589-672)	429	240 (55.9)	220	121 (55.0)
OL 9 (673-756)	310	183 (59.0)	220	127 (57.7)
OL 10 (757-840)	186	106 (57.0)	186	106 (57.0)
OL 11 (841-924)	134	81 (60.4)	134	81 (60.4)
OL 12 (925-1008)	106	62 (58.5)	106	62 (58.5)

OL = Open-label, NA = Not applicable.

[a] Data collected after initial requalification not included.

[b] Two year cohort defined by open-label exposure at initial requalification date for Studies 010 and -035 and by total open-label exposure for 1008–012.

APPEARS THIS WAY
ON ORIGINAL

Table 56. Summary of Percent Change[a]: Evaluable Population and 2 Year Cohort[b] of Evaluable Population: Open-Label Studies 010, -012, and -035

Period (Study Days)	Evaluable Population N = 881				2-year Cohort N = 220			
	N	Median	Min	Max	N	Median	Min	Max
OL 1 (1-84)	881	-37.8	-100	653.8	220	-51.0	-100	119.3
OL 2 (85-168)	785	-39.4	-100	8860.8	220	-49.4	-100	206.7
OL 3 (169-252)	687	-42.9	-100	4971.8	220	-49.2	-100	108.3
OL 4 (253-336)	610	-46.8	-100	676.6	220	-52.1	-100	77.4
OL 5 (337-420)	550	-48.9	-100	966.7	220	-50.7	-100	208.3
OL 6 (421-504)	507	-52.4	-100	2700.0	220	-57.3	-100	144.4
OL 7 (505-588)	481	-53.8	-100	2922.0	220	-57.8	-100	214.3
OL 8 (589-672)	429	-58.1	-100	2615.2	220	-57.1	-100	214.3
OL 9 (673-756)	310	-59.0	-100	191.7	220	-56.7	-100	191.7
OL 10 (757-840)	186	-60.0	-100	1125.0	186	-60.0	-100	1125.0
OL 11 (841-924)	134	-57.9	-100	260.0	134	-57.9	-100	260.0
OL 12 (925-1008)	106	-59.6	-100	304.4	106	-59.6	-100	304.4

OL = Open label.

[a] Data collected after initial requalification not included for Studies 010 and -035.

[b] Two year cohort defined by open label exposure at initial requalification date for Studies 010 and -035 and by total open-label exposure for 012.

7 Appendix 1 - Review of Individual Study Report – Study 009 (Protocol 1008-009)

7.1 Study 009 (Protocol 1008-009) Outline

Title of Study: Pregabalin BID/TID Add-On Study: A Double-Blind, Placebo-Controlled, Multicenter Study in Patients With Partial Seizures.

Investigators: [redacted]

Study Center(s): Thirty-seven centers in the United States and 6 centers in Canada

Publication (reference): Epilepsia 1999;40(7):108

Studied Period (years): 06/02/98 to 09/27/99 Clinical Phase: 3

Objective(s): The objectives of this study were to evaluate the efficacy and safety of 2 regimens of pregabalin as add-on treatment in patients with partial seizures.

Study Design: Following screening and an 8-week baseline period, patients entered a 12-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter study. Randomization was to either placebo, or 1 of 2 pregabalin 600 mg/day regimens, TID (200 mg TID) or BID (300 BID). Current antiepileptic drug (AED) therapy was maintained. After the treatment phase, there was a withdrawal phase. After completing the study, patients had the option of entering a follow on open label study (1008-010). This is illustrated in Sponsor Figure 1

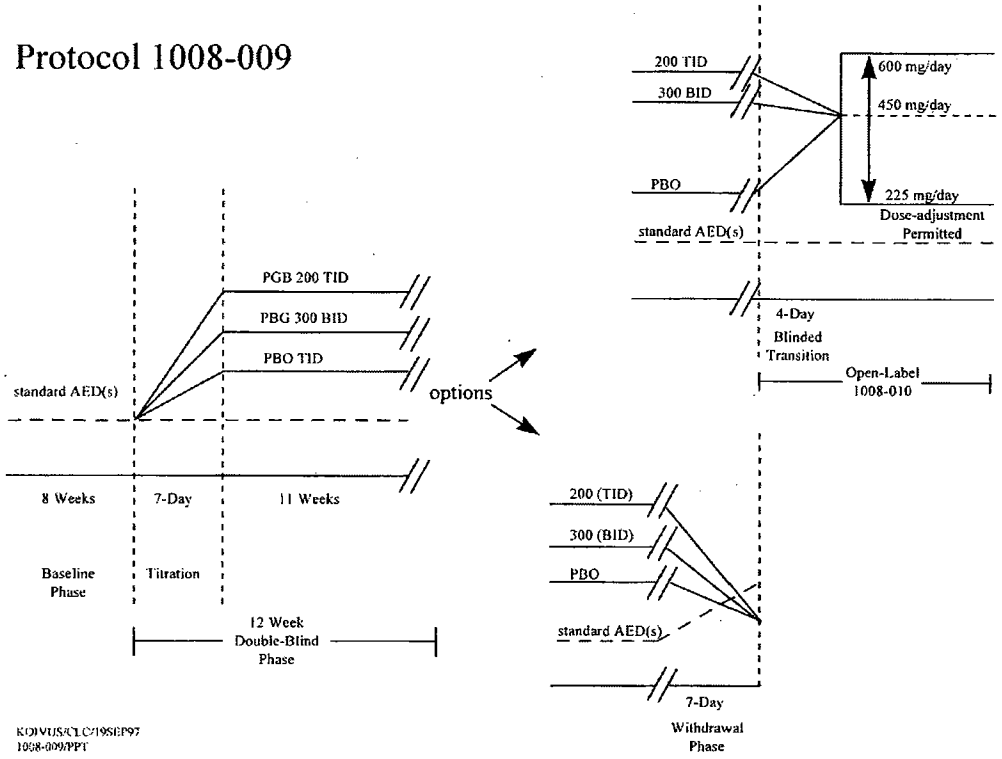


Figure 1. Study Design

Patient were required to have at least 6 partial seizures during the 8 week baseline phase with no 4 week seizure free period.

The double blind period included a 7-day blinded titration to final randomized dose. Current AED therapy was maintained at the same dosages as the baseline phase. Patients remained on study med with the dosage maintained unless seizures or adverse events required the patient to be withdrawn from the study.

The withdrawal period gave two options for patient, either to taper off the dose over 7 days or titrate to a common dose of 450mg/day over 4 days and enter the open label

Study 010. A final follow up visit occurred 4-6 weeks post the final dose of study medication for those patients not continuing into the open label phase.

Amendments and Addendum: There were 2 amendments and one addendum to the Study Design.

Amendment 1, signed February 1, 1999, modified several sections of the protocol as follows.

- The acceptable time period during which specific screening tests and procedures were completed was broadened. Previously, the protocol required these tests and procedures be performed only during screening; the amendment allowed for these tests to be performed during either screening or baseline.
- Amylase analysis was added to the chemistry profile, thus providing additional safety information on any potential effects of pregabalin on pancreatic activity.
- The [redacted] Device was allowed as an AED. This device had been previously prohibited by the protocol. This change was in response to Food and Drug Administration's (FDA) approval of the device for human use.
- Several revisions to the statistical section of the protocol were formalized. These included a change in the statistical comparison procedures from stepdown to Hochberg; a clarification of the analysis population name; the addition of a clustering definition; and, a correction to a statistical reference.

Amendment 2, signed April 14, 1999, changed the primary analysis population from the evaluable (all patients who are randomized, received 28 days of study medication, and had a minimum of 28 days of seizure diary data) to the intent-to-treat (ITT) population defined as all patients randomized who received at least 1 dose of study medication. The change occurred before the blind was broken for the interim analysis, and was made to be in closer compliance with recently issued International Conference on Harmonization (ICH) guidelines, and also as a result of discussions with FDA regarding the primary efficacy variable (response ratio).

Addendum A, signed February 4, 1999, increased the maximum number of patients to be enrolled at specific centers from 12 to 24 patients. This addendum only affected centers that had met the enrollment goals established in the protocol.

Number of Subjects: A total of 313 patients were randomized to treatment and 312 patients received at least 1 dose of study medication (ITT population): n = 98 placebo; n = 111 pregabalin TID; and n = 103 pregabalin BID. Per the sponsor, the blind was broken for one patient who became pregnant during the double blind phase, she was receiving placebo.

Diagnosis and Main Criteria for Inclusion: Men or nonpregnant, nonlactating women - 18 years of age, of any race, weighing between 50 to 135 kg (110-298 lb), and with

partial seizures (simple partial, complex partial, and/or secondarily generalized tonic clonic). Patients must have failed to have adequate seizure control in the past while on standard AEDs and must be receiving 1 to 3 standard AEDs at doses within an acceptable therapeutic range. Patients needed to have a minimum of 3 partial seizures during the 1 month prior to screening for entry into baseline and 6 seizures during the 8-week baseline period with no 4 week seizure free period.

Concomitant Medications: Single antidepressants for mild depression, benzodiazepines and phenobarbital were considered AEDs regardless of reason for use or frequency of administration. [redacted] were allowed. Concomitant AED therapy was allowed at therapeutic ranges. During the double blind phase, increasing the AED dose was not permitted, however, decreasing the dose was permitted if toxicity occurred.

Prohibited Medications: felbamate, vigabatrin, macrolide antibiotics, antihistamines, terfenadine, phenothiazines, and antiarrhythmic agents. (Reviewer note: these agents were prohibited because of the potential for cardiac arrhythmia - see study protocol for more information.) Gabapentin was also stopped prior to initiating pregabalin.

Reasons for Withdrawal: Epilepsy surgery, excessive or severe adverse events, including laboratory abnormalities or objective clinical signs and symptoms that were intolerable or incapacitating to the patient and/or posed a serious threat to well being. Occurrence of severe concurrent illness, i.e., illness that might interfere with the evaluation of study medication, illness requiring concomitant therapy or surgery, or associated with pathological clinical laboratory values, significant noncompliance with the study protocol or at the wish of the patient. All end-of-study procedures were to be completed at the final visit.

Test Product, Dose and Mode of Administration: pregabalin 25-mg and 100-mg capsules, Administration: All dosing TID; BID regimen blinded by using placebo as middle dose.

Criteria for Evaluation: The principal criterion to establish efficacy of pregabalin was reduction in frequency of all partial seizures from baseline to treatment in the pregabalin groups versus the placebo group. Efficacy was evaluated using response ratio (RRatio, the primary efficacy parameter). Secondary efficacy parameters were the responder rate and the percent change in 28-day seizure rates in treatment compared to the baseline. Safety was evaluated using frequency and intensity of adverse events, physical and neurological examinations, funduscopic examination, vision function testing, 12-lead ECG with a 2-minute cardiac rhythm strip, and laboratory tests including hematology, blood chemistry, and urinalysis during the study period. Standard AED serum concentration and pregabalin plasma concentrations were also assessed.

Statistical Methods: Statistical analyses compared the treatment effect of 2 dosing regimens of pregabalin to placebo. Due to a protocol-specified, planned interim analysis, all final testing was done using a significance level of 0.049. All testing was 2-sided.

The **primary analysis population** was the intent-to-treat population (all patients randomized who received at least one dose of study medication). Efficacy analyses were also performed on a secondary population, the evaluable population, which included all patients who were randomized to study medication, received at least 28 days of study medication, and had a minimum of 28 days of seizure diary data within both the baseline phase and the double-blind phase.

Summary Efficacy description

Efficacy of pregabalin was established by reduction in frequency of all partial seizures during the double-blind period compared with the baseline period. For each patient, the baseline period was defined as Days -56 to -1. The double-blind period was defined as starting on Day 1 and ending on the last day the patient took study medication during the double-blind treatment period. The number of days in the treatment period for a given patient could have been less or greater than the 12 weeks planned for in the protocol. The observed seizure rate during baseline and double-blind was standardized for a 28-day period. Patients with no double-blind seizure diary had their baseline seizure rate carried forward into the double-blind period. Because the amount of diary data and duration of time in the double-blind period of the study varied from patient to patient, the 28-day seizure rate was defined as follows:

$$28\text{-day rate} = \frac{\#\text{ of partial seizures in period}}{[\#\text{ of days in period} - \#\text{ of missing diary days in period}]} \times 28$$

Period in the above formula was either the baseline phase or double-blind phase of the study.

The **primary efficacy parameter**, response ratio (RRatio or symmetrized percent change) compares baseline seizure frequency (B) with treatment seizure frequency (T). The RRatio (or symmetrized percent change) is calculated by dividing the difference between 28-day seizure rates during treatment and baseline by the sum of baseline and double-blind seizures.

$$\mathbf{RRatio} = [(T - B)/(T + B)] \times 100.$$

The RRatio is between 100 and -100. Negative values indicate reduction in seizure rate and positive values indicate increase in seizure rate during treatment. An RRatio of -33 is equivalent to a 50% reduction in seizures. Analysis was performed using an analysis of variance (ANOVA) model with treatment (as main effect), center (clusters), and rank RRatio as the dependent variable.

Secondary efficacy parameters were the responder rate, defined as the proportion of patients who have at least a 50% reduction in 28-day partial seizure rate during treatment as compared to the baseline, and the percent change (PCH) in 28-day partial seizure rates in treatment compared to baseline. The responder rate was compared between treatments using a Cochran-Mantel-Haenszel chi-square statistic stratified by center (cluster). PCH results were summarized by descriptive statistics only; no inferential analysis was performed.

Additional secondary parameters assessed by descriptive statistics included the length of seizure- free intervals, and the number of seizure-free days per a 28-day period. RRatio, responder rate and PCH were also summarized for each seizure type. The number and percent of patients who were seizure free during specified periods of time during double-blind treatment were compared between each pregabalin treatment group and placebo using Fisher's exact test (ad hoc analysis).

Interim analysis –A protocol-specified, planned **interim analysis of efficacy** and select safety parameters was conducted for administrative and planning purposes using the first 129 patients randomized. The interim analysis results were used for planning purposes and were carefully restricted to a few individuals in Parke-Davis management not directly involved with the study. Treatment code break on a patient-by-patient basis was available only to the few individuals who performed the analyses. No amendments to the inferential analysis plan were made after the interim analysis.

7.2 Study 009 Efficacy Conclusions

7.2.1 Intent to Treat Patient Characteristics and Disposition:

The 3 treatment groups were well-matched on demographic parameters, including age, sex, and race. All of the patients who entered the double-blind treatment phase had medically refractory partial seizures. Minor differences among the treatment groups in epilepsy history were noted for the ITT population of 312 patients. The majority of the randomized patients (76%) completed the 12-week study. More patients in the placebo group withdrew due to lack of efficacy, while the rate for adverse event withdrawals was higher for the pregabalin groups. Specifically, 27 patients (26%) in the pregabalin BID group, 21 patients (19%) in the pregabalin TID group, and 7 patients (7%) in the placebo group withdrew due to adverse events.

Table 5: Summary of Patient Characteristics: ITT Population

Characteristic	Placebo N = 98		Pregabalin 600 mg/day (TID) N = 111		Pregabalin 600 mg/day (BID) N = 103		All Pregabalin N = 214		All Patients N = 312	
Gender, N (%)										
Male	50	(51.0%)	57	(51.4%)	49	(47.6%)	106	(49.5%)	156	(50.0%)
Female	48	(49.0%)	54	(48.6%)	54	(52.4%)	108	(50.5%)	156	(49.8%)
Premenarchal	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Premenopausal	32	(66.7%)	38	(70.4%)	37	(68.5%)	75	(69.4%)	107	(68.6%)
Postmenopausal	16	(33.3%)	16	(29.6%)	17	(31.5%)	33	(30.6%)	49	(31.4%)
Race, N (%)										
White, Non-Hispanic	87	(88.8%)	90	(81.1%)	89	(86.4%)	179	(83.6%)	266	(85.3%)
Black, Non-Hispanic	4	(4.1%)	4	(3.6%)	5	(4.9%)	9	(4.2%)	13	(4.2%)
Hispanic (White or Black)	3	(3.1%)	12	(10.8%)	8	(7.8%)	20	(9.3%)	23	(7.4%)
Asian or Pacific Islander	0	(0.0%)	4	(3.6%)	0	(0.0%)	4	(1.9%)	4	(1.3%)
American Indian or Alaskan Native	0	(0.0%)	0	(0.0%)	1	(1.0%)	1	(0.5%)	1	(0.3%)
Other	4	(4.1%)	1	(0.9%)	0	(0.0%)	1	(0.5%)	5	(1.6%)
Age (Years)	N = 98		N = 111		N = 103		N = 214		N = 312	
Mean (SD)	39.6	(11.8)	39.1	(12.0)	38.4	(11.9)	38.8	(11.9)	39.1	(11.9)
Median	38.5		40		38		38		38	
Range	17-82		18-75		18-68		18-75		17-82	
Estimated Creatinine Clearance at Baseline (mL/min)	N = 98		N = 108		N = 103		N = 211		N = 309	
Mean (SD)	104.53	(31.17)	104.69	(30.44)	110.08	(32.17)	107.32	(31.34)	106.44	(31.26)
Median	101.7		102.7		103		103		102.4	
Range	39.3-200.1		45.8-220.2		52.8-198.9		45.8-220.2		39.3-220.2	
Height (cm)	N = 98		N = 110		N = 101		N = 211		N = 309	
Mean (SD)	168.51	(10.22)	166.67	(13.21)	167.32	(12.53)	166.98	(12.86)	167.47	(12.09)
Median	167.6		167.3		167.6		167.6		167.6	
Range	140.8-185.4		98.5-193		105-194		98.5-194		98.5-194	
Weight (kg)	N = 98		N = 109		N = 103		N = 212		N = 310	
Mean (SD)	77.03	(19.88)	75.46	(18.14)	76.71	(19.77)	76.07	(18.92)	76.37	(19.20)
Median	75.4		72.7		75		73.85		74.2	
Range	45.3-126.4		41.8-142.7		44.5-131		41.8-142.7		41.8-142.7	

Table 6. Summary of Epilepsy History: ITT Population

Characteristic	Placebo N = 98		Pregabalin 600 mg/day (TID) N = 111		Pregabalin 600 mg/day (BID) N = 103		All Pregabalin N = 214		All Patients N = 312	
Age at Diagnosis (Years)										
N	98		110		103		213		311	
Mean (SD)	16.59	(12.11)	11.85	(10.47)	13.04	(12.7)	12.43	(11.59)	13.74	(11.89)
Median	15.65		8.5		10.3		9.1		11.3	
Range	0-73.5		0-50.4		0-63.2		0-63.2		0-73.5	
Duration of Epilepsy (Years)										
N	98		110		103		213		311	
Mean (SD)	23.53	(11.86)	27.66	(13.43)	25.88	(12.45)	26.8	(12.97)	25.77	(12.70)
Median	22.5		27.3		24.8		26.2		24.7	
Range	0.5-53.6		1.4-66.6		0.7-55.2		0.7-66.6		0.5-66.6	
Etiology, N (%)										
Unknown	54	(55.1%)	56	(50.5%)	45	(43.7%)	101	(47.2%)	155	(49.7%)
Infections	11	(11.2%)	17	(15.3%)	18	(17.5%)	35	(16.4%)	46	(14.7%)
Trauma	16	(16.3%)	14	(12.6%)	25	(24.3%)	39	(18.2%)	55	(17.6%)
Family History	5	(5.1%)	4	(3.6%)	9	(8.7%)	13	(6.1%)	18	(5.8%)
Birth Complications	4	(4.1%)	8	(7.2%)	5	(4.9%)	13	(6.1%)	17	(5.4%)
Other[a]	13	(13.3%)	18	(16.2%)	10	(9.7%)	28	(13.1%)	41	(13.1%)
Concurrent AEDs, N (%)										
1 AED	30	(30.6%)	35	(31.5%)	26	(25.2%)	61	(28.5%)	91	(29.2%)
2 AEDs	50	(51.0%)	57	(51.4%)	43	(41.7%)	100	(46.7%)	150	(48.1%)
3 AEDs	16	(16.3%)	17	(15.3%)	31	(30.1%)	48	(22.4%)	64	(20.5%)
4 AEDs	0	(0.0%)	1	(0.9%)	2	(1.9%)	3	(1.4%)	3	(1.0%)

[a] Includes structural lesions, febrile seizures, alcohol abuse, eclampsia, or hypoxia

Table 7. Summary of Disease Characteristics: ITT Population

	Placebo N = 98		Pregabalin 600 mg/day (TID) N = 111		Pregabalin 600 mg/day (BID) N = 103	
Baseline Partial Seizure Frequency Per 28 Days						
Mean (SD)	25.1	(37.8)	21.3	(30.7)	21.5	(48.4)
Median	11		10		9.5	
Range	2.5-245		2.5–189		2–435.8	
Types of Seizures Experienced (History at Screening)[a,b]						
Partial	98	(100.0%)	111	(100.0%)	103	(100.0%)
Simple Partial	59	(60.2%)	64	(57.7%)	52	(50.5%)
With Motor Symptoms	17	(17.3%)	15	(13.5%)	16	(15.5%)
With Somatosensory or Special Sensory Symptoms	31	(31.6%)	35	(31.5%)	27	(26.2%)
With Autonomic Symptoms	10	(10.2%)	13	(11.7%)	10	(9.7%)
With Psychic Symptoms	15	(15.3%)	12	(10.8%)	11	(10.7%)
Complex Partial	88	(89.8%)	100	(90.1%)	97	(94.2%)
Beginning as SP and Progressing to Impairment of Consciousness	55	(56.1%)	56	(50.5%)	54	(52.4%)
With Impairment of Consciousness at Onset	51	(52.0%)	65	(58.6%)	62	(60.2%)
Partial Secondarily Generalized	71	(72.4%)	83	(74.8%)	75	(72.8%)
Generalized	5	(5.1%)	4	(3.6%)	9	(8.7%)
Absence	0	(0.0%)	0	(0.0%)	1	(1.0%)
Myoclonic	0	(0.0%)	1	(0.9%)	3	(2.9%)
Tonic	0	(0.0%)	1	(0.9%)	0	(0.0%)
Tonic-Clonic	2	(2.0%)	3	(2.7%)	2	(1.9%)
Atonic	1	(1.0%)	1	(0.9%)	1	(1.0%)
Unclassified	2	(2.0%)	0	(0.0%)	2	(1.9%)

[a] Patients could have more than one category of epilepsy and more than one seizure type.
[b] Classified according to the Commission on Classification and Terminology of the International League Against Epilepsy

Within the ITT population, 54% of patients receiving pregabalin TID, 56% of patients receiving pregabalin BID, and 58% of patients receiving placebo had at least 12 weeks exposure to study medication (Table 9). Because of visit schedules, patients may have had their termination visit just prior to receiving 12 full weeks of study medication. Therefore, the number of patients who had at least 12 weeks exposure to study medication may be less than the number of patients who completed the study.

Table 9. Summary of Exposure: ITT Population

Duration of Exposure	Placebo N = 98	Pregabalin 600 mg/day (TID) N = 111	Pregabalin 600 mg/day (BID) N = 103
≥1 Day	98 (100.0%)	111 (100.0%)	103 (100.0%)
≥1 Week	96 (98.0%)	107 (96.4%)	95 (92.2%)
≥2 Weeks	94 (95.9%)	97 (87.4%)	91 (88.3%)
≥4 Weeks	91 (92.9%)	92 (82.9%)	84 (81.6%)
≥6 Weeks	91 (92.9%)	89 (80.2%)	78 (75.7%)
≥8 Weeks	89 (90.8%)	88 (79.3%)	77 (74.8%)
≥10 Weeks	82 (83.7%)	83 (74.8%)	73 (70.9%)
≥12 Weeks	57 (58.2%)	60 (54.1%)	58 (56.3%)

A total of 378 patients entered the baseline phase, of these, 65 did not qualify or withdrew, so that 313 were randomized. During the study, 76 patients (24%) withdrew, more in the placebo group due to lack of efficacy, while the rate for adverse event

withdrawals was higher for the pregabalin groups. Specifically, more patients in the pregabalin BID group withdrew due to adverse events (n = 27, 26%) compared to either the pregabalin TID (n = 21, 19%) or placebo (n = 7, 7%) groups. Completion rate was slightly higher in the placebo group (83%) compared to the pregabalin groups (77% for TID and 68% for BID). 237 patients (76%) completed the 12-week study and 260 patients entered the open-label extension Study 1008-010.

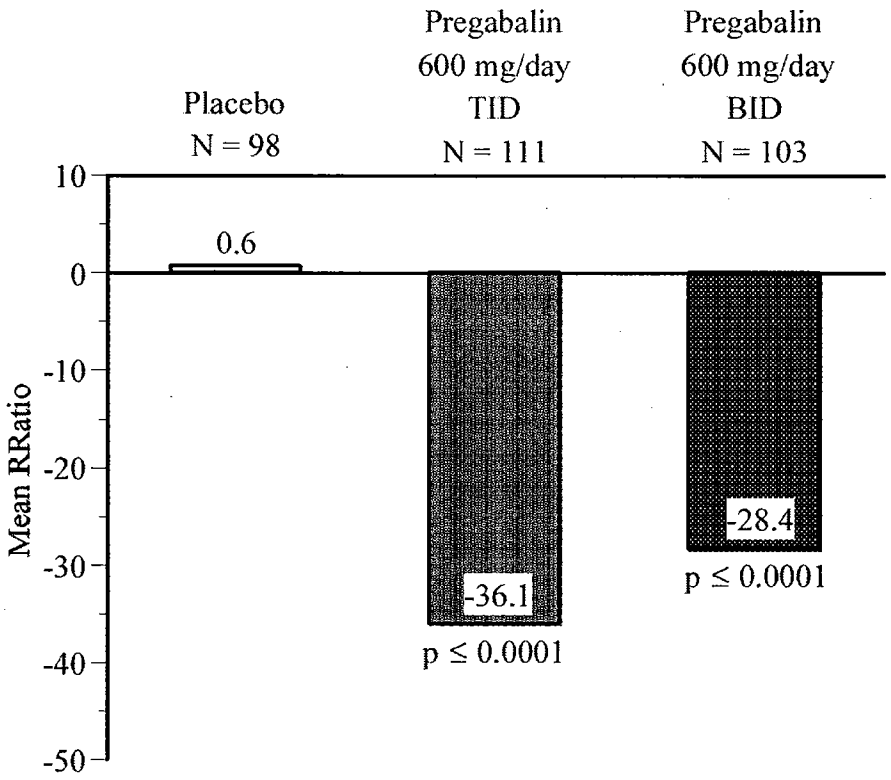
Table 10. Summary of Patient Disposition (All Patients)

Disposition	Placebo N = 98	Pregabalin 600 mg/day (TID) N = 111	Pregabalin 600 mg/day (BID) N = 104	All Patients N = 313
Entered Baseline				378
Withdrawn During Baseline				65
Adverse Event				1
Lack of Compliance				8
Other/Administrative				56
Entered Double-Blind (Randomized)	98	111	104	313
Withdrawn During Double-Blind	17 (17.3%)	26 (23.4%)	33 (31.7%)	76 (24.3%)
Status Epilepticus	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lack of Efficacy	5 (5.1%)	2 (1.8%)	1 (1.0%)	8 (2.6%)
Adverse Event	7 (7.1%)	21 (18.9%)	27 (26.0%)	55 (17.6%)
Lack of Compliance	2 (2.0%)	3 (2.7%)	2 (1.9%)	7 (2.2%)
Other/Administrative	3 (3.1%)	0 (0.0%)	3 (2.9%)	6 (1.9%)
Completed Study	81 (82.7%)	85 (76.6%)	71 (68.3%)	237 (75.7%)
Entered Open-Label Study	88 (89.8%)	94 (84.7%)	78 (75.0%)	260 (83.1%)

(Reviewer note: One can note that adverse events resulting in withdrawals were higher for the treatment groups relative to placebo and make up the majority of withdrawals from the study. Also, a high proportion of patients entered the open label study, relating that it was well tolerated.)

7.2.2 Primary Efficacy Results

Results from the planned primary analysis (RRatio) with the primary ITT population demonstrate that pregabalin 600 mg/day administered TID or BID resulted in highly significant reductions in seizure frequency compared with placebo (ANOVA, rank transformed analysis adjusted for cluster, all $p < 0.0001$). There was no significant treatment by cluster interaction ($p = 0.9387$) for the RRatio.



p-Values show comparison with placebo based on primary analysis, $\alpha = 0.049$.

VAL/CLC/022400
1008/009/Mean RRatio.DG4

Figure 2. Mean RRatio For All Partial Seizures

APPEARS THIS WAY
ON ORIGINAL

Table 11. RRatio for All Partial Seizures: ITT Population

Response Ratio	Placebo N = 98	PGB 600 mg/day (TID) N = 111	PGB 600 mg/day (BID) N = 103
During Double-Blind Treatment Period[a]			
N	98	111	103
Mean	0.6	-36.1	-28.4
SD	28.8	40	36.7
Median	-0.4	-31.7	-21.7
Range	-73.8 to 88.2	-100 to 99.5	-100 to 50.9

[a] Includes all partial seizures occurring during double-blind treatment period

Table 12. Summary of RRatio Analysis (All Partial Seizures): ITT Population

Treatment Comparisons (Group 1/Group 2)	Treatment Differences[a] N[d]	Means (SE)	95% CI	p-Value[b]	Generaliz-ability[c]
PGB 600 mg/day TID/PBO	111/98	-36.7 (5.0)	[-46.4, -27.0]	P ≤0.0001*	
PGB 600 mg/day BID/PBO	103/98	-29.0 (5.0)	[-38.9, -19.0]	P ≤0.0001*	
PGB 600 mg/day TID/PGB 600 mg/day BID	111/103	-7.7 (4.9)	[-17.4, 1.9]	P = 0.1092	P = 0.9387

PGB = Pregabalin; PBO = Placebo.

* = Statistically significant based on Hochberg's procedure (p ≤0.049).

[a] Based on treatment means for the raw RRatio

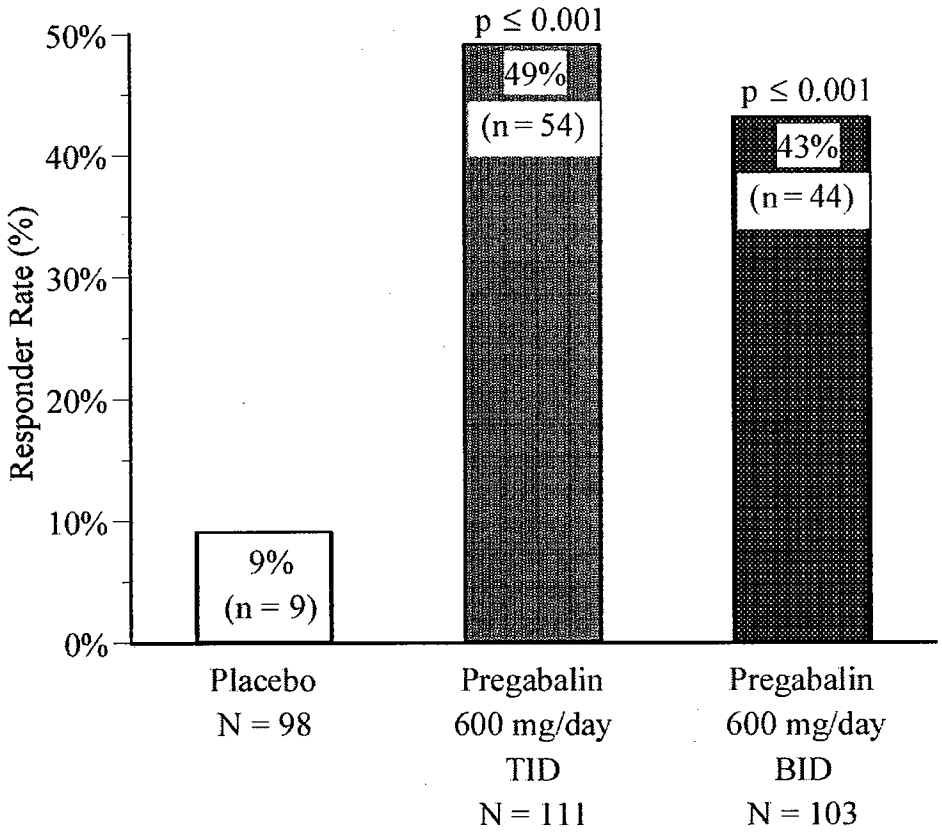
[b] Hochberg procedure applied to the ranked RRatio

[c] Treatment-by-cluster interaction for the ranked RRatio

[d] N for Group 1/N for Group 2

7.2.3 Secondary Efficacy Results:

Analysis of secondary efficacy parameters were consistent with the primary analysis. The responder rates for pregabalin TID and BID were statistically significantly greater than the responder rate for placebo and the median percent change results support the RRatio results. The evaluable results for the primary and secondary efficacy parameters support the ITT results.



p-Values show comparison with placebo based on CMH Chi Square, $\alpha = 0.049$.

VAL/CLC/022400
1008/009/Responder Rates.DG4

Figure 3. Responder Rates for All Partial Seizures

APPEARS THIS WAY
ON ORIGINAL

Table 13. Summary of RRatio by Seizure Type: ITT Population

All DB (1 –end[a])	Placebo N = 98	Pregabalin 600 mg/day (TID) N = 111	Pregabalin 600 mg/day (BID) N = 103
Simple Partial Seizures			
N	56	59	49
Mean	**8.4**	**-37.8**	**-10.4**
SD	59.3	62.5	70.5
Median	3.5	-42.9	-11.4
Minimum	-100	-100	-100
Maximum	100	100	100
Complex Partial Seizures			
N	85	97	94
Mean	**-5.9**	**-35.9**	**-31.1**
SD	35.5	44.6	42.5
Median	-1.5	-34.3	-21.1
Minimum	-100	-100	-100
Maximum	88.2	99.5	67
[redacted]			
N	45	36	45
Mean	**-8**	**-32.1**	**-33.2**
SD	70.6	66	74.3
Median	-11.9	-38.6	-64
Minimum	-100	-100	-100
Maximum	100	100	100
Partial Seizures Without Generalization			
N	97	109	98
Mean	**2.4**	**-33.8**	**-23.4**
SD	33.3	44.5	39.9
Median	1.1	-29.9	-17.4
Minimum	-73.8	-100	-100
Maximum	100	100	82.2

[a] Includes all partial seizures occurring during the double-blind treatment phase

7.2.4 Ad-Hoc analysis seizure free

In the ad hoc analysis, the number and percent of patients who had been seizure free for specified periods of time during their double-blind treatment were compared between treatments. Data were evaluated for the last 28 days of double-blind treatment as well as

for the last 42, 56, and 70 days of double-blind treatment. Significantly more patients in the pregabalin TID group were considered seizure free than those in the placebo group for the 28-, 42-, and 56-day seizure-free time periods.

Table 14. Seizure Free Ad Hoc Analysis: Restrictive Method[a]
ITT Population

Time Period	Placebo N = 98	Pregabalin 600 mg/day (TID) N = 111	Pregabalin 600 mg/day (BID) N = 103
Last 28 Days, n (%)	3 (3)	15 (14) p = 0.012*	3 (3)
Last 42 Days, n (%)	0 (0)	7 (6) p = 0.015*	2 (2)
Last 56 Days, n (%)	0 (0)	6 (5) p = 0.031*	1 (1)
Last 70 Days, n (%)	0 (0)	2 (2)	1 (1)

* = Significantly different from placebo (Fisher's Exact test).
[a] The restrictive method required patients to have at least 2 weeks of double-blind treatment prior to the seizure-free evaluation period and seizure diary data for at least 75% of each time period.

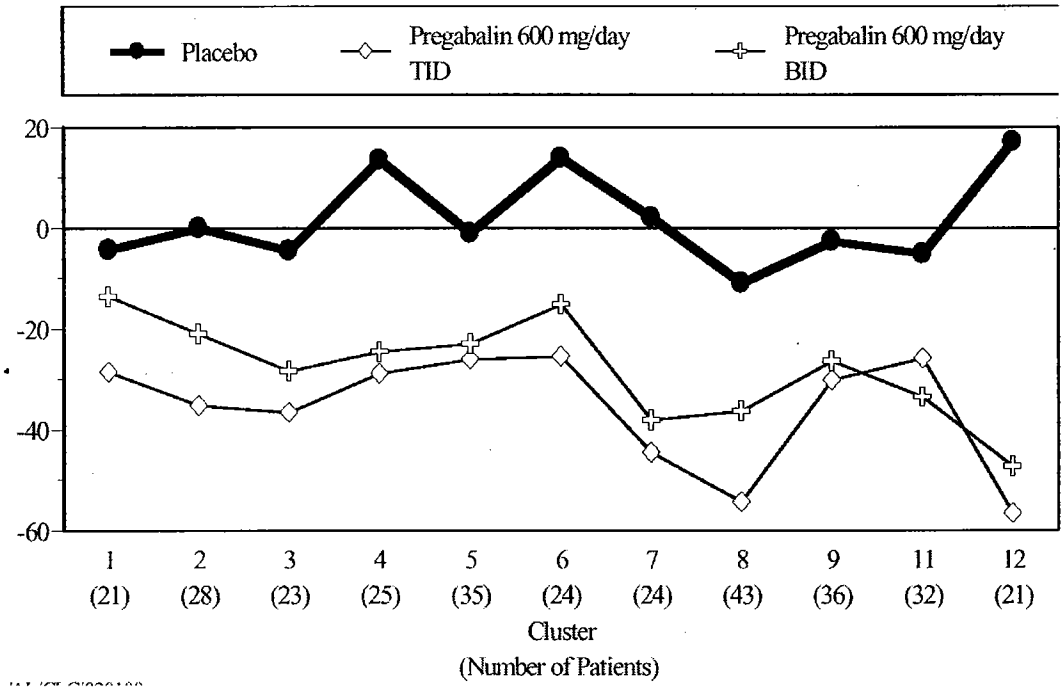
All Analyses with the evaluable population were consistent with the results of the primary ITT population analyses.

(Reviewer note: These Ad Hoc analyses indicate that the 600mg TID dosing schedule is superior to the 600mg BID.)

7.2.5 Appendices of interest

APPENDIX C.15

Figure for Mean RRatio by Cluster: ITT Population



8 Appendix 2 – Review of Individual Study Report - Study 011 (Protocol 1008-011)

8.1 Study 011 (Protocol 1008-011) Outline

Title of Study: Pregabalin TID Add-On Trial: A Double-Blind, Placebo-Controlled, Multicenter Study in Patients With Partial Seizures.

Investigators: [redacted]

Study Center(s): 45 international centers

Publication (reference): None

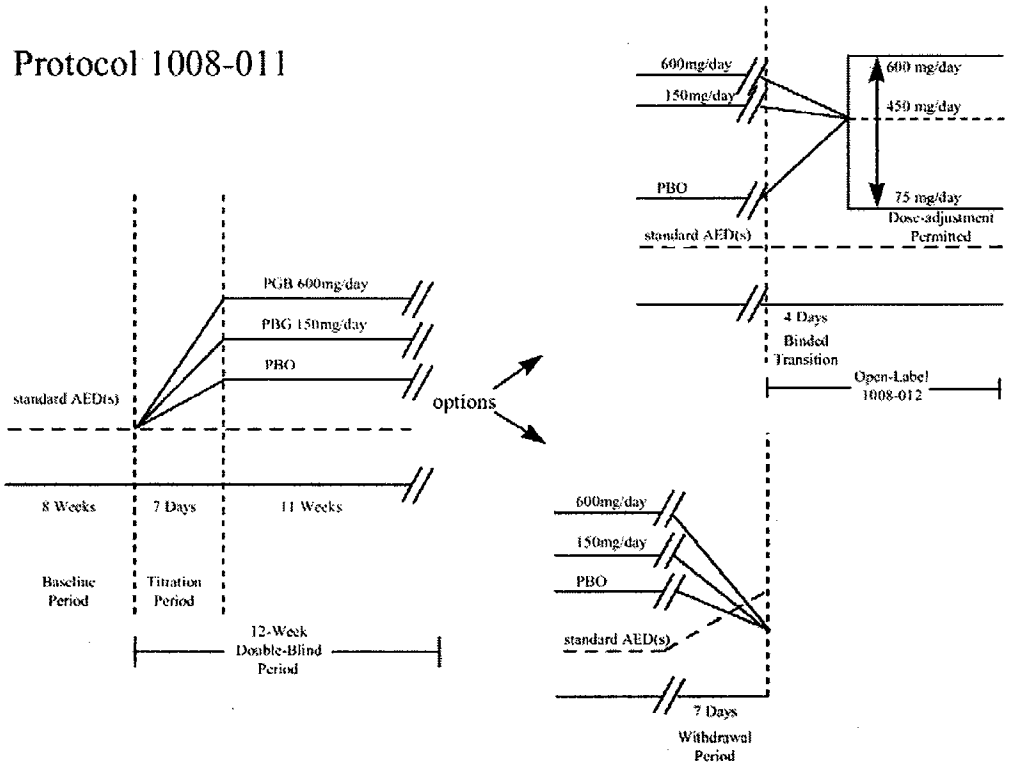
Studied Period (years): 04/23/98 to 11/19/99 Clinical Phase: 3

Objective(s): The objectives of this study were to evaluate the efficacy, safety, and dose-response characteristics of pregabalin as add-on treatment in patients with partial seizures.

Study Design: Following screening and an 8-week baseline period, patients entered a 12-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter study. Randomization was to placebo, pregabalin 150 mg/day, or pregabalin 600 mg/day with all study medication administered 3 times a day (TID). Current antiepileptic drug (AED) therapy was maintained. After completing the study, patients had the option of entering a follow on open label study (Study 1008-012).

APPENDIX A.2

Study Design



To be randomized, patients must have had at least 6 partial seizures during the 8-week baseline phase and no 4-week period free of seizures.

The double blind phase included a 7-day blinded titration to randomized dose. Concurrent AED therapy was maintained at the same dosages administered during baseline. Patients remained on study medication for the 12-week period unless seizures of adverse events required patients to be withdrawn from the study.

The withdrawal period gave two options for each patient. They were to either withdraw off the blinded medication and titrated to a new AED or a higher dose of concurrent AED over 1 week, or enter the open-label study and titrated in a blinded fashion to a common dose of pregabalin 450mg/day over 4 days. A final follow up visit was performed for all patients not continuing into the open label study.

Amendments and Addenda

There were 2 amendments and 5 addenda.

Amendment 1, dated February 10, 1999, modified several sections of the protocol as follows. **Approximately one-third of the patients were enrolled before these changes were implemented.**

- Ophthalmologic examinations (funduscopic examination, vision assessment, confrontational field testing, and color perception testing) were deleted from the study procedures. The preferred method to monitor potential peripheral field constriction, the primary ophthalmologic assessment of interest, was automated perimetry testing utilizing [redacted] Analyzer. As this equipment is not available in all participating countries, these examinations were not conducted in this study.

- The acceptable time period during which specific screening tests and procedures were completed was broadened. Previously, the protocol required these tests and procedures were to be performed only during screening; the amendment allowed for these tests to be performed during either screening or baseline.

- The washout period for patients who stopped vigabatrin treatment prior to baseline was defined. While the protocol excluded patients using vigabatrin in the trial, the protocol would allow entry of patients who discontinued vigabatrin therapy at least 6 weeks prior to baseline. These patients were to have no clinically significant findings on visual field examinations prior to entering the study (Goldman's or Humphrey visual field testing).

- The [redacted] Device was allowed and recorded as an AED.

- Several revisions to the statistical section of the protocol were formalized. These included a clarification of the analysis population name, the addition of a clustering definition, and a correction to a statistical reference.

Amendment 2, dated April 27, 1999, changed the primary analysis population from the evaluable population (defined as all patients who were randomized, received 28 days of study medication, and had a minimum of 28 days of seizure diary data) to the intent-to-treat (ITT) population (defined as all patients who were randomized who received at least

1 dose of study medication). The change occurred before the blind was broken, and was made in order for the study to be in compliance with recently issued ICH guidelines.

Five addenda were added to accommodate specific international centers. Details of the addenda are as follows:

- Addendum A changed the lowest age to 19 to be in compliance with Austrian Drug Law.
- Addendum B included a list of prohibited medications specific to the Spanish sites.
- Addendum C added a CSF evaluation add on trial to the open label protocol to evaluate the uptake of pregabalin into the CNS and the effect on amino acids and neurotransmitters in the CSF in patients with partial seizures.
- Addendum D adjusted the maximum enrollment from 12 patients per center to 24.
- Addendum E adjusted the enrollment from 12 patients per center to up to 36 patients at one center.

Number of Subjects (total and for each treatment): A total of 288 patients were randomized to treatment. Of those patients, 287 received study medication: 92 received pregabalin 600 mg/day; 99 received pregabalin 150 mg/day; and 96 received placebo. Patient 80004 was randomized to treatment (placebo) but did not take any study medication and was excluded from the intent-to-treat population (ITT). The blind was broken for 3 patients it Patient 073016 (placebo group) due to an adverse event (dizziness) occurring 2 days into the transition to the open-label study, Patient 092002 (600 mg/day pregabalin group) due to an unintended pregnancy, and Patient 094004 (600 mg/day pregabalin group) due to status epilepticus.

Diagnosis and Criteria for Inclusion: Men or nonpregnant, nonlactating women > 18 years of age, of any race, weighing between 50 to 135 kg (110-298 lb), and with partial seizures (simple partial, complex partial, and/or secondarily generalized tonic clonic) Patients must have failed to have adequate seizure control in the past while on standard AEDs and must be receiving 1 to 3 standard AEDs at doses within an acceptable therapeutic range. Patients needed to have a minimum of 3 partial seizures during the month prior to screening for entry to baseline, and a minimum of 6 partial seizures within an 8 week baseline period with no 4 week seizure free period.

Concomitant Medications: Single antidepressants were allowed for mild depression, benzodiazepines and phenobarbitol were considered antiepileptics regardless of reason for use or frequency of administration. Current AED at stable doses without increase, however, decreasing the dose was allowed for toxicity. Benzodiazepines as needed were permitted during the double-blind phase of the study but was not to exceed 4 dosage

administrations for the entire double-blind period. Any use of AEDs in excess of this was to be equated with lack of efficacy and the patient was to be withdrawn from the study. Concurrent treatment with other investigational agents or devices was not allowed during the study.

Prohibited medications: felbamate, vigabatrin, macrolide antibiotics, antihistamines, terfernadine, phenothiazines and antiarrhythmic agents. (Reviewer note: These agents were prohibited due to possible proarrhythmic effects-see original protocol for more details.) Gabapentin was stopped prior to initiation of pregabalin.

Guidelines for patient withdrawal: Epilepsy surgery, excessive or adverse events, including laboratory abnormalities or objective clinical signs and symptoms that were intolerable or incapacitating to the patient and/or posed a serious threat to well being. Occurrence of severe concurrent illness, i.e., illness that might interfere with the evaluation of study medication, required concomitant therapy or surgery, or associated with pathological clinical laboratory values, significant noncompliance with the study protocol; or at the wish of the patient, legal guardian, or by physician choice. All end-of-study procedures were to be completed at the final visit.

Test Product, Dose and Mode of Administration, Batch Number: Pregabalin 25 and 100-mg capsules Administration: Capsules administered orally, TID.

Duration of Treatment: 12 weeks

Criteria for Evaluation: The principal criterion to establish efficacy of pregabalin was reduction in frequency of all partial seizures from baseline to treatment in the pregabalin groups versus the placebo group. Efficacy was evaluated using Response Ratio (the primary efficacy parameter). [redacted], and the length of seizure-free intervals and number of seizure-free days per 28-day period. Safety was evaluated using frequency and intensity of adverse events, physical, ophthalmological, and neurological examinations, 12-lead electrocardiogram (ECG) with a 2-minute cardiac rhythm strip, and laboratory tests including hematology, blood chemistry, and urinalysis during the trial period. Standard AED serum concentrations and pregabalin plasma concentrations were also assessed.

Statistical Methods: The primary population used to make inferences was the ITT, (all patients randomized to treatment who received at least one dose of study medication). Analyses of efficacy were also performed using data for the evaluable population, (all patients who were randomized, received 28 days of study medication, and had a minimum of 28 days of seizure diary data in both the baseline and double-blind phases of the study). All testing was done using a significance level of 0.05. All testing was 2-sided.

The **primary efficacy parameter**, response ratio (RRatio or symmetrized percent change) compared baseline seizure frequency (B) with treatment seizure frequency (T) among the treatment groups. (See Appendix 7 - Study 009 report for details under "Efficacy Description).

Secondary efficacy parameters were the responder rate, (the proportion of patients who have a 50% reduction in partial seizure rate during treatment as compared to the baseline), the percent change (PCH) in 28-day partial seizure rates in treatment compared to baseline, and the percent of patients exhibiting a . The responder rate was compared among treatments using a Cochran-Mantel-Haenszel chi-square statistic stratified by center (cluster). PCH results were summarized by descriptive statistics providing median and 95% confidence interval.

An ad hoc analysis of the ITT patients who were seizure free during their last 28, 42, 56, and 70 days of double-blind treatment was performed. The number and percent of patients who were seizure free in each of the 4 time periods were compared among treatment groups using Fisher's exact test.

No interim analysis was performed. Although planned, an optional interim analysis of efficacy and select safety parameters to be conducted for administrative and planning purposes using the first 120 patients randomized, the Sponsor determined it was not necessary to conduct such an analysis for this study.

8.2 Study 011 Efficacy Conclusions

8.2.1 ITT Patient Characteristics and Disposition:

Of the 344 patients who entered the baseline phase of the study, 288 patients were randomized to treatment and 287 went on to receive study drug (145 men, 142 women). The mean age of all patients was 37 years and 93% were white. The 3 treatment groups were well matched on all demographic parameters. Ninety-two patients received 600 mg/day pregabalin, 99 received 150 mg/day pregabalin, and 96 received placebo. A total of 241 patients completed the study. Forty-seven patients withdrew from the double-blind phase of the study, 33 of these withdrew due to adverse events.

Table 5. Summary of Patient Characteristics: ITT Population

Characteristic	Placebo N = 96	PGB 150 mg/day N = 99	PGB 600 mg/day N = 92	All Pregabalin N = 191	All Patients N = 287
Gender, N (%)					
Male	54 (56.3%)	44 (44.4%)	47 (51.1%)	91 (47.6%)	145 (50.5%)
Female	42 (43.8%)	55 (55.6%)	45 (48.9%)	100 (52.4%)	142 (49.5%)
Premenarchal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Premenopausal	32 (76.2%)	43 (78.2%)	34 (77.3%)	77 (77.8%)	109 (77.3%)
Postmenopausal	10 (23.8%)	12 (21.8%)	10 (22.7%)	22 (22.2%)	32 (22.7%)
Race, N (%)					
White, Non-Hispanic	89 (92.7%)	93 (93.9%)	84 (91.3%)	177 (92.7%)	266 (92.7%)
Black, Non-Hispanic	1 (1.0%)	2 (2.0%)	2 (2.2%)	4 (2.1%)	5 (1.7%)
Hispanic (White or Black)	2 (2.1%)	2 (2.0%)	1 (1.1%)	3 (1.6%)	5 (1.7%)
Asian or Pacific Islander	1 (1.0%)	0 (0.0%)	3 (3.3%)	3 (1.6%)	4 (1.4%)
American Indian or Alaskan Native	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	3 (3.1%)	2 (2.0%)	2 (2.2%)	4 (2.1%)	7 (2.4%)
Age (Years)	N = 96	N = 99	N = 92	N = 191	N = 287
Mean (SD)	38.1 (12.4)	36.5 (11.3)	36.4 (10.5)	36.5 (10.9)	37.0 (11.4)
Median	37.5	34	35	35	36
Range	17 to 73	18 to 65	18 to 70	18 to 70	17 to 73
Creatinine Clearance at Baseline (mL/min)	N = 95	N = 98	N = 89	N = 187	N = 282
Mean (SD)	105.72 (27.05)	114.31 (32.44)	110.71 (34.86)	112.59 (33.57)	110.28 (31.65)
Median	104	114	105	108	106.5
Range	50 to 191	47 to 220	59 to 297	47 to 297	47 to 297
Height (cm)	N = 96	N = 99	N = 92	N = 191	N = 287
Mean (SD)	168.29 (9.62)	168.87 (10.59)	168.68 (11.08)	168.78 (10.80)	168.62 (10.41)
Median	168	168	168.75	168	168
Range	146 to 190	142 to 193	147 to 196	142 to 196	142 to 196
Weight (kg)	N = 95	N = 99	N = 92	N = 191	N = 286
Mean (SD)	73.00 (14.49)	75.12 (18.39)	71.22 (16.21)	73.24 (17.44)	73.16 (16.49)
Median	71.5	71.4	67.8	70	70.6
Range	45 to 111	47 to 130	41.2 to 127	41.2 to 130	41.2 to 130

PGB = Pregabalin.

Table 8. Summary of Epilepsy History: ITT Population

Characteristic	Placebo N = 96	Pregabalin 150 mg/day N = 99	Pregabalin 600 mg/day N = 92	All Pregabalin N = 191	All Patients N = 287
Age at Diagnosis (Years)					
N	96	98	92	190	286
Mean (SD)	15.8 (14.23)	12.23 (10.40)	11.78 (10.62)	12.01 (10.48)	13.29 (11.99)
Median	12	9.65	9.15	9.25	10.25
Range	0 to 52.8	0 to 50.8	0 to 52.4	0 to 52.4	0 to 52.8
Duration of Epilepsy (Years)					
N	96	98	92	190	286
Mean (SD)	22.78 (13.58)	24.8 (12.65)	25.06 (11.63)	24.93 (12.13)	24.21 (12.66)
Median	21.25	23.15	25.05	24.05	23
Range	2.2 to 58.2	4.2 to 53.4	2.2 to 53.3	2.2 to 53.4	2.2 to 58.2
Etiology, N (%)					
Unknown	45 (46.9)	57 (57.6)	44 (47.8)	101 (52.9)	146 (50.9)
Infections	8 (8.3)	7 (7.1)	12 (13.0)	19 (9.9)	27 (9.4)
Trauma	8 (8.3)	9 (9.1)	10 (10.9)	19 (9.9)	27 (9.4)
Family History	7 (7.3)	6 (6.1)	8 (8.7)	14 (7.3)	21 (7.3)
Birth Complications	13 (13.5)	6 (6.1)	8 (8.7)	14 (7.3)	27 (9.4)
Other[a]	21 (21.9)	16 (16.2)	19 (20.7)	35 (18.3)	56 (19.5)
Concurrent AEDs, N (%)					
1 AED	23 (24.0)	14 (14.1)	16 (17.4)	30 (15.7)	53 (18.5)
2 AEDs	42 (43.8)	54 (54.5)	51 (55.4)	105 (55.0)	147 (51.2)
3 AEDs	30 (31.3)	31 (31.3)	24 (26.1)	55 (28.8)	85 (29.6)
4 AEDs	1 (1.0)	0 (0.0)	1 (1.1)	1 (0.5)	2 (0.7)

[a] Other includes structural lesions, febrile seizures, alcohol abuse, multiple narcosis.

Table 9. Summary of Disease Characteristics: ITT Population

	Placebo N = 96	PGB 150 mg/day N = 99	PGB 600 mg/day N = 92	All Pregabalin N = 191	All Patients N = 287
Baseline Partial Seizure Frequency Per 28 Days					
Mean (SD)	23.5 (41.1)	26.2 (40.8)	19.3 (24.4)	--	--
Median	9.3	11.5	12.3	--	--
Range	1.5 to 327.5	3 to 219	2 to 141	--	--
Seizure History at Screening[a,b] N (%)					
Partial	96 (100.0)	99 (100.0)	92 (100.0)	191 (100.0)	287 (100.0)
Simple Partial	47 (49.0)	40 (40.4)	37 (40.2)	77 (40.3)	124 (43.2)
With Motor Symptoms	17 (17.7)	12 (12.1)	10 (10.9)	22 (11.5)	39 (13.6)
With Somatosensory or Special Sensory Symptoms	20 (20.8)	18 (18.2)	20 (21.7)	38 (19.9)	58 (20.2)
With Autonomic Symptoms	6 (6.3)	10 (10.1)	7 (7.6)	17 (8.9)	23 (8.0)
With Psychic Symptoms	10 (10.4)	6 (6.1)	13 (14.1)	19 (9.9)	29 (10.1)
Complex Partial	88 (91.7)	89 (89.9)	88 (95.7)	177 (92.7)	265 (92.3)
Beginning as SP and Progressing to Impairment of Consciousness	44 (45.8)	43 (43.4)	53 (57.6)	96 (50.3)	140 (48.8)
With Impairment of Consciousness at Onset	59 (61.5)	66 (66.7)	55 (59.8)	121 (63.4)	180 (62.7)
Partial Secondarily Generalized	72 (75.0)	65 (65.7)	69 (75.0)	134 (70.2)	206 (71.8)
Generalized	3 (3.1)	9 (9.1)	6 (6.5)	15 (7.9)	18 (6.3)
Myoclonic	0 (0.0)	2 (2.0)	0 (0.0)	2 (1.0)	2 (0.7)
Tonic	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.5)	1 (0.3)
Tonic-Clonic	3 (3.1)	7 (7.1)	4 (4.3)	11 (5.8)	14 (4.9)
Unclassified	0 (0.0)	1 (1.0)	1 (1.1)	2 (1.0)	2 (0.7)

PGB = Pregabalin.
[a] Patients could have more than one category of epilepsy and more than one seizure type.
[b] Classified according to the Commission on Classification and Terminology of the International League Against Epilepsy

NDA

Within the ITT population, 62% of patients receiving pregabalin 600 mg/day, 71% of patients receiving pregabalin 150 mg/day, and 68% of patients receiving placebo had at least 12-weeks exposure to study medication (Table 11). Because of visit schedules, patients had their termination visit prior to receiving 12 full weeks of study medication exposure. Thus, the number of patients who had at least 12-weeks exposure to study medication was less than the number of patients who completed the study.

Table 11. Summary of Exposure: ITT Population
[Number (%) of Patients]

Duration of Exposure	Placebo N = 96	Pregabalin 150 mg/day N = 99	Pregabalin 600 mg/day N = 92
≥1 Day	96 (100.0%)	99 (100.0%)	92 (100.0%)
≥1 Week	94 (97.9%)	97 (98.0%)	88 (95.7%)
≥2 Weeks	92 (95.8%)	93 (93.9%)	84 (91.3%)
≥4 Weeks	88 (91.7%)	91 (91.9%)	78 (84.8%)
≥6 Weeks	87 (90.6%)	90 (90.9%)	73 (79.3%)
≥8 Weeks	86 (89.6%)	89 (89.9%)	72 (78.3%)
≥10 Weeks	86 (89.6%)	88 (88.9%)	70 (76.1%)
≥12 Weeks	65 (67.7%)	70 (70.7%)	57 (62.0%)

Patient Disposition –

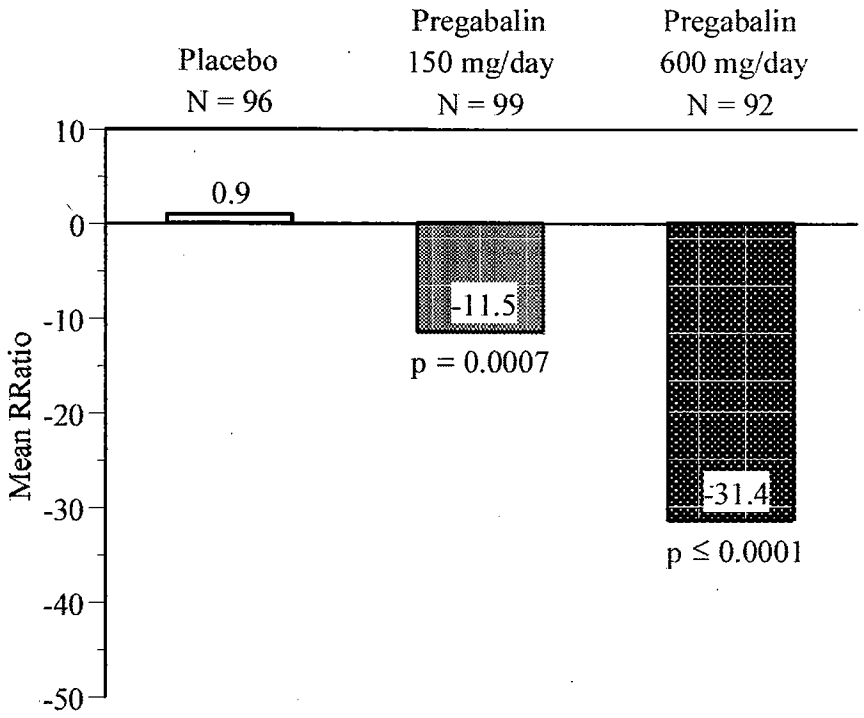
A total of 69 (75%) patients treated with pregabalin 600 mg/day, 88 (89%) patients treated with pregabalin 150 mg/day, and 84 (87%) patients who received placebo completed the study (Table 12). One of the 288 patients randomized to treatment did not receive study medication and was not included in the ITT population. Patients entering the open-label follow-on study included 69 (75%) in the pregabalin 600 mg/day group, 82 (83%) in the pregabalin 150 mg/day group, and 81 (84%) in the pregabalin group. The majority of all patients withdrawing from the study did so due to adverse events (11.5%) but a higher percentage of patients in each of the pregabalin treatment groups (18.5%, pregabalin 600 mg/day; 10%, pregabalin 150 mg/day) withdrew due to adverse events compared to the placebo group (6%).

Table 12. Patient Disposition
[Number (%) of Patients]

Disposition	Placebo N = 97		PGB 150 mg/day N = 99		PGB 600 mg/day N = 92		All Patients N = 288	
Entered Baseline							344	
Withdrawn During Baseline							56	
Adverse Event							4	
Lack of Compliance							13	
Other/Administrative							39	
Entered Double-Blind (Randomized)	97		99		92		288	
Withdrawals During Double-Blind	13	(13.4)	11	(11.1)	23	(25.0)	47	(16.3)
Status Epilepticus	0	(0.0)	1	(1.0)	1	(1.1)	2	(0.7)
Lack of Efficacy	5	(5.2)	0	(0.0)	1	(1.1)	6	(2.1)
Adverse Event	6	(6.2)	10	(10.1)	17	(18.5)	33	(11.5)
Lack of Compliance	2	(2.1)	0	(0.0)	1	(1.1)	3	(1.0)
Other/Administrative	0	(0.0)	0	(0.0)	3	(3.3)	3	(1.0)
Completed Study	84	(86.6)	88	(88.9)	69	(75.0)	241	(83.7)
Entered Open-Label Study	81	(83.5)	82	(82.8)	69	(75.0)	232	(80.6)

8.2.2 Primary Efficacy Results:

Results for the primary efficacy parameter, (RRatio) with the primary ITT population, demonstrated the efficacy of pregabalin at doses of 600 and 150 mg/day. Statistically significant differences favoring both pregabalin treatment groups compared to the placebo group were seen in the analysis of RRatio for all partial seizures (during the double-blind phase) at the endpoint of the study compared to baseline. ($p<0.0001$ and $p=0.0007$ respectively. The comparison of the 600and 150mg/day pregabalin treatment groups showed a statistically significant difference in RR ratio that favored the higher dosage group ($P<0.0001$). The decreasing linear trend in the mean RRatio was statistically significant ($P<0.0001$) and there was no significant treatment-by-cluster interaction ($P=0.7028$)



p-Values show comparison with placebo based on primary analysis, $\alpha = 0.05$.

VAL/CLC/031500
1008/011/Mean RRatio.DG4

Figure 2. Mean RRatio for All Partial Seizures: ITT Population

Table 13. RRatio for All Partial Seizures During the Double-Blind Phase: ITT Patient Population

Variable	Placebo N = 96	PGB 150 mg/day N = 99	PGB 600 mg/day N = 92
N	96	99	92
Mean	0.9	-11.5	-31.4
SD	26	22.9	36.3
Median	0.7	-9	-27.1
Minimum	-100	-100	-100
Maximum	71.1	47.1	95.6

PGB = Pregabalin.

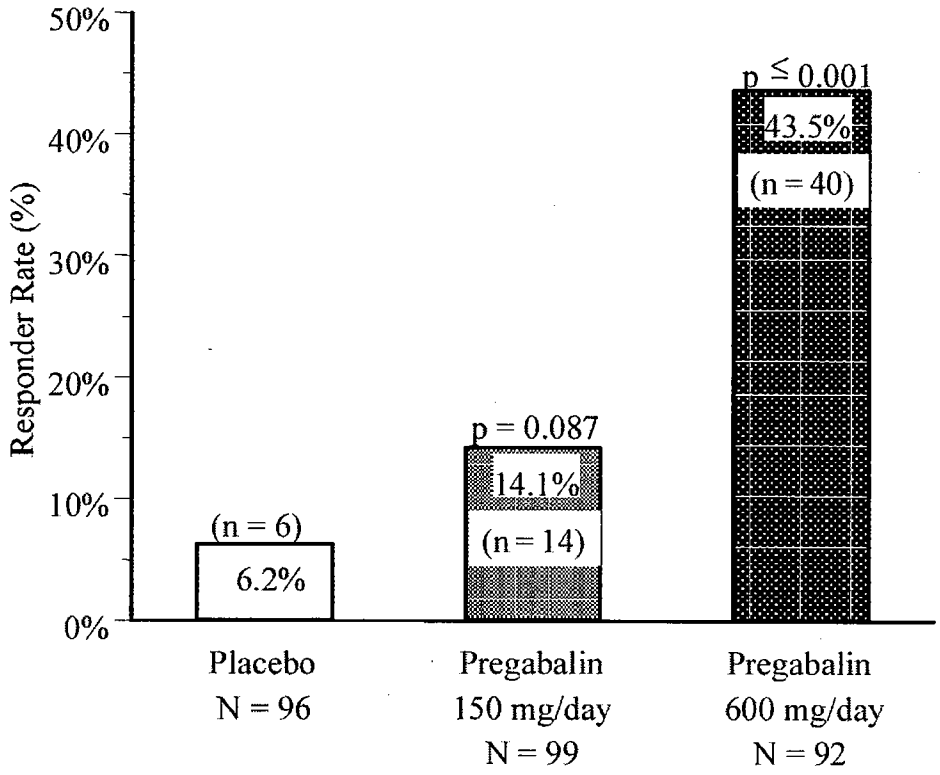
Table 14. Summary of RRatio Analysis for All Partial Seizures: ITT Population

Treatment Comparisons	Treatment Differences[a]			p-value
	N[b]	Mean (SE)	95% CI	
PGB 600 mg/day TID vs Placebo	92/96	-32.3 (4.2)	[-40.6, -24.0]	p <0.0001*
PGB 150 mg/day TID vs Placebo	99/96	-12.4 (4.1)	[-20.5, -4.3]	p = 0.0007*
PGB 600 mg/day TID vs 150 mg/day TID	92/99	-19.9 (4.2)	[-28.1, -11.7]	p <0.0001†
Generalizability[c]	p = 0.7028			
Linear Trend[d]	p <0.0001†			

* Statistically significant based on the Ruberg procedure ($p \leq 0.05$).
† Statistically significant ($p \leq 0.05$).
[a] Based on means for the untransformed RRatio data
[b] N in Group 1/N in Group 2
[c] Treatment-by-cluster interaction for the model-ranked RRatio
[d] Linear contrast

8.2.3 Secondary Efficacy Results

In the analysis of responder rate, the proportion of responders in the 600 mg/day pregabalin group (43%) was significantly higher when compared to the 150 mg/day (14%) and placebo (6%) group. The comparison of responder rates between the 150 mg/day pregabalin and placebo groups also favored the active treatment and approached, but did not reach, statistical significance ($p = 0.087$). When the 2 pregabalin groups were compared, the difference between the higher responder rate in the 600 mg/day group and the rate seen in the 150 mg/day group was statistically significant ($p < 0.001$). The Breslow-Day test for generalizability was not statistically significant except for the comparison between the 2 pregabalin groups ($p = 0.081$). This was due to larger treatment effects in favor of the 600 mg/day group observed in some clusters (benign interaction).



p-Values show comparison with placebo based on CMH Chi Square, $\alpha = 0.05$.

Figure 3. Responder Rate for All Partial Seizures: ITT Population

Table 15. Summary of Responder Rate (All Partial Seizures): ITT Population

	Placebo	Pregabalin 150 mg/day	Pregabalin 600 mg/day
N	96	99	92
Responders	6 (6.2%)	14 (14.1%)	40 (43.5%)
Nonresponders	90 (93.8%)	85 (85.9%)	52 (56.5%)

Table 16. Summary of Responder Rate Analysis (All Partial Seizures): ITT Population

Treatment Comparisons[a]	N[b]	Percent (SE)	95% CI[c]	Probability[d]	Generalizability Across Clusters[e]
PGB 600 mg/day vs placebo	92/96	37.2 (5.7)	[26.0, 48.5]	p <0.001*	p = 0.821
PGB 150 mg/day vs placebo	99/96	7.9 (4.3)	[0.05, 16.3]	p = 0.087	p = 0.290
PGB 600 mg/day vs 150 mg/day TID	92/99	29.3 (6.2)	[17.1, 41.6]	p <0.001†	p = 0.081
Linear Dose Response[f]	p <0.001†				

* Statistically significant based on the Ruberg procedure ($p \leq 0.05$).
† Statistically significant ($p \leq 0.05$).
[a] Percent responders
[b] N in Group 1/N in Group 2
[c] Based on binomial approximation
[d] Cochran-Mantel-Haenzel stratified by cluster
[e] Treatment-by-cluster generalizability, Breslow-Day test
[f] Cochran-Mantel-Haenzel correlation statistic

The results of the median percent change from baseline for all partial seizures was more favorable for patients receiving pregabalin (-42.6%, pregabalin 600mg/day, -16.5%, pregabalin 150mg/day) than for those who received placebo (+1.3%).

Mean RR ratio, when evaluated by seizure type. For all but partial seizures with generalization, the greatest reductions in mean RRatio were seen in the 600mg/day group followed by the 150mg/day group. This is illustrated in Sponsor table 17 below.

Table 17. Summary of RRatio by Seizure Type: ITT Population

All Double-Blind Results	Placebo N = 96	PGB 150 mg/day N = 99	PGB 600 mg/day N = 92
Simple Partial Seizures			
N	40	32	30
Mean	-6.1	-11.4	-26.0
SD	59.4	54.2	60.5
Median	3.8	-11.2	-29
Minimum	-100	-100	-100
Maximum	100	100	100
Complex Partial Seizures			
N	85	88	83
Mean	-3.1	-14.3	-37.0
SD	37.3	37.4	42.4
Median	-1.7	-12.8	-36.7
Minimum	-100	-100	-100
Maximum	100	100	100
Partial Seizures Without Generalization			
N	92	96	88
Mean	1.9	-10.6	-30.7
SD	30.6	30.6	40.8
Median	2.2	-9.8	-28.6
Minimum	-100	-100	-100
Maximum	100	100	100

PGB = Pregabalin.

8.2.4 Ad-Hoc analysis seizure free

In the analyses of mean percent change in seizure-free intervals and mean percent change in number of seizure-free days per 28-day interval from baseline, the results favored treatment with pregabalin over placebo. Significantly more patients in the 600 mg/day pregabalin group were considered seizure free during the last 28-day period when compared to the placebo group (p=0.002). The number of seizure-free patients was also greater in the 150 mg/day group compared to the placebo group but the difference was not statistically significant.

Table 19. Seizure-Free Ad Hoc Analysis: Restrictive Method[a]: ITT Population

	Placebo N = 96	Pregabalin 150 mg/day N = 99	Pregabalin 600 mg/day N = 92
Last 28 Days, n (%)	1 (1%)	7 (7%) p = 0.065	11 (12%) p = 0.002*
Last 42 Days, n (%)	1 (1%)	1 (1%)	5 (5.4%) p = 0.112
Last 56 Days, n (%)	1 (1%)	1 (1%)	2 (2.2%)
Last 70 Days, n (%)	1 (1%)	0 (0%)	2 (2.2%)

* Significantly different from placebo (Fisher's Exact test)

[a] The restrictive method required patients to have at least 2 weeks of double-blind treatment prior to the seizure-free evaluation period and seizure diary data for at least 75% of each time period.

New seizure types occurring after baseline were reported for 3 patients. Patient 036003 in the 600 mg/day pregabalin and Patient 051012 in the placebo group experienced generalized myoclonic seizures, and Patient 037005 in the 600 mg/day pregabalin group experienced simple partial seizures with motor symptoms.

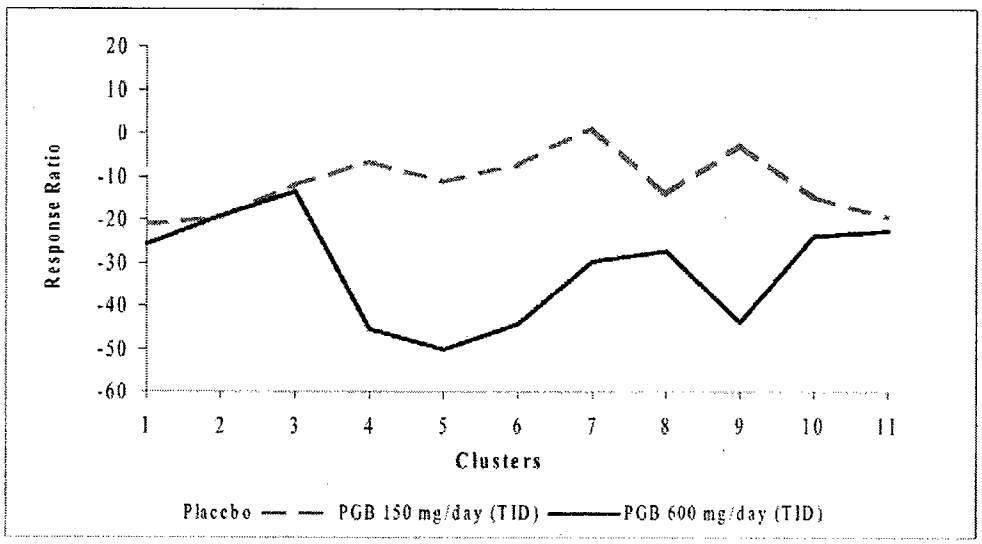
Per the sponsor, the results seen for the efficacy analyses performed using the evaluable population supported those seen for the ITT population.

8.2.5 Appendices of interest

Appendix C.13

Pregabalin TID Add-On Trial: A Double-Blind, Placebo-Controlled, Multicenter Study in Patients With Partial Seizures (Protocol 1008-011)

Mean RRatio (All Partial Seizures) By Cluster: ITT Population



Reviewer note: Placebo is not drawn on the diagram in the report.

9 Appendix 3 – Review of Individual Study Report - Study 034 (Protocol 1008-034)

9.1 Study 034 (Protocol 1008-034) Outline

Title of Study: Pregabalin BID Add-On Trial: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study in Patients With Partial Seizures (Protocol 1008-034)

Investigators: [redacted]

Study Center(s): 71 US centers and 5 centers in Canada

Publication (reference): None

Studied Period (years): 11/11/98 to 09/17/99 Clinical Phase: 3

Objective(s): The objectives of this study were to evaluate the efficacy and safety of 4 dosages of pregabalin administered BID as add-on treatment in patients with partial seizures.

Study Design: Following screening and an 8-week baseline period, patients entered a 12-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter study. Randomization was to either placebo, or to 1 of 4 pregabalin dose groups: 50, 150, 300, or 600 mg/day administered BID. Current antiepileptic drug (AED) therapy was maintained. After completing the study or withdrawing from the double blind period, patients had the option of entering a follow on, open label study (1008-035).

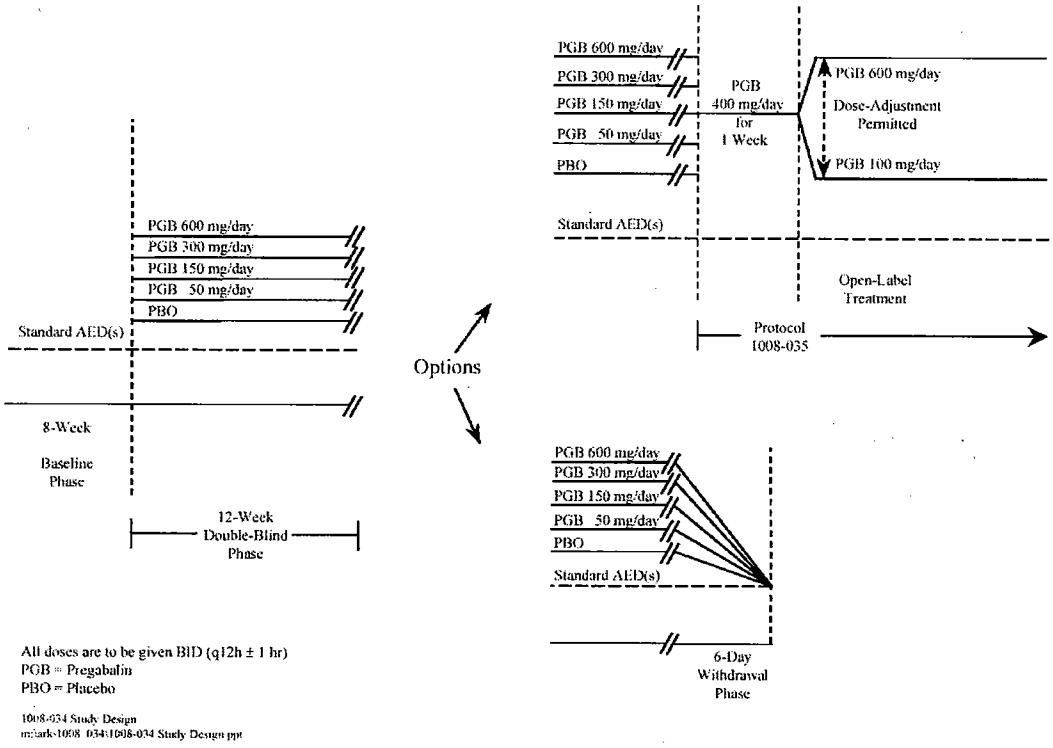


Figure 1. Study Design

All patients entered an 8-week baseline phase where they continued their concurrent AEDs at a stable dose. To be randomized, the patient must have had at least 6 partial seizures during the 8-week baseline phase and no 4-week period free of partial seizures.

The double-blind period started the day following randomization to 1 of 5 treatment groups. At the time of randomization, patients were dispensed double-blind study medication and instructed to start taking it the next day. (Reviewer note: in Study 034

there was no blinded one week titration phase like Studies 009 and 011). Patients continued their concurrent standard AEDs at the same dosage(s) administered during baseline. However, decreasing the dose of concurrent AEDs was allowed if central nervous system (CNS) toxicity occurred. Patients remained on study medication treatment with the dosage maintained for the remainder of the 12-weeks unless the patient withdrew early.

Patients entered the withdrawal/transition phase after exiting double-blind. Patients choosing to enter the open-label follow-on Study 1008-035 were brought to a common dose of pregabalin 400 mg/day over 1 week in a blinded fashion. For patients not continuing in the open-label trial, study medication was withdrawn in a blinded fashion over 6 days. Titration of another AED or titration to a higher dose of the concurrent AEDs was allowed at the discretion of the investigator. Two to 4 weeks following the final dose of study medication, a follow up visit was performed for all patients not entering the open label study.

Amendments and Addenda: There was one amendment and one addendum to the protocol.

Addendum A limited the minimum eligible age to 16 years for patients to be enrolled by Canadian study sites in order to comply with Canadian regulatory agency.

Amendment 1, changed the primary analysis population from the evaluable (all patients who were randomized, received 28 days of study medication, and had a minimum of 28 days of seizure diary data) to the intent-to-treat population (ITT), defined as all patients randomized who received at least 1 dose of study medication.

A protocol-specified, planned **interim analysis of efficacy** and select safety parameters was conducted for administrative and planning purposes using the first 165 patients randomized. The interim analysis results were used for planning purposes and were carefully restricted to a few individuals in Parke-Davis management not directly involved with the study. Treatment code break on a patient-by-patient basis was available only to the few individuals who performed the analyses. No amendments to the inferential analysis plan were made after the interim analysis.

Number of Subjects (total and for each treatment): A total of 455 patients were randomized to treatment: 100 to the placebo; 88 to the 50 mg/day pregabalin; 88 to the 150 mg/day pregabalin; 90 to the 300 mg/day pregabalin; and 89 to the 600 mg/day pregabalin. The **blind** could be broken for individual patients at any time during the study if necessary for proper treatment of a serious adverse event. The blind was broken for Patient 027-027009 after the occurrence of a visual field defect; the patient was receiving placebo. The blind was broken for patients whose data were included in the planned, protocol-specified interim analysis. With these exceptions, the blind was maintained until the study completed and all decisions regarding data

Diagnosis and Criteria for Inclusion: Men or nonpregnant, nonlactating women **12** years of age (**other trials were age 18 and above**), of any race, weighing > 40 kg (88 lb) with partial seizures (simple partial, complex partial, and/or secondarily generalized tonic clonic) were eligible. Patients failed to have adequate seizure control in the past while on standard AEDs and were receiving 1 to 3 standard AEDs at doses within an acceptable therapeutic range. Patients were required to have a minimum of 3 partial seizures in the baseline 1 month prior to screening and for entry into baseline and 6 seizures in the 8 week baseline with no 4 week seizure free period (Reviewer note: this was the same for all 3 double blind trials).

Concomitant medications: single antidepressants were allowed. Like the other trials benzos and phenobarb were consider AEDs. Patients were to be maintained on stable dosages of concurrently administered AEDs. These stable dosages were to provide plasma/serum AED concentrations within therapeutic range and also be tolerable for the patient. During the double-blind phase, increasing the dose of AED was not allowed; however, decreasing the dose was allowed if CNS toxicity occurred.

Prohibited medications: Felbamate, vigabatrin, vagus nerve stimulators, other investigational agents or devices. In addition, gabapentin was tapered off prior to initiating pregabalin in the trial.

Guidelines for patient withdrawal: Patients experiencing an increase in seizure frequency, duration or severity could be withdrawn and considered for the open label study. Patients were removed from the study for the same reasons as studies 009 and 011)

Test Product, Dose and Mode of Administration: Pregabalin 25-mg capsules 100-mg capsules Administration: Capsules administered BID

Duration of Treatment: 12 weeks

Criteria for Efficacy Evaluation: The principal criterion to establish efficacy of pregabalin was the reduction in frequency of all partial seizures during the double-blind period compared with the baseline period in the pregabalin groups versus the placebo group. Efficacy was evaluated using response ratio (the primary efficacy parameter). Secondary efficacy parameters were the responder rate and the percent change in 28-day seizure rates in treatment compared to the baseline.

Statistical Methods:

A **planned interim analysis** was performed when the first 165 patients randomized had completed or were withdrawn from the study. The interim analysis was done on all the planned analysis measures using the ITT population only. The final efficacy analyses were performed using both populations. The final safety analyses were performed using the ITT population only. Haybittle and Peto methods were used as an adjustment of α =

0.001 for the interim and $\alpha = 0.049$ for the final analyses. All testing was 2-sided and was done using SAS procedures.

The **primary efficacy parameter** was response ratio (RRatio or symmetrized percent change) as a comparison of baseline 28-day partial seizure rate (B) with treatment 28-day partial seizure rate (T) according to the formula: RRatio = [(T-B)/(T+B)] × 100. Analysis was performed using an analysis of variance (ANOVA) model with treatment (as main effect) and center (clusters) and RRatio as the dependent variable ($\alpha = 0.049$, 2-sided).

The **primary efficacy variable** was the response for all partial seizures at the end of the study (Week 12 of Treatment/ Termination). The primary analysis was performed on the ITT population using an analysis of variance (ANOVA) model with treatment and cluster as main effects, and rank of the RRatio as the dependent variable. ITT patients with no double-blind seizure diary data had their baseline seizure frequency carried forward. The primary efficacy outcomes were pairwise comparisons of pregabalin versus placebo, with pregabalin 600 mg/day versus placebo being the primary comparison of interest. These comparisons used a step-down procedure starting with the 600-mg/day dose versus placebo ($\alpha = 0.049$). If nonsignificant, all doses were declared not statistically significant from placebo. If the first pairwise comparison was significant, then the procedure was repeated, with $\alpha = 0.049$, until either a nonsignificant result was obtained or the last (50 mg/day pregabalin versus placebo) comparison was made. All pregabalin versus pregabalin comparisons were tested at $\alpha = 0.049$.

The study was considered positive if the 600 mg/day treatment group versus placebo, the primary comparison using the ITT population, was statistically significant in favor of the 600 mg/day treatment group.

The difference in unadjusted means was summarized for each pairwise comparison of treatment groups overall, and by cluster. A 95% confidence interval for each difference in means was also computed.

Generalizability of the ANOVA models was examined. Consistency of treatment effects across clusters was explored by adding a treatment-by-cluster interaction term to the ANOVA model. The interaction term was tested at a significance level of 0.15 to increase the power of the test.

Secondary efficacy parameters: The responder rate, defined as the proportion of patients who had a >50% reduction in seizure rate during treatment as compared to baseline, and the percent change (PCH) in 28-day seizure rates in treatment compared to baseline. The responder rate was compared between treatments at Week 12 of treatment/termination using a Cochran-Mantel-Haenszel chi-square analysis adjusting for cluster to test for a treatment difference. Data from the patients in the 4 pregabalin groups and the placebo group were used to characterize the dose-response relationship between pregabalin and partial seizure control as measured by the RRatio and the responder rate. (Reviewer note: This dose response relationship was unique to Study 034).

The percent change from baseline in 28-day partial seizure rates was summarized by treatment group for both the ITT and evaluable populations at Week 12 of treatment/Termination. These data were summarized by descriptive statistics only, no inferential analysis was performed.

Descriptive statistics were used to summarize all 3 efficacy parameters by treatment group for each seizure type including all partial, simple partial, complex partial, partial with secondary generalization, and partial without secondary generalization.

RRatio, responder rate, and percent change were also summarized by seizure type. The length of seizure-free intervals and the number of seizure-free days per a 28-day period (planned evaluation) and number and percent of patients who were seizure free (ad hoc analysis) were also assessed. The **ad hoc efficacy parameter** was the number and percent of patients who were seizure free for the last 28 days, 42 days, 56 days and last 70 days of their double blind treatment.

Primary analysis population was the intent-to-treat (ITT) population (all patients randomized who received at least one dose of study medication). The secondary analysis population was the evaluable population (all patients randomized who received at least 28 days of study medication and had a minimum of 28 days of seizure diary data within both the baseline phase and the double-blind phase).

Ad hoc efficacy analysis

Based on the robust effect on efficacy seen in other endpoints after the blind was broken, as well as anecdotal evidence from investigators during the study, the question of whether pregabalin could enable refractory patients to become seizure free was explored. An ad hoc analysis of the patients who were seizure free during their last 28, 42, 56, and 70 days of double-blind treatment was performed.

It was theorized that pregabalin may need a period of several weeks before reaching a level of efficacy sufficient to totally eliminate seizures in some patients within a refractory population. Two different sets of criteria were used to define which patients were to be considered seizure free during the specified evaluation periods. The restrictive method required patients to have at least 2 weeks of double-blind treatment prior to the seizure-free evaluation period and seizure diary data for at least 75% of each time period. A second, broader method put no restriction on missing diary data and did not require patients to have at least 2 weeks of double-blind treatment prior to the seizure-free evaluation period; rather, the evaluation period could begin on the first day of study medication. The denominator for calculation of the percentage of seizure free patients in each treatment group was the total number of ITT patients in the treatment group. The number and percent of patients who were seizure free in each of the 4 time periods (using both definitions of seizure-free) were compared between each pregabalin treatment group and placebo using Fisher's exact test.

9.2 *Study 034 Efficacy Conclusions*

9.2.1 ITT Patient Characteristics and Disposition

No important differences were found between treatment groups in demographic characteristics. All of the patients who entered the double-blind treatment phase had medically refractory partial seizures. A total of 455 patients were randomized to treatment, and 453 received treatment (ITT) population (Table 5). Of the 453 patients in the ITT population, 100 were randomized to the placebo group, 88 to the 50 mg/day pregabalin group, 86 to the 150 mg/day pregabalin group, 90 to the 300 mg/day pregabalin group, and 89 to the 600 mg/day pregabalin group. Patients were primarily white (85%) and at screening had a mean age of 38 years (range, 12 through 75 years), with a mean age of 14 years at diagnosis of epilepsy. The majority of the randomized patients (83%) completed the study. However, there was a dose-related increase in the incidence of withdrawals due to adverse events in the 600 mg/day (24%) and 300 mg/day (14%) pregabalin groups relative to the placebo group (5%).

Table 5. Summary of Patient Characteristics: ITT Population

Characteristic	Placebo N = 100	Pregabalin 50 mg/day (BID) N = 88	Pregabalin 150 mg/day (BID) N = 86	Pregabalin 300 mg/day (BID) N = 90	Pregabalin 600 mg/day (BID) N = 89	All Pregabalin N = 353	All Patients N = 453
Gender, N (%)							
Male	52 (52.0%)	39 (44.3%)	36 (41.9%)	48 (53.3%)	43 (48.3%)	166 (47.0%)	218 (48.1%)
Female	48 (48.0%)	49 (55.7%)	50 (58.1%)	42 (46.7%)	46 (51.7%)	187 (53.0%)	235 (51.9%)
Premenarchal	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.4%)
Premenopausal	35 (72.9%)	36 (73.5%)	40 (80.0%)	35 (83.3%)	34 (73.9%)	145 (77.5%)	180 (76.6%)
Postmenopausal	13 (27.1%)	13 (26.5%)	9 (18.0%)	7 (16.7%)	12 (26.1%)	41 (21.9%)	54 (23.0%)
Race, N (%)							
White, Non-Hispanic	84 (84.0%)	76 (86.4%)	73 (84.9%)	78 (86.7%)	74 (83.1%)	301 (85.3%)	385 (85.0%)
Black, Non-Hispanic	7 (7.0%)	5 (5.7%)	8 (9.3%)	4 (4.4%)	7 (7.9%)	24 (6.8%)	31 (6.8%)
Hispanic (White or Black)	7 (7.0%)	3 (3.4%)	4 (4.7%)	7 (7.8%)	5 (5.6%)	19 (5.4%)	26 (5.7%)
Asian or Pacific Islander	1 (1.0%)	2 (2.3%)	1 (1.2%)	1 (1.1%)	2 (2.2%)	6 (1.7%)	7 (1.5%)
American Indian or Alaskan Native	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Other	1 (1.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	2 (0.6%)	3 (0.7%)
Age (Years)	N = 100	N = 88	N = 86	N = 90	N = 89	N = 353	N = 453
Mean (SD)	39.5 (12.6)	38.9 (11.0)	37.4 (13.3)	37.8 (11.4)	38.0 (11.1)	38.0 (11.7)	38.4 (11.9)
Median	40	40	38.5	38	37	38	38
Range	16-73	14-61	12-75	12-64	13-66	12-75	12-75
Estimated Creatinine Clearance at Baseline (mL/min)	N = 100	N = 88	N = 85	N = 90	N = 89	N = 352	N = 452
Mean (SD)	111 (32.4)	110 (27.5)	103 (27.8)	109 (32.7)	114 (34.6)	109 (31.0)	109 (31.3)
Median	108	105.9	97.7	101.6	109.8	102.8	104.2
Range	42.5-224.5	59.5-189.4	55.3-177.1	53-225	59.9-245.5	53-245.5	42.5-245.5
Height (cm)	N = 99	N = 88	N = 84	N = 89	N = 88	N = 349	N = 448
Mean (SD)	170 (10.3)	168 (10.1)	167 (11.2)	167 (11.2)	169 (9.3)	168 (10.5)	168 (10.5)
Median	170	166	165	169	170	168	168
Range	147-198	144-191	134-206	140-191	152-188	134-206	134-206
Weight (kg)	N = 100	N = 88	N = 86	N = 90	N = 89	N = 353	N = 453
Mean (SD)	80 (19.7)	79 (19.4)	73 (17.8)	80 (23.8)	80 (21.6)	78 (20.9)	79 (20.6)
Median	77	77	71	76	78	76	76
Range	45-128	43-137	44-129	42-146	42-180	42-180	42-180

Table 6. Summary of Epilepsy History: ITT Population

Characteristic	Placebo N = 100	Pregabalin 50 mg/day (BID) N = 88	Pregabalin 150 mg/day (BID) N = 86	Pregabalin 300 mg/day (BID) N = 90	Pregabalin 600 mg/day (BID) N = 89	All Pregabalin N = 353	All Patients N = 453
Age at Diagnosis (Years)							
N	100	88	86	89	89	352	452
Mean (SD)	16 (13.6)	15 (13.0)	14 (13.3)	12 (11.3)	13 (12.2)	13.5 (12.4)	14 (12.7)
Median	12.2	11.9	9.5	9.5	10.8	11.0	11.3
Range	0-60.2	0-51.9	0-49.4	0-49.3	0-60.1	0-60.1	0-60.2
Duration of Epilepsy (Years)							
N	100	88	86	89	89	352	452
Mean (SD)	24 (14.0)	25 (11.8)	24 (12.8)	26.2 (13.5)	25.5 (13.7)	25 (13.0)	25 (13.2)
Median	22.7	24.45	22.7	26.8	26.1	25.0	24.3
Range	0.8-63.2	1.1-52	1.1-71.2	3.3-59.2	1.7-62.9	1.1-71.2	0.8-71.2
Etiology, N (%)							
Unknown	43 (43.0%)	39 (44.3%)	37 (43.0%)	47 (52.2%)	42 (47.2%)	165 (46.7%)	208 (45.9%)
Infections	8 (8.0%)	7 (8.0%)	15 (17.4%)	12 (13.3%)	8 (9.0%)	42 (11.9%)	50 (11.0%)
Trauma	21 (21.0%)	22 (25.0%)	16 (18.6%)	13 (14.4%)	20 (22.5%)	71 (20.1%)	92 (22.3%)
Family History	9 (9.0%)	5 (5.7%)	7 (8.1%)	8 (8.9%)	6 (6.7%)	26 (7.4%)	35 (7.7%)
Birth Complications	3 (3.0%)	7 (8.0%)	4 (4.7%)	7 (7.8%)	7 (7.9%)	25 (7.1%)	28 (6.2%)
Other	19 (19.0%)	15 (17.0%)	11 (12.8%)	11 (12.2%)	13 (14.6%)	50 (14.2%)	69 (15.2%)
28-Day Seizure Rate at Baseline							
N	100	88	86	90	89		
Mean (SD)	22.3 (42.1)	27.4 (50.2)	23.1 (36.5)	19.1 (26.7)	18.6 (26.9)		
Median	9.5	10.3	8.8	9.8	9		
Range	2.7-311	1-356	3-253.5	2-205	2-162		
Concurrent AEDs, N (%)							
1 AED	26 (26.0%)	30 (34.1%)	27 (31.4%)	30 (33.3%)	22 (24.7%)	109 (30.9%)	135 (29.8%)
2 AEDs	48 (48.0%)	39 (44.3%)	44 (51.2%)	46 (51.1%)	49 (55.1%)	178 (50.4%)	226 (49.9%)
3 AEDs	24 (24.0%)	18 (20.5%)	15 (17.4%)	14 (15.6%)	18 (20.2%)	65 (18.4%)	89 (19.6%)
4 AEDs	2 (2.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	3 (0.7%)

Table 7. Summary of History of Seizure Types: ITT Population
[Number (%) of Patients]

Seizure Type	Placebo N = 100	Pregabalin 50 mg/day (BID) N = 88	Pregabalin 150 mg/day (BID) N = 86	Pregabalin 300 mg/day (BID) N = 90	Pregabalin 600 mg/day (BID) N = 89	All Pregabalin N = 353	All Patients N = 453
Partial	100 (100.0%)	88 (100.0%)	86 (100.0%)	90 (100.0%)	89 (100.0%)[a]	353 (100.0%)[a]	453(100.0%)[a]
Simple Partial	56 (56.0%)	42 (47.7%)	41 (47.7%)	51 (56.7%)	50 (56.2%)	184 (52.1%)	240 (53.0%)
With Motor Symptoms	20 (20.0%)	13 (14.8%)	11 (12.8%)	22 (24.4%)	19 (21.3%)	65 (18.4%)	85 (18.8%)
With Somatosensory or Special Sensory Symptoms	30 (30.0%)	27 (30.7%)	19 (22.1%)	27 (30.0%)	28 (31.5%)	101 (28.6%)	131 (28.9%)
With Autonomic Symptoms	7 (7.0%)	5 (5.7%)	7 (8.1%)	9 (10.0%)	6 (6.7%)	27 (7.6%)	34 (7.5%)
With Psychic Symptoms	18 (18.0%)	18 (20.5%)	18 (20.9%)	17 (18.9%)	14 (15.7%)	67 (19.0%)	85 (18.8%)
Complex Partial	88 (88.0%)	86 (97.7%)	72 (83.7%)	83 (92.2%)	82 (92.1%)[a]	323 (91.5%)[a]	411 (90.7%)[a]
Beginning as SP and Progressing to Impairment of Consciousness	50 (50.0%)	52 (59.1%)	41 (47.7%)	46 (51.1%)	50 (56.2%)	189 (53.5%)	239 (52.8%)
With Impairment of Consciousness at Onset	54 (54.0%)	51 (58.0%)	45 (52.3%)	55 (61.1%)	47 (52.8%)	198 (56.1%)	252 (55.6%)
Partial Secondarily Generalized	56 (56.0%)	55 (62.5%)	55 (64.0%)	59 (65.6%)	56 (62.9%)[a]	225 (63.7%)[a]	281 (62.0%)[a]
Generalized	13 (13.0%)	5 (5.7%)	14 (16.3%)	9 (10.0%)	12 (13.5%)	40 (11.3%)	53 (11.7%)
Absence	0 (0.0%)	0 (0.0%)	2 (2.3%)	2 (2.2%)	0 (0.0%)	4 (1.1%)	4 (0.9%)
Myoclonic	2 (2.0%)	0 (0.0%)	2 (2.3%)	1 (1.1%)	0 (0.0%)	3 (0.8%)	5 (1.1%)
Clonic	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	2 (0.6%)	2 (0.4%)
Tonic	1 (1.0%)	0 (0.0%)	2 (2.3%)	0 (0.0%)	1 (1.1%)	3 (0.8%)	4 (0.9%)
Tonic-Clonic	10 (10.0%)	5 (5.7%)	10 (11.6%)	7 (7.8%)	11 (12.4%)	33 (9.3%)	43 (9.5%)
Atonic	0 (0.0%)	0 (0.0%)	2 (2.3%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	2 (0.4%)
Unclassified							

[a] Includes seizure history data from 1 patient (Patient 027014) not entered in database

Complex partial seizures were the most frequent seizure type occurring in 91% of patients.

Exposure to study medication in Study 034

Table 9. Summary of Exposure: ITT Population

Duration of Exposure	Placebo N = 100	Pregabalin 50 mg/day (BID) N = 88	Pregabalin 150 mg/day (BID) N = 86	Pregabalin 300 mg/day (BID) N = 90	Pregabalin 600 mg/day (BID) N = 89
≥1 Day	100 (100.0%)	88 (100.0%)	86 (100.0%)	90 (100.0%)	89 (100.0%)
≥1 Week	99 (99.0%)	88 (100.0%)	86 (100.0%)	82 (91.1%)	75 (84.3%)
≥2 Weeks	99 (99.0%)	84 (95.5%)	85 (98.8%)	80 (88.9%)	72 (80.9%)
≥4 Weeks	98 (98.0%)	81 (92.0%)	82 (95.3%)	78 (86.7%)	70 (78.7%)
≥6 Weeks	96 (96.0%)	79 (89.8%)	82 (95.3%)	74 (82.2%)	67 (75.3%)
≥8 Weeks	92 (92.0%)	78 (88.6%)	82 (95.3%)	74 (82.2%)	66 (74.2%)
≥10 Weeks	89 (89.0%)	78 (88.6%)	80 (93.0%)	72 (80.0%)	63 (70.8%)
≥12 Weeks	65 (65.0%)	54 (61%)	57 (66.3%)	50 (55.6%)	42 (47.2%)

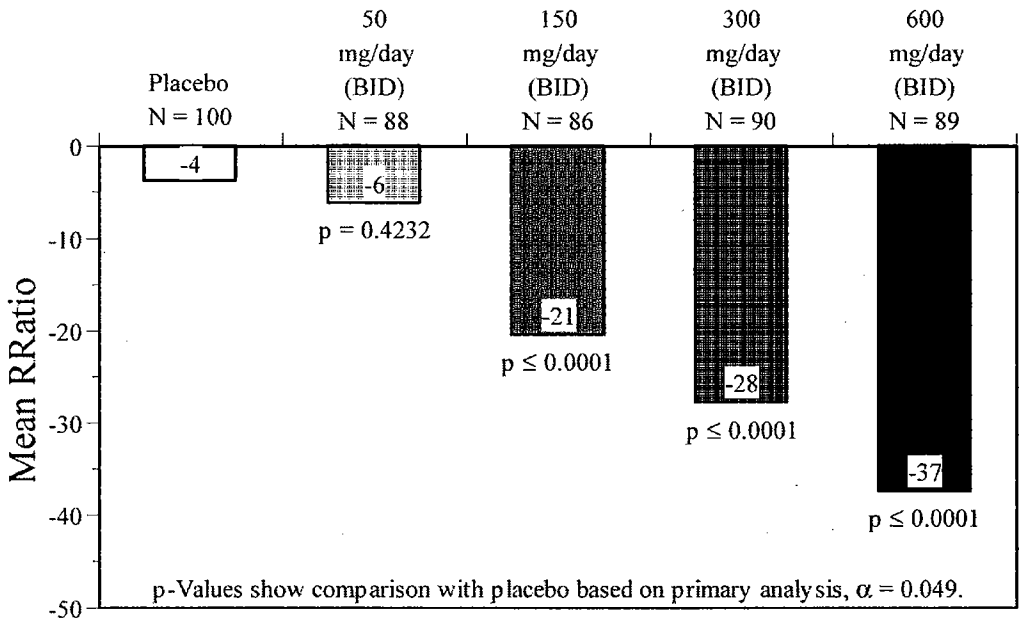
Patient disposition in Study 034

Table 10. Summary of Patient Disposition
[Number (%) of Patients]

Disposition	Placebo	Pregabalin 50 mg/day (BID)	Pregabalin 150 mg/day (BID)	Pregabalin 300 mg/day (BID)	Pregabalin 600 mg/day (BID)	All Patients
Entered Baseline						586
Withdrawn During Baseline						131
Adverse Event						4
Lack of Compliance						13
Other/Administrative						114
Entered Double-Blind (Randomized)	100	88	88	90	89	455
Withdrawals During Double-Blind	13 (13.0%)	10 (11.4%)	7 (8.0%)	19 (21.1%)	28 (31.5%)	77 (16.9%)
Lack of Efficacy	5 (5.0%)	1 (1.1%)	1 (1.1%)	2 (2.2%)	4 (4.5%)	13 (2.9%)
Adverse Event	5 (5.0%)	6 (6.8%)	1 (1.1%)	13 (14.4%)	21 (23.6%)	46 (10.1%)
Lack of Compliance	0 (0.0%)	0 (0.0%)	1 (1.1%)	1 (1.1%)	2 (2.2%)	4 (0.9%)
Other/Administrative	3 (3.0%)	3 (3.4%)	4 (4.5%)	3 (3.3%)	1 (1.1%)	14 (3.1%)
Completed Study	87 (87.0%)	78 (88.6%)	81 (92.0%)	71 (78.9%)	61 (68.5%)	378 (83.1%)
Entered Open-Label Study	87 (87.0%)	78 (88.6%)	81 (92.0%)	75 (83.3%)	73 (82.0%)	394 (86.6%)

9.2.2 Primary Efficacy Results

Based on the RRatio, all pregabalin treatment groups, except for the 50 mg/day group, showed statistically significantly greater reductions in seizures compared to the placebo group (based on the Ruberg step down procedure for controlling the overall type I error rate at 0.049). The 150 mg/day group was a minimum effective dose. Mean RRatio data are summarized in Figure 2 and Table 11. RR ratio by cluster is reproduced from Appendix C.15.



VAL/CLC/030200
1008/034/RRatio1.DG4

Figure 2. Mean RRatio (All Partial Seizures): ITT Population

Table 11. Summary of RRatio (All Partial Seizures): ITT Population

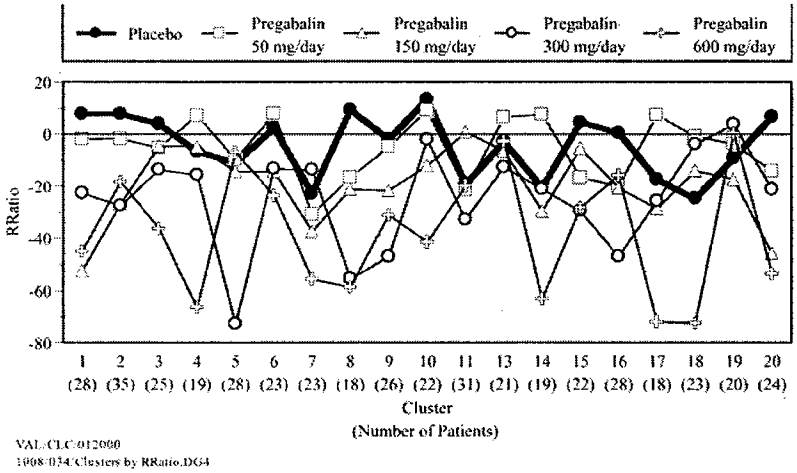
Period	Placebo N = 100	Pregabalin 50 mg/day (BID) N = 88	Pregabalin 150 mg/day (BID) N = 86	Pregabalin 300 mg/day (BID) N = 90	Pregabalin 600 mg/day (BID) N = 89
All Double-Blind					
Mean	-3.8	-6.2	-20.5	-27.8	-37.4
SD	25.6	23.7	29.6	36.5	44.4
Median	0	-4.5	-21	-22.5	-34.1
Minimum	-78.9	-65	-100	-100	-100
Maximum	72.8	81.1	53.1	72	92

RR Ratio by Cluster (compare to the Responder Rate Appendix C18 below.)

(Reviewer Note: There is a large range of mean RR ratios per cluster in all dose groups with no clear trend to this reviewer for a more robust difference between the 300mg and 600mg dose groups.)

APPENDIX C.15

Figure of Response Ratio (All Partial Seizures) by Cluster: Intent-to-Treat Population



VAL/CLC/012000
1008/034/Clusters by RRatio.DG4

This figure summarizes the mean RRatio by treatment for each of the 19 clusters in the study. During the blinded review, it was noted Cluster 12 had dropped to below N = 18 randomized (minimum planned cluster size), and was thus combined with another cluster (Cluster 2) from the same area of the country. As a result, Cluster 12 is absent.

9.2.3 Secondary Efficacy analyses

Responder rate - A patient was classified as a responder if they experienced at least a 50% reduction in seizure frequency compared to the baseline. All pregabalin groups, except for the 50 mg/day group, had statistically significantly greater responder rates, compared to placebo. The percent responders in each group are presented in Figure 3. (Reviewer note: It is interesting to see the more robust results in this study in the 150mg dose group and compare it to the results in Study 11 – see section 8.2.3 for comparison. The reason for the more robust results is unknown.)

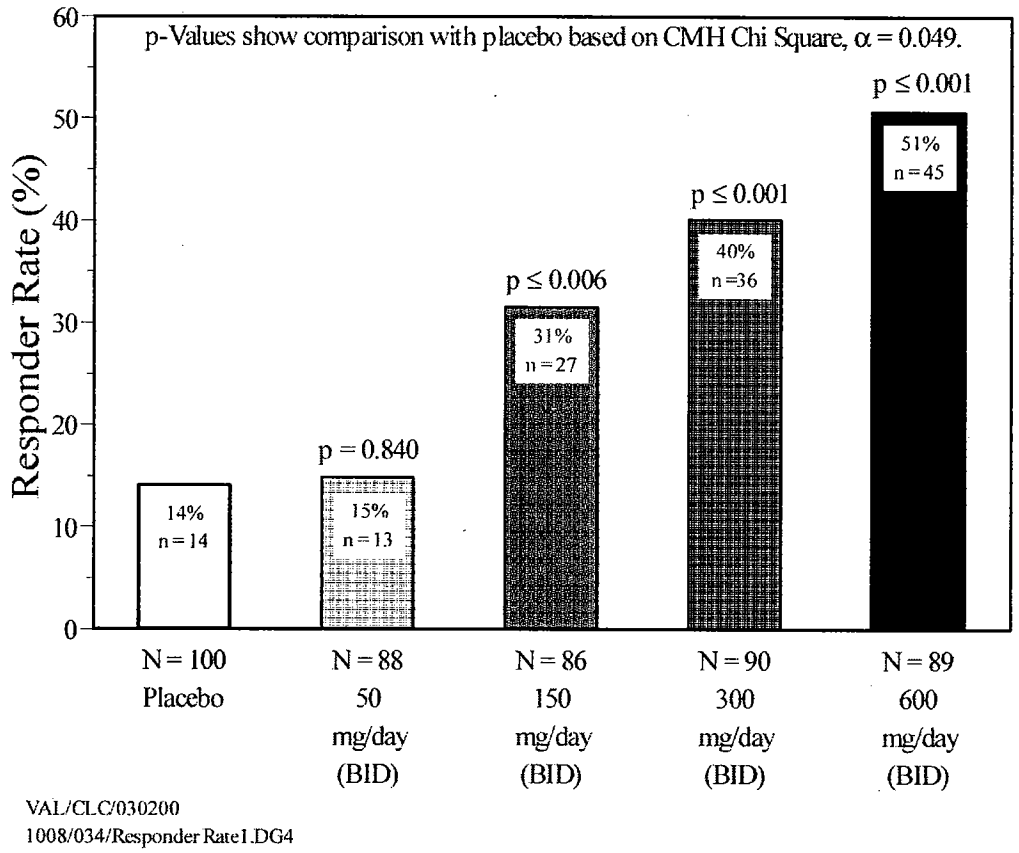
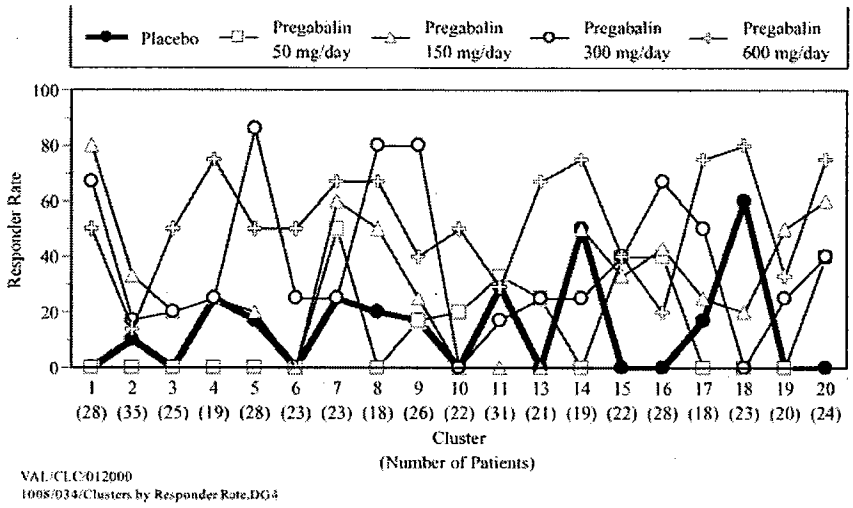


Figure 3. Responder Rate (All Partial Seizures): ITT Population

Statistically significant treatment-by-cluster interactions were found with the 50 and 300 mg/day groups relative to placebo, but were not considered of sufficient magnitude to significantly impact results. (Reviewer note: This graph provided in Appendix C.18 of the study report is almost uninterpretable. The range of responder rates in all cluster groups vary so much that I cannot see any trend.) A majority of the clusters favored 300 mg/day over placebo. It is also noted that these interactions were not present with the RRatio. (Reviewer note: The RR Ratio show a high degree of variability as well, refer to Appendix C.15 above.)

APPENDIX C.18

Figure of Responder Rate (All Partial Seizures) by Cluster: Intent-to-Treat Population



This figure summarizes the percent responder rate by treatment for each of the 19 clusters in the study. During the blinded review, it was noted Cluster 12 had dropped to below N = 18 randomized (minimum planned cluster size), and was thus combined with another cluster (Cluster 2) from the same area of the country. As a result, Cluster 12 is absent.

The median percent change from baseline for the ITT population was -51% in the 600 mg/day, -37% in the 300 mg/day, -35% in the 150 mg/day, -9% in the 50 mg/day pregabalin groups and 0% in the placebo group. These results support the RRatio results. The median treatment differences and corresponding confidence intervals are presented in Appendix C.20.

APPENDIX C.20

Summary of Median Percent Change From Baseline and Confidence Intervals: Intent-to-Treat

Summary of Median Percent Change From Baseline (All Partial Seizures): ITT Population

Treatment Comparisons	Median Treatment Differences[a]		
	N[b]	Medians	95% CI
PGB 600 mg/day BID/Placebo	89/100	-43.9	[-57.8, -31.1]
PGB 300 mg/day BID/Placebo	90/100	-33.0	[-46.0, -20.4]
PGB 150 mg/day BID/Placebo	86/100	-25.9	[-38.3, -13.9]
PGB 50 mg/day BID/Placebo	88/100	-5.2	[-15.8, 6.7]
PGB 600 mg/day BID/50 mg/day BID	89/88	-39.8	[-53.0, -26.3]
PGB 300 mg/day BID/50 mg/day BID	90/88	-28.7	[-40.9, -15.7]
PGB 150 mg/day BID/50 mg/day BID	86/88	-22.1	[-33.5, -9.6]
PGB 600 mg/day BID/150 mg/day BID	89/86	-19.5	[-32.3, -5.1]
PGB 300 mg/day BID/150 mg/day BID	90/86	-7.0	[-20.1, 5.8]
PGB 600 mg/day BID/300 mg/day BID	89/90	-11.2	[-24.7, 1.5]

[a] Based on median treatment differences for the percent change
[b] N in Group 1/N in Group 2

Results by seizure type

In general, the efficacy endpoint for each seizure type showed similar trends to those seen for all partial seizures combined, with dose-related reductions over the entire double-blind period seen at doses of 600, 300, and 150 mg/day. The primary efficacy endpoint, mean RRatio, by seizure type is presented in Table 13. An exception to the dose-related trend seen at the 3 highest dose levels occurred for partial seizures with secondary generalization. The mean RRatio, median percent change and the responder rate for this seizure type showed some reduction in seizures at the 2 highest dose levels relative to placebo but the response was not as pronounced as for all partial seizures; and, no effect was seen at the 150 mg/day dose level. Per the sponsor, it should be noted that across the groups relatively few patients experienced this seizure type, resulting in small sample sizes per group and more variation.

Table 13. Summary of RRatio by Seizure Type (All Partial Seizures): ITT Population

All Double-Blind	Placebo	Pregabalin Dose, mg/day (BID)			
		50	150	300	600
	N = 100	N = 88	N = 86	N = 90	N = 89
Simple Partial Seizures					
N	48	44	42	46	45
Mean	2.2	0.3	-10.7	-23.5	-46.5
SD	58.5	54.6	61.3	48.4	58.2
Median	-5	-3.7	-11	-17.6	-61.4
Minimum	-100	-100	-100	-100	-100
Maximum	100	100	100	100	100
Complex Partial Seizures					
N	90	82	75	79	80
Mean	0.5	-5.8	-18	-25.5	-36.7
SD	38	37.8	41.3	47.4	52.7
Median	1.5	-5.7	-23.3	-21.1	-37.2
Minimum	-80	-100	-100	-100	-100
Maximum	100	100	100	100	100
Partial Seizures Without Generalization					
N	100	87	84	87	89
Mean	-0.7	-5.1	-21.4	-28.3	-35.3
SD	30.6	27.6	35.3	37.9	49.9
Median	0.4	-4.5	-23.1	-21.1	-38.5
Minimum	-78.9	-100	-100	-100	-100
Maximum	100	100	100	72	100
All Partial Seizures					
N	100	88	86	90	89
Mean	-3.8	-6.2	-20.5	-27.8	-37.4
SD	25.6	23.7	29.6	36.5	44.4
Median	0	-4.5	-21	-22.5	-34.1
Minimum	-78.9	-65	-100	-100	-100
Maximum	72.8	81.1	53.1	72	92

New partial seizures - New partial seizure types were observed after baseline for a few patients in the placebo and the 50, 150, and 300 mg/day pregabalin groups, but there were no treatment-related differences, and no pronounced increase in any seizure type.

9.2.4 Ad Hoc Analyses

There was a treatment-related increase in both the median and maximum length of seizure-free intervals, in terms of mean percent change from baseline, for patients in the 600, 300, and 150 mg/day groups when compared to patients in the placebo group. Similarly, there was a slight increase in the percent change from baseline in median number of seizure-free days per 28-day interval in the 600, 300, and 150 mg/day dose groups relative to placebo.

The planned descriptive statistics summarized the length of seizure-free intervals and the number of seizure-free days per a 28-day period, but did not summarize the number of patients that were seizure free during all or part of the double-blind period. Based on the robust effect on efficacy seen in other endpoints after the blind was broken, as well as anecdotal evidence from investigators during the study, the question of whether pregabalin could enable refractory patients to become seizure free was explored in ad hoc analyses.

In the ad hoc analysis of the number and percent of patients seizure free, trends were seen favoring the 300 and 600 mg/day doses of pregabalin compared to placebo at the 28- and 42-day seizure-free periods but no statistically significant differences were found. This is illustrated in Sponsor Table 14.

Table 14. Summary of Seizure Free Ad Hoc Analysis (All Partial Seizures): Restrictive Method[a]: ITT Population

	Placebo	Pregabalin Dose, mg/day (BID)			
		50	150	300	600
	N = 100	N = 88	N = 86	N = 90	N = 89
Last 28 days					
n	8	4	5	10	15
%	8	5	6	11	17
Last 42 days					
n	3	1	2	3	7
%	3	1	2	3	8
Last 56 days					
n	2	1	2	2	5
%	2	1	2	2	6
Last 70 days					
n	0	1	0	0	1
%	0	1	0	0	1

[a] For the purpose of this summary, the seizure-free period started if patients: 1) had been receiving study medication for at least 2 weeks prior to the start of the seizure-free period; and 2) had at least 3 weeks of seizure diary data in a 4 week period.

For the pregabalin 600 mg/day, 15 (17%) of patients were seizure free for the last 28 days compared with 10 (11%) in pregabalin 300 mg/day and 8 (8%) in placebo. Trends were seen favoring the 300 and 600 mg/day doses of pregabalin compared to placebo at the 28- and 42-day seizure-free periods, but no statistically significant differences were found

(Fisher's Exact test). (Reviewer note: These are small numbers of patients considering the overall size of the study and should be interpreted with caution.)

10 Appendix 4 Review of Individual Study Report- Study 145 (Protocol 1008-145)

(Discontinued due to carcinogenicity concerns by FDA)

10.1 Study 145 – (Protocol 1008-145) Outline

Title of Study: Pregabalin BID Add-On Titration Trial: A Randomized, Double-Blind, Placebo- Controlled, Parallel-Group, Multicenter Study in Patients With Partial Seizures.

Investigators: [redacted]

Study Center(s): Twenty-three centers in the United States (US) and Canada were shipped drug and/or entered patients into baseline; 1 of these centers had patients who received study medication.

Publication (reference): None

Studied Period (years): 01/16/01 to 02/16/01 Phase of Development: 3

Objective(s): The original objectives were to assess the efficacy, safety, and tolerability of 2 pregabalin treatments (600 mg/day fixed dose; 150-600 mg/day titration) to placebo as adjunctive therapy in reducing seizure frequency in patients with partial seizures.

However, based on the results of a 2-year mouse bioassay in which there was an increased incidence of hemangiosarcoma, the Food and Drug Administration (FDA) required a reassessment of pregabalin studies conducted in the US. This study, which was to investigate the effects of titration by direct comparison of concurrent groups, was not considered necessary to support the initial New Drug Application (NDA) registration. Pregabalin had been administered without titration in 1 pivotal epilepsy study, and with titration in 2 pivotal epilepsy studies. Because sufficient data on the efficacy and safety of pregabalin administered with and without titration already existed, patient participation in this study did not meet risk-benefit criteria acceptable to the FDA. This study was discontinued early in enrollment. The low enrollment did not permit assessment of efficacy. The revised objective of the study was to assess the safety of pregabalin.

Methodology: Following screening and a 6-week baseline phase, patients entered a 12-week double-blind, randomized, placebo-controlled, parallel group, multicenter study. Randomization was to 1 of 3 treatment groups: (1) pregabalin 600 mg/day administered in a divided dose twice daily (BID), (2) escalating doses of pregabalin 150, 300, 450, and 600 mg/day (BID) titrated based on patient response and tolerability at 2- or 4-week

intervals, or (3) placebo administered BID for the 12-week double-blind treatment. Current antiepileptic drug (AED) therapy was maintained.

Number of Patients: This study was discontinued after 3 patients were randomized and had received study medication. Two patients were randomized to 600 mg/day fixed dose pregabalin group and 1 patient was randomized to the 150 to 600 mg/day titration pregabalin groups.

Diagnosis and Main Criteria for Inclusion: Men or nonpregnant, nonlactating women, 16 years of age, of any race, weighing 40 kg (88 lb) with partial seizures (simple partial, complex partial, and/or secondarily generalized tonic clonic) were eligible. Patients were on stable dosages of 1 to 3 standard AEDs, with at least 4 partial seizures during the 6-week baseline phase and no 28-day period free of partial seizures.

Test Product: 50-mg, 75-mg, 150-mg, 300mg capsules of Lyrica ™ Pregabalin : Capsules administered BID

Duration of Treatment: 12 weeks

Criteria for Evaluation:

Efficacy: Because the study was discontinued, the sample size did not permit efficacy evaluation.

10.2 Study 145 - Results summary

Patient Characteristics: Two women (1 white, 1 black) were randomized to the fixed-dose group, and 1 white woman was randomized to the titration pregabalin group. The patients ranged from 39 to 49 years of age, with the duration of epilepsy ranging from 6 to 40 years. One patient in the fixed-dose group withdrew due to lack of compliance after 19 days of exposure (12 days at full dose, 1 week taper to withdrawal). The other 2 patients (1 fixed dose, 1 titration) terminated because the study closed; they were exposed approximately 1 month (28 days, 34 days). The titration patient had received 150 mg/day for 2 weeks and 300 mg/day for 1 week before tapering to withdrawal.

11 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 1A

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Howard Chazin
8/13/04 03:56:39 PM
MEDICAL OFFICER

John, this is my final document (after fixes we discussed)

John Feeney
8/16/04 01:52:52 PM
MEDICAL OFFICER
See my cover memo.