CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-724

STATISTICAL REVIEW(S)

Addendum to Statistical Review

NDA#:	**21724 N_000 (linked with NDA 21446)**
Name of Drug:	**Pregabalin**
Name of Firm:	**Pfizer**
Indication:	**Adjunctive Therapy of Epilepsy**
Date of Document:	**October 30, 2003**
Medical Officer:	**Howard Chazin, M.D. (HFD-120)**
Statistical Reviewer:	**Tristan Massie, Ph.D. (HFD-710)**

This is an addendum to my statistical review dated July 16, 2004 of the NDA application dated October 30, 2003. Dr. Feeney, the medical team leader, requested analyses relating to the efficacy of Pregabalin added on to each of the most frequently used concomitant AEDs, as such analyses were not provided by the sponsor. These analyses are important because Pfizer is seeking to have Pregabalin indicated for adjunctive therapy of partial seizures and it's effectiveness could vary with the concomitant AED.

Each of the three main studies in the application had an 8-week baseline period and a 12 week double blind treatment period. Patients were to be on stable doses of 1-4 concomitant AEDs throughout the baseline and double blind periods. Between the three studies there were 1043 patients with at least one seizure diary entry for the double blind treatment period. Since many different concomitant AEDs were used and 73% of patients had more than one concomitant AED it is difficult to isolate the efficacy of pregabalin with a given AED. For example, the subgroup who took Carbamazepine may have had a different distribution of other concomitant AEDs than the subgroup that did not take Carbamazepine. We can get an idea though by comparing the efficacy of the subgroup of patients who took a particular AED to the overall results. The most frequently used AEDs in the three studies are shown below:

Table 1 Most Frequent Concomitant AEDs

Concomitant AED	Number of Patients	Percent of Patients
CARBAMAZEPINE	588	56.38
LAMOTRIGINE	291	27.90
PHENYTOIN SODIUM	200	19.18
TOPIRAMATE	199	19.08
VALPROATE SEMISODIUM	118	11.31
PHENYTOIN	87	8.34
PHENOBARBITAL	83	7.96

Concomitant AED	Number of Patients	Percent of Patients
CLOBAZAM	70	6.71
TIAGABINE HYDROCHLORIDE	65	6.23
VALPROIC ACID	57	5.47
CLONAZEPAM	54	5.18
TIAGABINE	34	3.26
VALPROATE SODIUM	32	3.07

The following table shows the efficacy results by dose (mg/day) for the different concomitant AED subgroups. The results are pooled over the three studies and over regimen, e.g., 150 mg/day (TID) and 150 mg/day (BID) are combined. The p-values should not be taken at face value since these analyses are post-hoc and the treatment groups may not be balanced with respect to important predictors of outcome in these subgroups.

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

		Pregabalin Dose (mg/day)				
		0	50	150	300	600
	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
	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

The efficacy of the 600 mg/day groups seems to be reasonably consistent across the groups of patients who took carbamazepine, lamotrigine, phenytoin, topiramate, and the other concomitant AEDs shown in table 2. The same appears to be true for the 300 mg/day and 150 mg/day groups for the most part. The few exceptions for the 150 and 300 mg/day groups could be attributable to a lack of power since there were fewer patients at these doses than at 600 mg/day. Note that Neurontin is one AED for which we cannot assess the effect of adding Pregabalin because patients on Neurontin had to stop taking it in order to be eligible for the studies.

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Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21724 / N_000 (linked with NDA 21446)

Drug Name: Pregabalin

Indication(s): Epilepsy - Adjunctive Therapy

Applicant: Pfizer

Date(s): 10/30/2003

Review Priority: Standard

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Keywords: add-on design; analysis of variance; multiple comparisons; dose response; interim analysis

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The data support the efficacy of pregabalin as adjunctive therapy in the treatment of partial seizures. Doses of 150 mg/day, 300 mg/day, and 600 mg/day were identified as effective. There was evidence of increasing benefit with increasing dose but withdrawals due to adverse events increased with increasing dose also. The 600 mg/day groups tended to have more patients with less than 28 days of double blind diary data and therefore less chance to experience seizures. Sensitivity analyses still supported the efficacy of the 600 mg/day doses and the differences between 600 mg/day and placebo were larger than the differences between 150 mg/day and placebo but they were also less reliable, i.e., the differences between 600 mg/day and placebo had wider confidence intervals.

1.2 Brief Overview of Clinical Studies

The sponsor submitted three randomized, double-blind, placebo-controlled, fixed-dose group studies of pregabalin as adjunctive therapy in patients with partial seizures. Each of these studies consisted of an 8 week baseline period followed by a 12 week double-blind treatment period. Seizure activity was recorded daily in a diary. Study 0009 utilized a placebo group and two 600 mg/day dose groups, one administered BID and the other administered TID. Study 0011 utilized a placebo group, a 150 mg/day group, and a 600 mg/day group all administered TID. Study 0034 included 50 mg/day, 150 mg/day, 300 mg/day, 600 mg/day, and placebo groups and all treatments were administered BID. Eligible patients were to be on stable doses of between one and three AEDs prior to and during the study. In order to be randomized they should have had at least 6 seizures during the eight week baseline period, with no seizure free period of four weeks or more. The randomized patient population was about 50% males and was 87% white. The average age was about 38 years and the vast majority of patients were older than 17, but a small number of patients (18/455 ≈ 4%) aged 12 to 17 years were included in study 0034.

Studies 0009 and 0034 were conducted primarily in the U.S. with a handful of centers in Canada, while study 0011 was conducted entirely in Europe. Across all studies the median baseline seizure rate per 28 days was about 10 and the mean baseline seizure rate per 28 days was about 22. Baseline seizure rates ranged from 1 to 356 per 28 days. The primary efficacy measure was the Response Ratio, RRatio = $100 \times (T - B) / (T + B)$, where T and B are the average seizures rates per 28 days in the double-blind and baseline periods respectively. T is determined as 28 times the number of seizures in the entire double blind period divided by the number of days with non-missing diary entries in the entire double blind period and B is determined in the same way for the baseline period. The RRatio takes values between -100 and 100 and is related to the percent change as follows, RRatio= 100 * (percent change)/(percent change+200). Note that a patient whose condition worsens can have a Percent Change much greater than 100, in fact, there is no upper limit, but the RRatio can be at most 100.

The primary analysis was based on the ranks of the RRatio values and these are the same as the ranks of the percent change, i.e., ordering the Percent Change values from smallest to largest yields the same order as ordering the RRatios from smallest to largest. Therefore, the primary analysis, an analysis of variance of the ranks of the RRatios, is equivalent to an analysis of variance of the ranks of the percent change values.

The double-blind phase for efficacy evaluations included titration and lasted from Day 1 of study medication through the last day of double-blind treatment (not including downward titration during the withdrawal phase or transition to open-label). There was one week of upward titration in studies 0009 and 0011, but no titration in study 0034. Although most patients were treated for about the protocol specified length of time, some patients were treated beyond the planned 84 days (up to 114 days) and others withdrew in the first week (some after only 1 day). Patients with at least 1 day of utilizable seizure record had an estimated 28-day rate computed using the data collected.

Table 1 Relevant Clinical Studies in Epilepsy

Study	Study Dates	N Rand-omized	Number of Centers	Age: Mean Range	Length (weeks)	Dose Groups	Primary Endpoint
						Gabapentin	
0009 (add-on)	Jun 98 - Sep 99	313	37 US 6 Can	39.1 (17-82)	B: 8 DB: 12 1-week titration	PBO or 600 mg/day: 200(TID)or 300(BID)	100 × (T-B)/(T+B)
0011(add-on)	Apr 98 - Nov 99	288	45 (int)	37.0 (17-73)	B: 8 DB: 12 1-week titration	PBO or 150 or 600 mg/day (TID)	100 × (T-B)/(T+B)
0034(add-on)	Nov 98 - Sep 99	455	71 US 5 Can	38.4 (12-75)	B: 8 DB: 12 no titration	PBO or 50/150/ 300/600 mg/day (BID)	100 × (T-B)/(T+B)

* T- Double Blind Period Seizure Rate (per 28 days)
B- Baseline Period Seizure Rate (per 28 days)

1.3 Statistical Issues and Findings

The sponsor seeks an indication for adjunctive therapy of partial seizures in patients [redacted], but only a small number of patients (20/1056 ≈ 2%) in the three randomized, double-blind, placebo-controlled studies of Pregabalin as adjunctive therapy were between the ages of 12 and 17, so no definitive conclusions can be reached on efficacy in this subgroup. While the three add-on studies demonstrated the efficacy of 150, 300, and 600 mg/day doses for individuals age 18 and above, there is little direct evidence and no independent verification that pregabalin is effective as adjunctive therapy for partial seizures in individuals under 18 years of age (see Table 32 on page 56).

A concern for the efficacy of the 600 mg/day doses is that in the majority of studies the number of days with seizure diary entries in the double blind period was less for the 600 mg/day group than for placebo which means that there was less chance for seizures to be recorded in the 600 mg/day group and is a possible source of bias. This is illustrated with the boxplots in the figure below. Note that the 150 mg/day groups are not shown because they were comparable to placebo. Comparison of the boxplots within a study shows that the 600 mg/day groups had a higher percentage of patients with a small number of days of double blind diary data than placebo since, for example, the bottoms of the boxes are lower for the 600 mg/day groups. Note that, in the figure, the + symbol indicates the average number of DB diary days. The effect was most dramatic in study 0034 where the amount of double-blind diary data was significantly less for the 600 mg/day BID and 300 mg/day BID groups than for the placebo group (Wilcoxon rank sum p=0.0005 and p=0.0158, respectively). The 600 mg/day group(s) also tended to have less diary data than placebo in studies 009 and 011, but the differences were smaller. It is important to note that there was no titration in study 0034, whereas in studies 0009 and 0011 there was one week of titration.

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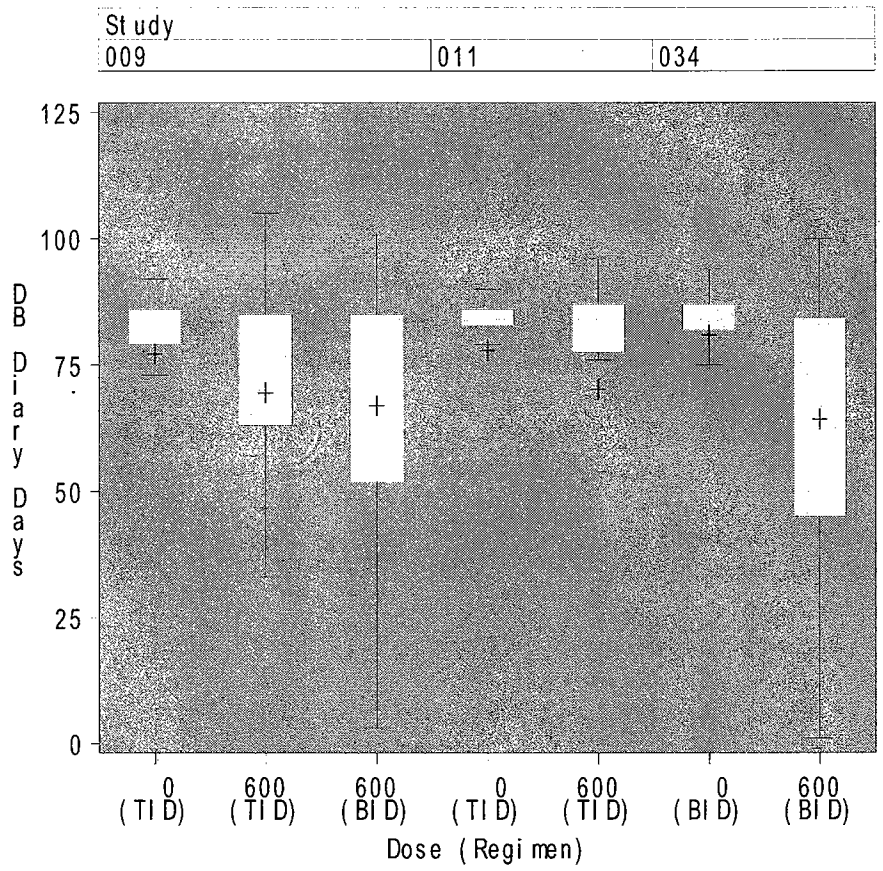
Figure 1 Comparison of Distributions of Number of DB Diary Days for Placebo and 600 mg/day groups



In each study the primary analysis, a 2-way ANOVA of the ranks of the RRatios in the ITT population with effects for center clusters (small centers were pooled geographically) and treatment groups, found the primary comparison of the 600 mg/day group to the placebo group to be significant ($p<0.0001$) in favor of pregabalin. All other pregabalin vs. placebo group comparisons were also significant except for the 50 mg/day vs. placebo comparison in study 0034. It should be noted though that the ANOVA method assumes constant variance across the groups, but both the RRatios and the ranks of the RRatios (primary analysis) failed a test for equal group variances $p<0.02$ in all three studies, except for the ranks of the RRatios in study 11. In particular, the variability of the RRatios was larger in the 600 mg/day groups than in the placebo groups. This may be related to the fact that the 600 mg/day group tended to provide less double blind diary data. This means that the sponsor's ANOVA based confidence intervals for the treatment difference between the 600 mg/day group and placebo are slightly overconfident. However, several alternative tests, performed by this reviewer as a check, yielded the same general conclusions, so the non-constancy of the variance is not a serious issue here. These alternative methods were the Van-Elteren test (a center stratified Wilcoxon rank sum test) and an

ANOVA with observations weighted according to the number of days with seizure diary entries in the post-baseline period. The ordinary unweighted ANOVA does not account for the fact that seizure rates (and RRatios) based on less diary data are less reliable. The weighted ANOVA gives more weight to patients with more diary data than to those with less diary data and, in so doing, may also help to correct the observed group differences in the variability of the RRatios.

The following table summarizes the primary analysis results for the three add-on studies.

Table 2 Mean RRatios by Study – ITT Population

		Dose Group						
		Placebo	50 mg/day BID	150 mg/day BID	150 mg/day TID	300 mg/day BID	600 mg/day BID	600 mg/day TID
Study								
0009	N	98	.	.	.	.	101	110
	Mean RRatio	0.58	.	.	.	.	-28.94	-36.45
	StdDev	28.85	.	.	.	.	36.83	40.05
	P-value	.	.	.	.	.	<0.001	<0.001
0011	N	96	.	.	99	.	.	92
	Mean RRatio	0.88	.	.	-11.55	.	.	-31.41
	StdDev	26.02	.	.	22.87	.	.	36.30
	P-value	.	.	.	0.001	.	.	<0.001
0034	N	99	87	86	.	88	87	.
	Mean RRatio	-3.89	-6.25	-20.47	.	-28.43	-38.22	.
	StdDev	25.74	23.88	29.56	.	36.63	44.49	.
	P-value	.	0.446	<0.001	.	<0.001	<0.001	.

The primary (ITT) results were complimented by the results in the evaluable population (patients with at least 28 days of double blind seizure diary data) and the completers population. Patients with very limited double-blind diary data were excluded from these populations and, yet, the analyses specific to these populations yielded the same conclusions for the pregabalin vs. placebo group comparisons. As seen in the following table, most of the 600 mg/day patients who were not evaluable withdrew because of adverse events but still had very good efficacy results. Excluding these non-evaluable patients did not affect the conclusions regarding the efficacy of the 600 mg/day groups. The 150 mg/day groups were more comparable to placebo in terms of the amount of double blind seizure diary data provided, so the placebo vs. 150 mg/day group comparisons are fairer and more reliable than the 600. The 150 mg/day groups also had fewer withdrawals due to adverse events and still demonstrated efficacy.

Table 3 Status and Efficacy in Non-Evaluable 600 mg/day Group Patients

		N	Patient Status					Rratio	
			Adverse Event	Lack of Compliance	Lack of Efficacy	Other	Status epilepticus		
			N	N	N	N	N	Mean	Std
Protocol	RXGROUP								
009	600 mg/day BID	18	16	1	.	1	.	-34.7	56.3
	600 mg/day TID	19	16	2	1	.	.	-52.2	55.3
011	600 mg/day TID	15	11	1	1	1	1	-38.8	50.6
034	600 mg/day BID	18	17	.	1	.	.	-70.1	55.9

The protocols allowed for a single interim analysis to take place when approximately half of the patients had completed or withdrawn. The interim analysis was described as for administrative and planning purposes rather than for stopping early. A Haybittle-Peto approach was planned to adjust the significance levels so as not to inflate the type I error. In this approach the tests are conducted at α=0.001 significance level at the interim analysis and α=0.049 at the final analysis. According to the sponsor interim analyses were only conducted in studies 0009 and 0034. The interim analysis results were in line with the final results and did not seem to affect the integrity of the studies.

Each of the three studies involved multiple dose groups and therefore multiple comparisons. Study 009 used the Hochberg procedure to adjust the significance level for the two comparisons, 600 mg/day BID vs. placebo and 600 mg/day TID vs. placebo. This procedure first compares the largest of the two p-values with 0.05[1]. If it is smaller than 0.05 then both comparisons are considered positive. If it is larger than 0.05 then the corresponding comparison is considered not positive and the other comparison, corresponding to the smallest p-value, is compared with the 0.025 level. Studies 011 and 034 controlled between-group comparisons using a step-down procedure starting with the 600-mg/day dose versus placebo. If this comparison was not significant at the 0.05 level, all doses were declared not significantly different 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.

In addition to the pregabalin vs. placebo group comparisons the sponsor reported the results of pairwise comparisons between the different pregabalin groups, but the Hochberg procedure (study 0009) and the step-down procedure (0034) do not cover the pregabalin vs. pregabalin comparisons. Therefore, the pregabalin vs. pregabalin comparisons should be ignored or at least considered exploratory so as to preserve the overall type I error. An exception is the 600 mg/day (TID) vs. 150 mg/day (TID) comparison in study 0011 which is covered by that step-down testing procedure because it is the only pregabalin vs. pregabalin comparison in study 0011 and thus the order of testing is indisputable.

[1] Actually the significance levels are smaller because of the interim analysis: at the final analysis the largest p-value is compared with 0.049 and the smallest with 0.0245.

Study 0009 alone and the three studies taken together permit a comparison of the BID and TID regimens, although the studies were not powered to detect differences in the pregabalin regimens. The 600 mg/day (TID) regimen was numerically better in terms of the mean RRatio than the 600 mg/day (BID) regimen in study 0009, but the combined data from studies 11 and 34 leans in the other direction. Therefore, overall, the two 600 mg/day regimens appear to be roughly equivalent in terms of efficacy. Comparing the treatment effects for the 150 mg/day groups across studies 11 and 34 it appears that the BID regimen is slightly better than the TID regimen, but the data are not conclusive. Therefore, overall, the BID and TID regimens appear to be roughly equivalent in terms of efficacy.

In study 0034 which explored the dose-response relationship most fully it appeared that the dose-response relationship had both a linear and a quadratic term. The fitted quadratic model suggests that the RRatio decreases (i.e., improves) more rapidly as the dose is increased in the lower dose range and less rapidly as the dose is increased in the higher dose range than it would for a purely linear dose-response. Although it was not significant there was a hint of a quadratic component to the dose-response in study 11 also. After pooling the data from studies 11 and 34 the quadratic component was more compelling. This suggests that the 300 mg/day dose (and to a lesser extent the 150 mg/day dose) may achieve nearly the same efficacy as the 600 mg/day group and be more tolerable at the same time, since withdrawals due to adverse events increased with increasing dose also. Unfortunately though, overall, fewer patients were studied at the 300 mg/day dose.

One notable deviation from the protocol was that 25% of all patients provided more than the planned 84 days (12 weeks) of diary data and about 10% provided more than 13 weeks (up to a maximum of 114 days). This was fairly consistent across all three studies. Group differences in the proportion of patients who provided more than 84 days were small, except for the 600 mg/day (TID) group in study 0009 and the 300 and 600 mg/day (BID) groups in study 0034 which had smaller proportions than placebo. This is consistent with the trend for the high dose groups to provide less double blind diary data noted earlier. The sponsor's analyses included double-blind diary data beyond 84 days where applicable. Since the patients who provided more than 84 days of diary data are not a random sample of the ITT population (may have important differences from those who did not), including the data beyond 84 days may cause bias. However, this reviewer found no significant changes in the results after excluding data beyond 84 days.

Finally, note that there are very slight differences in the sponsor's and this reviewer's analyses because the sponsor included randomized patients with no double blind seizure diary data by assuming that these patients had no change from the baseline seizure rate, whereas this reviewer excluded such patients. However, there were only nine such patients among the three studies and the conclusions are the same regardless of their inclusion/exclusion.

2 INTRODUCTION

2.1 Overview

The new molecular entity, Pregabalin [CI-1008, (S)-3-(aminomethyl)-5-methylhexanoic acid], which is an analogue of the mammalian neurotransmitter gamma-aminobutyric acid (GABA), is being investigated as an anticonvulsant for the treatment of patients with partial seizures. This agent is also being investigated for the treatment of chronic pain, as well as for treatment of [redacted] The mechanism of pregabalin appears different from agents that alter GABA receptors or uptake carriers, Na^+ channel blockers, opiates, or nonsteroidal anti-inflammatory drugs.

In the application the sponsor highlighted the efficacy of Pregabalin in three randomized, double-blind, multi-center, placebo controlled add-on studies in patients with refractory partial seizures. Each of these studies (study numbers 0009, 0011, and 0034) consisted of three phases: screening, an 8-week baseline period, and a 12-week double-blind period. Patients on stable doses of several (1-3[2]) AEDs were maintained on their medications and were randomized to also receive one of several fixed doses of Pregabalin or matching placebo. To be eligible for randomization patients had to have at least six seizures in the eight week baseline period with no 4-week seizure free period. Seizures were to be recorded by the patients, a family member, or legal guardian and documented in a daily seizure diary. The principal efficacy measure, termed the RRatio, is 100 times the difference in double-blind and baseline seizure rates (per 28 days) divided by the sum of the double-blind and baseline seizure rates (per 28 days). Studies 0009 and 0034 were conducted in the U.S. and Canada with the vast majority of centers in the U.S. Study 0011 was conducted exclusively in Europe.

[2] One patient was on 4 and thus exceeded the protocol limit of 3

Study 0007 was a small proof of concept monotherapy study. This study was not thoroughly reviewed here because it involved monotherapy rather than adjunctive therapy and had a low dose active control instead of a placebo control. It also had a shorter treatment period of variable length (up to 8 days). In particular, if certain seizure activity criteria were satisfied the patient was withdrawn from the study and the time of withdrawal was noted. The primary efficacy endpoint in this study was time to withdrawal rather than a measure of seizure frequency. Although the results appeared to favor 600 mg/day Pregabalin, the study failed to clearly demonstrate the superiority of 600 mg/day Pregabalin over the low-dose active control, 300 mg/day Gabapentin.

2.2 Data Sources

The locations of the data (SAS transport files) are as follows:

Study 0009: \\cdsesub1\n21446\n_000\2003-10-30\crt\datasets\00009
Study 0011: \\cdsesub1\n21446\n_000\2003-10-30\crt\datasets\00011
Study 0034: \\cdsesub1\n21446\n_000\2003-10-30\crt\datasets\00034

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study 1008-009

3.1.1.1 Objectives

- To evaluate the efficacy of 2 regimens of pregabalin or placebo as add-on treatment in patients with partial seizures.

- To assess the safety of pregabalin by comparing the frequency and severity of adverse events and clinical laboratory values during treatment with either pregabalin regimen or placebo as add-on treatment.

3.1.1.2 Study Design

A total of 240 patients with medically uncontrolled partial seizures will participate in this randomized, double-blind, parallel-group, multicenter study. There will be 6 to 12 patients per site. Participants will be patients who are receiving 1 to 3 standard AEDs at doses within an acceptable therapeutic range. Approximately 6 to 12 patients will be enrolled at each site. This study is comprised of 3 phases: (1) an 8-week baseline phase; (2) a 12-week double-blind phase, including a 7-day study drug titration; and (3) a withdrawal phase for patients choosing to exit the study.

To qualify for the study patients must have at least 3 partial seizures during the 1 month preceding entry to baseline. Patients meeting the inclusion/exclusion criteria on the first baseline visit (Visit B1) are enrolled in the study. Patients will continue their current AEDs at the same dosages throughout the baseline. They return at 4-week intervals for 2 additional visits, one during the baseline phase (Visit B2), and one at the end of the baseline (i.e., Visit DB1, the first double-blind visit) at which time seizure counts will be assessed to determine a baseline seizure frequency and to confirm eligibility to be randomized. Seizures are defined here as partial seizures. The patient must have at least 6 partial seizures during the 8-week baseline phase and no 4-week seizure-free period.

As assessed during Visit DB1 (Week 8), patients who continue to meet the inclusion/exclusion criteria, and who have had at least 6 partial seizures during the 8-week baseline phase with no 4-week seizure-free period, are eligible to enter the double-blind phase. The 12-week double-blind treatment begins the day following randomization to 1 of 3 treatment groups: pregabalin 200 mg given TID, pregabalin 300 mg given BID, or placebo administered TID. Patients are titrated to either pregabalin treatment or placebo over 7 days in a blinded fashion beginning the day after Visit DB1. Patients will continue their concurrent standard AEDs at the same dosages administered during baseline. Following randomization and initiation of DB medication, 4 visits follow at the ends of Double-Blind Weeks 2, 4, 8, and 12.

3.1.1.3 Efficacy Assessments

Primary

The principal efficacy criterion will be the reduction in the frequency of all partial seizures during the double-blind treatment period as compared with the baseline period. Seizures will be recorded by the patients, a family member, or legal guardian and documented in a daily seizure diary. The primary efficacy parameter is response ratio (RRatio or symmetrized percent change), a comparison of baseline seizure rate (B) with treatment seizure rate (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 seizure rates. RRatio = $[(T-B)/(T+B)] \times 100$.

Secondary

Secondary efficacy parameters are the response rate, defined as the proportion of patients who have a ≥50% reduction in seizure rate during treatment as compared to the baseline and the percent change (PCH) in 28-day seizure rates in treatment as compared to baseline.

3.1.1.4 Statistical Analysis Plan

Analysis Populations

The primary population will be the ITT population, defined as all patients randomized to treatment who receive at least one dose of study medication.

A secondary population will be the Evaluable population, defined as all patients who are randomized to study medication, received 28 days of study medication, and have a minimum of 28 days of seizure diary data evaluable within both the baseline phase and the double-blind phase.

Sample Size

The sample size estimate is based on the primary efficacy parameter, response ratio, and the secondary parameter responder rate. Based on previous add-on trials with Neurontin (945-210P, 945-05, 945-06), assumptions for mean response ratio at the final visit are -15 (±25) for the pregabalin treatment and -3 (±25) the placebo treatment, with a 12 point difference between treatments. Assuming a 10% dropout rate, a total of 80 patients will be randomized to provide 70

patients per treatment group in the Evaluable population and provide 80% power ($\alpha = 0.05$, 2-sided) for both the primary ITT and secondary Evaluable populations.

Pooling of Centers
This study will enroll a total of 240 patients with 6 to 12 patients per site. Up to 24 patients will be allowed at centers that have met the specified enrollment goals. Centers will be managed by pooling small centers (n <18 patients) of the same region. A cluster is a single center (at least 18 patients) or an aggregation of centers which are located in the same country, or region, or if possible in the same area (town or part of a town). The nearest center is added to a cluster until a minimum of 18 patients is reached. The clustering will be done before the code breaking.

Primary Analysis
The primary efficacy variable will be the rank of the response ratio (RRatio or symmetrized percent change) for all partial seizures across all patients at end point of the study (Week 20/Termination). ITT patients with no seizure diary will be assigned a missing value. The primary population will be the ITT population using Week 20/end point RRatio for completers or last RRatio up to and including the last diary entry for those withdrawing prior to Week 20. ITT patients with no double-blind seizure diary data will carry forward the baseline seizure data for the double-blind seizure rate. Analysis will be performed using an analysis of variance (ANOVA) model with treatment (as main effect) and center (cluster), and the ranking of the RRatio as the dependent variable ($\alpha = 0.05$, 2-sided).

Pairwise treatment comparisons will use a Hochberg procedure with the 200-mgTID dose versus placebo and the 300 mg BID versus placebo comparisons. The ranked p-values (largest to smallest) of the 2 comparisons will be tested against $\alpha = 0.05$ and 0.025, respectively. If the largest p-value is <=0.05 then both comparisons are considered positive. If the largest p-value is greater than 0.05 then the comparison with the smallest p-value is only positive if the p-value is <=0.025. In addition, 95% confidence intervals will be provided for all pairwise comparison differences versus placebo and 200 mg TID versus 300 mg BID.

Secondary Analysis
The responder rate will be compared between treatments using a Cochran Mantel- Haenszel chi-square analysis stratified by center (cluster), at the Week 20/endpoint ($\alpha = 0.05$, 2-sided) with the ITT Population. Treatment comparisons will be done using the same Hochberg procedure as in the primary analysis. Confidence intervals of 95% will be provided for all pairwise comparison differences versus placebo and 200 mg TID versus 300 mg BID.

All 3 efficacy parameters will be summarized by treatment group for each seizure type. These include the following:
- All partial seizures;
- Simple partial;
- Complex partial;
- [redacted]

• Partial seizures without secondary generalization.

Re-Estimation of Sample Size
The withdrawal rate for patients not completing 28 days in either baseline or double-blind will be blindly monitored while the study is ongoing. Any trend in the rate to increase considerably from 10% may require a sample size adjustment upward.

Interim Analysis
An interim analysis may be conducted when the first 120 patients have been randomized and either completed 12 weeks in double-blind or withdrawn from the study. The interim analysis will evaluate only the primary efficacy parameter RRatio. The purpose of the interim analysis is administrative. A Haybittle-Peto method will be applied, using $\alpha = 0.001$ at the interim and $\alpha = 0.049$ at the final analysis.

Notable amendments to the original protocol

- The primary endpoint was changed from the RRatio to the rank over all patients of the RRatio.
- The Multiple Comparisons adjustment procedure was changed from Step-down starting with 200 mg TID dose to Hochberg.
- Definition of clusters for pooling small centers and the use of clusters instead of individual centers in the analyses.
- Primary population changed from Evaluable (all randomized patients with at least 28 days of diary data in both the baseline and double-blind periods) to ITT (all randomized patients who received at least one dose). The sponsor will carry the baseline seizure rate forward for ITT patients with no double-blind seizure diary data.
- Maximum number of patients allowed per center increased from 12 to 24.

3.1.1.5 Study Population

A total of 313 patients were randomized 98 (31.3%) to placebo 111 (35.5%) to 600 mg/day (TID) Pregabalin and 104 (33.2%) to 600 mg/day (BID) Pregabalin. Of these 7 placebo, 19 600 mg/day (TID) and 20 600 mg/day (BID) had less than 28 days of seizure diary data for the double-blind treatment period. During the study, 76 patients (24%) withdrew, resulting in an overall completion rate of 76%. More patients in the placebo group than either pregabalin group withdrew 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. The completion rate was slightly higher in the placebo group (83%) than the pregabalin groups (77% for TID and 68% for BID).

Table 4 Study 0009: Patient Disposition

Population	Placebo	Pregabalin 600 mg/day (TID)	Pregabalin 600 mg/day (BID)	All Patients N (%)[a]
Randomized to Treatment	98	111	104	313 (100)
Total Included in ITT	98	111	103	312 (99.7)
Total Excluded From ITT			1	
Did Not Take Study Medication			1	
Total Included in Evaluable Patient Population	91	91	83	263 (84.7)
Total Excluded from Evaluable Patient Population[b]	7	20	20	
<28 Days of Seizure Diary Data During Baseline	0	1	0	
<28 Days of Seizure Diary Data During Double-Blind	7	19	20	
<28 Days of Double-Blind Study Medication	7	19	19	

[a] Percentage of patients based on number of patients randomized to treatment

[b] A patient may have had more than one reason for his or her data being excluded.

table copied from Table 4 of Pfizer's research report RR 720-04094 1008-009 (Page 35)

Population Demographics at Baseline

Of the 312 ITT patients, 111 (57 men and 54 women) received pregabalin TID, 103 (49 men and 54 women) received pregabalin BID, and 98 (50 men and 48 women) received placebo. The 3 treatment groups were well-matched on demographic parameters, including age, sex, and race. Most patients in the study were white (85%) and had a mean (range) estimated creatinine clearance at baseline of 106.4 mL/min (39-220 mL/min).

Table 5 Study 0009: Baseline Demographic Characteristics

Characteristic	Placebo		Pregabalin 600 mg/day (TID)		Pregabalin 600 mg/day (BID)		All Pregabalin		All Patients	
	N = 98		N = 111		N = 103		N = 214		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 copied from Table 5 of Pfizer's Research Report RR 720-04094 1008-009 (Page 37)

There were minor group differences in age at diagnosis and duration of epilepsy. The 600 mg/day (BID) group had a higher proportion of patients with 3 or 4 concurrent AEDs than the placebo and 600 mg/day (TID) groups. There were also slight differences in the etiology of epilepsy.

Table 6 Study 0009: Summary of Epilepsy History

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 copied from Table 6 of Pfizer's Research Report RR 720-04094 1008-009 (Page 39)

The treatment groups were similar with respect to history of types of seizures experienced and baseline phase seizure frequency.

Table 7 Study 0009: Summary of Disease Characteristics

	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

table copied from Table 7 of Pfizer's Research Report RR 720-04094 1008-009 (Page 40)

3.1.1.6 Sponsor's Results

A higher proportion of placebo patients completed the study than Pregabalin 600 mg/day (TID) or Pregabalin 600 mg/day (BID). The most frequent reason given for withdrawal was adverse events (17%) and the proportion was higher in the Pregabalin groups than placebo. The next most frequent reason for withdrawal was lack of efficacy (2.6 %) and a higher proportion of placebo patients withdrew for lack of efficacy.

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Table 8 Study 0009: Patient Disposition II

Disposition	Placebo	Pregabalin 600 mg/day (TID)	Pregabalin 600 mg/day (BID)	All Patients
	N = 98	N = 111	N = 104	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%)

This table was copied from Table 10 of Pfizer's Research Report RR 720-04094 1008-009 (Page 44)

Primary Analysis

The primary analysis, an ANOVA of the ranks of the RRatios adjusted for clusters (pooled centers), showed that both Pregabalin 600 mg/day groups were superior to placebo in terms of efficacy. Although the 600 mg/day (TID) group had a smaller mean RRatio than the 600 mg/day (BID) group, suggesting more improvement, the difference was not statistically significant so the two dosing regimens were equally efficacious. Note that although the mean RRatios are shown in the tables the primary analysis was conducted on the ranks of the RRatios as planned.

Table 9 Study 0009: Summary Statistics for RRatio (All Partial Seizures): ITT Population

Response Ratio	Placebo	PGB 600 mg/day (TID)	PGB 600 mg/day (BID)
	N = 98	N = 111	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

This table was copied from Table 11 of Pfizer's Research Report RR 720-04094 1008-009 (Page 47)

Table 10 Study 0009: 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

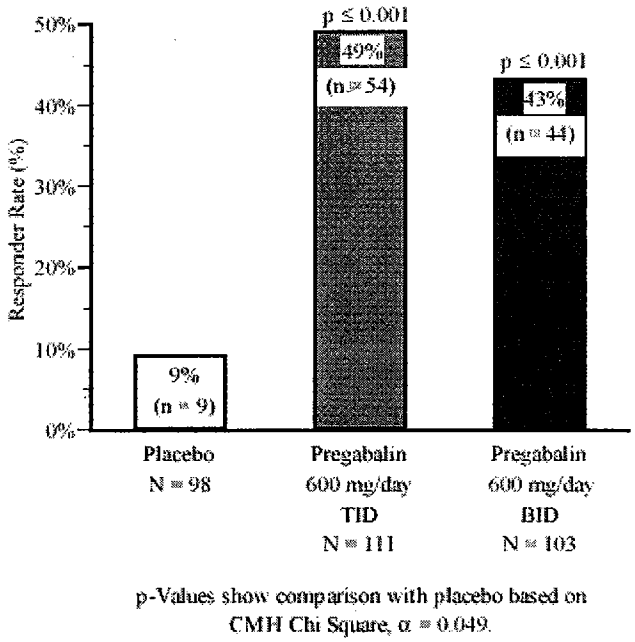
PGB = Pregabalin; PBO = Placebo.
* = Statistically significant based on Hochberg's procedure (p ≤0.049).
[a] Based on treatment means for the raw RRatio
[b] Hochberg procedure applied to the ranked RRatio
[c] Treatment-by-cluster interaction for the ranked RRatio
[d] N for Group 1/N for Group 2

This table was copied from Table 12 of Pfizer's Research Report RR 720-04094 1008-009 (Page 47)

Secondary Analyses

A patient was classified as a responder if he/she experienced at least a 50% reduction in DB seizure frequency compared to baseline seizure frequency. Results of the analysis of responder rate for all partial seizures showed highly significant differences between pregabalin and placebo for both the TID (p<= 0.001) and BID (p<= 0.001) treatment groups. The responder rates for TID and BID were similar and not statistically significantly different.

Figure 2 Study 0009: Responder Rates for all partial seizures



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

This figure was copied from Figure 3 of Pfizer's Research Report RR 720-04094 1008-009 (Page 48)

3.1.1.7 Reviewer's Results

Eight of the seventeen 600 mg/day group (BID or TID) patients who became seizure free had 7 days or less of double blind seizure diary data. This reviewer also noticed that the standard deviations of the RRatios were significantly higher for the 600 mg/day (BID) and 600 mg/day (TID) groups than the placebo group. In fact, both the observed RRatios and the ranks of the RRatios failed a test for equal group variances, thus violating an assumption of the primary analysis method (ANOVA). In order to check the robustness of the results this reviewer employed several other methods which are more appropriate when group variances are not equal. These alternative methods were the Van-Elteren test (a cluster stratified (nonparametric) Wilcoxon rank sum test) and Welch's ANOVA, which do not assume equal group variances, and an ANOVA with observations weighted according to the number of diary entries in the double-blind treatment period. Another problem with the ordinary unweighted ANOVA is that it does not account for the fact that seizure rates (and RRatios) based on less diary data are less reliable. The weighted ANOVA gives more weight to patients with more diary data than to those with less diary data and in so doing helps to correct the observed group differences in the variability of the RRatios. These alternative analysis methods all yielded the same conclusions so the primary analysis results seem to be robust and the non-constancy of the variance does not seem to be a problem in this case.

The primary analysis population was the ITT population - all randomized patients that had at least one day of double-blind seizure diary data. To check for sensitivity of the results to the effect of dropouts and incomplete diary data, analyses were carried out on the Evaluable and Completers populations. The evaluable population excluded patients with less than 28 days of seizure diary data. This reviewer defined the completers population as all randomized patients that completed at least part of all 3 months of the double-blind phase. It appears that the sponsor's completers population included some patients that opted to enter the open label extension before the beginning of the third month. Nevertheless, the sponsor's and this reviewer's results were similar for their respectively defined completers populations. The results seem to be insensitive to the exclusion of incomplete diaries and dropouts.

Table 11 Study 0009: Primary Analysis Results for Primary Population (ITT) and Secondary Populations

POPULATION	RRATIO	PLACEBO	600 MG/DAY(TID)	600 MG/DAY(BID)
ITT	N	98	110	101
	Mean	0.58	-36.45	-28.94
	Std. Dev.	28.85	40.05	36.83
	Comparison with Placebo P-value	.	<0.0001	<0.0001
Evaluable[#]	N	91	91	83
	Mean	-1.85	-33.15	-27.68
	Std. Dev.	26.63	35.60	31.46
	Comparison with	.	<0.0001	<0.0001

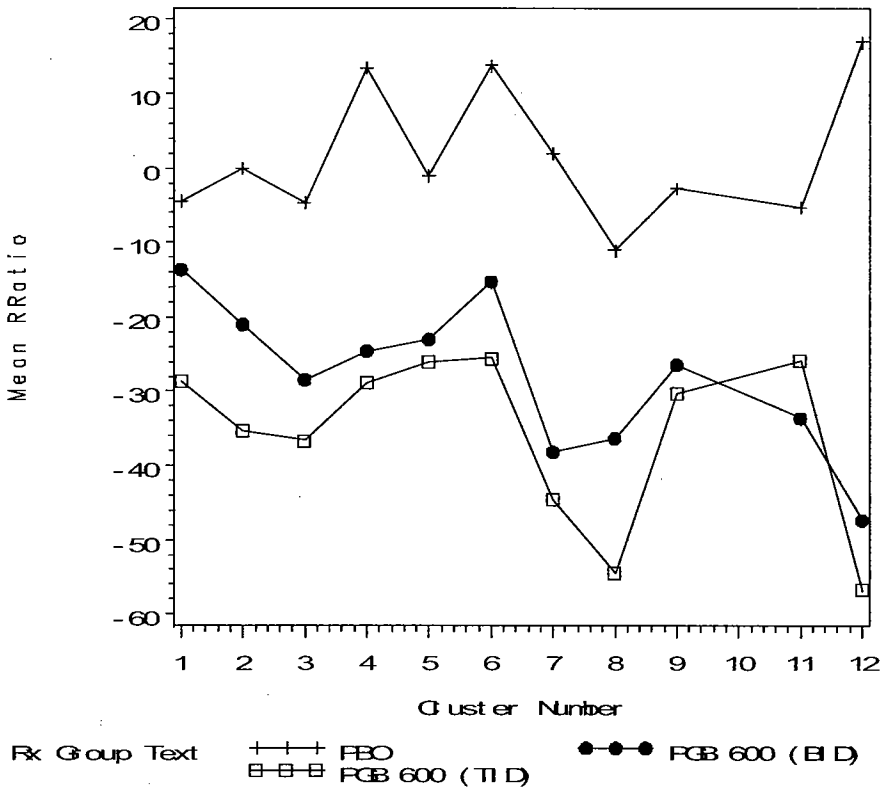
POPULATION	RRATIO	PLACEBO	600 MG/DAY(TID)	600 MG/DAY(BID)
	Placebo P-value			
Completer*	N	88	86	76
	Mean	-3.06	-32.78	-28.75
	Std. Dev.	25.85	35.78	31.58
	Comparison with Placebo P-value		<0.0001	<0.0001

Had at least 28 days of seizure diary data in both baseline and double-blind periods
* Had double blind seizure diary data in all 3 months

Impact of Individual Sites and Clustered Sites

Clusters were formed by pooling sites according to geographic proximity until each cluster had at least 18 patients. The within cluster results were reasonably consistent across all clusters and the overall results were not excessively influenced by or dependent on any one cluster (or site).

Figure 3 Study 0009: Group Mean RRatios within each Cluster



Interim Analysis

The sponsor conducted a single interim analysis after the first 129 patients. A Haybittle-Peto approach was planned to adjust the significance levels so as not to inflate the type I error. In this approach the tests are conducted at α=0.001 significance level at the interim analysis and α=0.049 at the final analysis. Both the 600 mg/day (BID) and 600 mg/day (TID) vs. placebo comparisons based on the ANOVA for the ranks of the RRatios had p-values less than the 0.001 critical level for the interim analysis. However, the sponsor stated that the interim analysis was for administrative purposes only, so the study was not terminated early. Ninety Six percent of Placebo patients involved in the interim analysis completed at least part of all 3 double-blind study months compared to 85% of placebo patients that were randomized after the interim analysis. Also, the mean RRatio of placebo patients was worse for those that were not involved in the interim analysis: 4.07 (+/- 4.24 S.E.) compared to -3.54 (+/- 3.88 S.E.). However, these differences are small enough and the results at the interim analysis are strong enough that the interim analysis doesn't seem to have adversely affected the integrity of the study.

The planned sample size, 240 total patients, was exceeded by 62 (26%). This reviewer carried out an additional analysis on the first 240 patients randomized. It was found that the additional patients had no effect on the significance of any of the group comparisons. The addition of the 62

patients did slightly increase the difference between the 600 mg/day (BID) and 600 mg/day (TID) groups (2 point difference in mean RRatios).

3.1.2 Study 1008-011

3.1.2.1 Objectives

To evaluate the efficacy and dose-response characteristics of 2 doses of pregabalin or placebo as add-on treatment in patients with partial seizures.

To assess the safety of pregabalin by comparing the frequency and severity of adverse events and clinical laboratory values during treatment with either pregabalin regimen or placebo as add-on treatment.

3.1.2.2 Study Design

A total of 240 patients with medically uncontrolled partial seizures will participate in this randomized, double-blind, parallel-group, multicenter study. Participants will be patients who are receiving 1 to 3 standard AEDs at doses within an acceptable therapeutic range. Approximately 6 to 12 patients will be enrolled at each site.

This study is comprised of 3 phases: (1) an 8-week baseline phase; (2) a 12-week double-blind phase, including a 7-day study drug titration; and (3) a withdrawal phase for patients choosing to exit the study. Those patients choosing to continue treatment, a double-blind transition of study medication will be provided into the follow-on study (1008-012).

To qualify for the study patients must have at least 3 partial seizures during the 1 month preceding entry to baseline. Patients will continue their current AEDs at the same dosages throughout baseline. Patients return at 4-week intervals for 2 additional visits, one during baseline (Visit B2), and one at the end of baseline (Visit DB1), the first double-blind visit, at which time seizure counts will be assessed to determine a baseline seizure frequency and to confirm eligibility to be randomized. 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.

As determined at Visit DB1, patients who continue to meet inclusion/exclusion criteria, and who have had at least 6 partial seizures during the 8-week baseline phase with no 4-week seizure-free period, are eligible to enter the double-blind phase. The 12-week double-blind treatment begins the day following randomization to 1 or 3 treatment groups: pregabalin 150 mg/day, pregabalin 600 mg/day, or placebo administered TID. Patients are titrated to either pregabalin treatment or placebo over 7 days in a blinded fashion beginning the day after Visit DB1. Patients will continue their concurrent standard AEDs at the same dosages administered during baseline.

Following randomization and initiation of DB medication 4 visits follow in 2- or 4-week intervals (DB2; DB3; DB4, and DB5/Term).

3.1.2.3 Efficacy Assessments

Primary

The principal efficacy criterion will be the reduction in the frequency of all partial seizures during the double-blind treatment period as compared with the baseline period. Seizures will be recorded by the patients, a family member, or legal guardian and documented in a daily seizure diary. The primary efficacy parameter is response ratio (RRatio or symmetrized percent change), a comparison of baseline seizure rate (B) with treatment seizure rate (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 seizure rates. RRatio = $[(T-B)/(T+B)] \times 100$.

Secondary

Secondary efficacy parameters are the response rate, defined as the proportion of patients who have a ≥50% reduction in seizure rate during treatment as compared to the baseline and the percent change (PCH) in 28-day seizure rates in treatment as compared to baseline.

3.1.2.4 Statistical Analysis Plan

Analysis Populations

The primary population will be the ITT population, defined as all patients randomized to treatment who receive at least one dose of study medication.

A secondary population will be the Evaluable population, defined as all patients who are randomized to study medication, received 28 days of study medication, and have a minimum of 28 days of seizure diary data evaluable within both the baseline phase and the double-blind phase.

Sample Size

The sample size estimate is based on the primary efficacy parameter, response ratio, and the secondary parameter responder rate. Based on previous add-on trials with Neurontin (877-210P, 945-05, 945-06), assumptions for mean response ratio (in decimal form from previous studies) at the final visit are -15 (±25) for the pregabalin treatment and -3 (±25) the placebo treatment, with a 12 point difference between treatments. Assuming a 10% dropout rate, a total of 80 patients will be randomized to provide 70 patients per treatment group in the Evaluable population and provide at least 80% power ($\alpha = 0.05$, 2-sided) in both the primary ITT and secondary Evaluable analyses.

Pooling of Centers

The study will enroll a total of 240 patients with 6 to 12 patients per site. Up to 36 patients will be allowed at centers that have met the specified enrollment goals. Centers will be managed by pooling small centers (n <18 patients) of the same region. A cluster is a single center (at least 18 patients) or an aggregation of centers which are located in the same country, or region, or if possible, in the same area (town or part of a town). The nearest center is added to a cluster until a minimum of 18 patients is reached. The clustering will be done before the code breaking.

Primary Analysis
The primary efficacy variable will be the rank of the response ratio (RRatio or symmetrized percent change) for all partial seizures across all patients at end point of the study (Week 20/Termination). ITT patients with no double-blind seizure diary will carry forward the baseline seizure rate for the double-blind seizure rate. The primary population will be the ITT population using Week 20/end point RRatio for completers or RRatio up to and including the last diary entry for those withdrawing prior to Week 20. The RRatio will be ranked across patients and analysis will be performed using an analysis of variance (ANOVA) model with treatment (as main effect) and center (cluster), and the ranking of the RRatio as the dependent variable (α = 0.05, 2-sided).

Pairwise treatment comparisons will follow overall significant treatment results and use a step-down procedure starting with the 600 mg/day dose versus placebo as the primary comparison, followed by 150 mg/day dose versus placebo and then 600 mg/day vs. 150 mg/day. In addition, 95% confidence intervals will be provided for all pairwise comparison differences versus placebo and 600 mg/day versus 150 mg/day.

The primary analysis (ANOVA) main model will be used with treatment x center added to the model to test the significant interaction (α=0.05 as strong evidence against generalizability).

Secondary Analysis
The responder rate will be compared between treatments using a Cochran-Mantel-Haenszel chi-square analysis stratified by center (cluster), at the Week 20/endpoint (α = 0.05, 2-sided) with the ITT Population. Treatment comparisons will be done using the same pairwise step-down procedure as in the primary analysis. Confidence intervals of 95% will be provided for all pairwise comparison differences versus placebo and 600 mg/day versus 150 mg/day.

Percent change in 28-Day Seizure Rate will be summarized by treatment group at the Week 20/endpoint. No inferential analysis will be performed as this endpoint is a direct transformation of the RRatio.

All 3 efficacy parameters will be summarized by treatment group for each seizure type. These include the following:
- All partial seizures;
- Simple partial;
- Complex partial;
- Partial seizures with secondary generalization; and
- Partial seizures without secondary generalization.

Re-Estimation of Sample Size
The withdrawal rate for patients not completing 28 days in either baseline or double-blind will be blindly monitored while the study is ongoing. Any trend in the rate to increase considerably from 10% may require a sample size adjustment upward.

Interim Analysis

An interim analysis may be conducted when the first 120 patients have been randomized and either completed 12 weeks in double-blind or withdrawn from the study. The interim analysis will evaluate only the primary efficacy parameter RRatio. The purpose of the interim analysis is administrative. A Haybittle-Peto method will be applied, using $\alpha = 0.001$ at the interim and $\alpha = 0.049$ at the final analysis.

Notable amendments to the original protocol

- The primary endpoint was changed from the RRatio to the rank over all patients of the RRatio.
- Definition of clusters for pooling small centers and use of clusters instead of individual centers in the analyses.
- Primary population changed from Evaluable (all randomized patients with at least 28 days of diary data in both the baseline and double-blind periods) to ITT (all randomized patients who received at least one dose). ITT patients with no diary data will have baseline seizure rate carried forward.
- Number of patients allowed at a particular site was originally 6-12. It was first increased to allow a maximum of 24 at one site and then further increased to allow up to 36 at that site.

3.1.2.5 Study Population

A total of 288 patients were randomized: 97 (33.7%) to placebo, 99 (34.4%) to 150 mg Pregabalin and 92 (31.9%) to 600 mg Pregabalin. 8 Placebo, 8 150 mg Pregabalin and 15 600 mg Pregabalin patients had less than 28 days of seizure diary data for the double blind treatment period. A total of 47 (16.3%) patients withdrew during the double blind period: 13 (13.4%) Placebo, 11 (11.1%) 150 mg Pregabalin, and 23 (25.0%) 600 mg Pregabalin.
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 Study 0011: Patient Disposition

Population	Placebo	Pregabalin 150 mg/day	Pregabalin 600 mg/day	All Patients N (%)[a]
Randomized to Treatment	97	99	92	288 (100)
Total Included in ITT	96	99	92	287 (99.7)
Total Excluded From ITT	1	0	0	
Did Not Take Study Medication	1			
Total Included in Evaluable Patient Population	88	91	77	256 (88.9)
Total Excluded From Evaluable Patient Population[b]	8	8	15	
<28 Days of Seizure Diary Data During Baseline	0	0	0	
<28 Days of Seizure Diary Data During Double-Blind	8	8	15	
<28 Days of Double-Blind Study Medication	8	8	14	

[a] Percentage of patients based on number of patients randomized to treatment
[b] A patient may have had more than one reason for their data being excluded.

table copied from Table 4 of Pfizer's Research Report RR 720-04098 1008-011 (Page 37)

Population Demographics

Of the 287 ITT patients, 92 (47 men and 45 women) received 600 mg/day pregabalin, 99 (44 men and 55 women) received 150 mg/day pregabalin, and 96 (54 men and 42 women) received placebo. The majority of patients in the study were white (93%), had a mean age of 37 years, and had a mean estimated creatinine clearance of 110.3 mL/min at baseline.

Table 13 Study 0011: Baseline ITT Population Demographics

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 copied from Table 5 of Pfizer's Research Report RR 720-04098 1008-011 (Page 39)

Several patients with potentially clinically important protocol deviations participated in the study. One patient took 4 concomitant AEDs in addition to pregabalin. A total of 5 patients entered the study with estimated creatinine clearances that were not > 60 ml/min. Additionally, 6 patients who had less than the protocol-specified minimum of 6 partial seizures during the 8-week baseline phase participated in the trial but no patient had any 4-week seizure-free period during the baseline phase.

Minor differences were noted in the historical parameters describing age at diagnosis and duration of epilepsy. There were also slight differences among the treatment groups in the number of concurrent AEDs patients were taking and etiology of epilepsy. The treatment groups were similar with respect to baseline seizure frequency and the types of seizures patients had experienced at any time prior to baseline, but a slightly higher proportion of patients in both the pregabalin 600 mg/day group (6.5%) and the pregabalin 150 mg/day group (9.1%) had a history of generalized seizures compared to the placebo group (3.1%)..

Table 14 Study 0011: Summary of Epilepsy History

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 copied from Table 8 of Pfizer's Research Report RR 720-04098 1008-011 (Page 42)

Table 15 Study 0011: Summary of Disease Characteristics

	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

table copied from Table 9 of Pfizer's Research Report RR 720-04098 1008-011 (Page 43)

3.1.2.6 Sponsor's Results

The proportions of patients that completed the study were similar in the placebo (86.6%) and Pregabalin 150 mg/day (TID) (88.9%) groups, but the proportion in the 600 mg/day (TID) group was slightly smaller (75.0%). The most frequent reason given for withdrawal was adverse events (11.5%). The proportions that withdrew due to an adverse event were higher in the Pregabalin groups than placebo and the proportions appeared to increase with the Pregabalin dose. The next most frequent reason for withdrawal was lack of efficacy (2.1 %) and a higher proportion of placebo patients withdrew for lack of efficacy.

Table 16 Study 0011: Patient Disposition II

Disposition	Placebo		PGB 150 mg/day		PGB 600 mg/day		All Patients	
	N = 97		N = 99		N = 92		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)

Table copied from Table 12 of Pfizer's Research Report RR 720-04098 1008-011 (Page 47)

Primary Analysis

The primary analysis, an ANOVA of the ranks of the RRatios adjusted for clusters (pooled centers), showed that both the 600 mg/day (TID) and the 150 mg/day (TID) Pregabalin groups were superior to placebo in terms of efficacy ($p < 0.0001$ and $p = 0.0007$, respectively). The higher dose was found to be more effective based on a pairwise comparison of the two doses ($p < 0.0001$) and also a significant linear trend in dose-response ($p < 0.0001$).

Table 17 Study 0011: Summary Statistics for RRatio (All Partial Seizures): ITT 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 copied from Table 13 of Pfizer's Research Report RR 720-04098 1008-011 (Page 49)

Table 18 Study 0011: Summary of RRatio Analysis (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†			

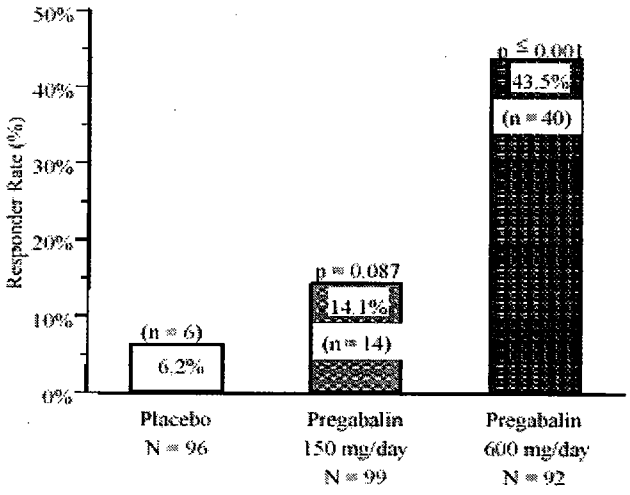
* Statistically significant based on the Ruberg procedure (p ≤0.05).
† Statistically significant (p ≤0.05).
[a] Based on means for the untransformed RRatio data
[b] N in Group 1/N in Group 2
[c] Treatment-by-cluster interaction for the model-ranked RRatio
[d] Linear contrast

table copied from Table 14 of Pfizer's Research Report RR 720-04098 1008-011 (Page 50)

Secondary Analyses

A patient was classified as a responder if he or she had at least a 50% reduction in seizure rate compared to the baseline seizure rate. The proportion of responders in the 600 mg/day (TID) group was significantly higher than the proportion in the placebo group (43.5 % to 6.2 % p<=0.001). The difference between the 150 mg/day (TID) group and the placebo group in proportions responding approached but did not achieve significance (14.1 % vs. 6.2% p=0.087). The proportion responding in the 600 mg/day (TID) group was also significantly higher than the proportion responding in the 150 mg/day (TID) group (p<0.001).

Figure 4 Study 0011: Responder Rates: ITT Population



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

figure copied from Figure 3 of Pfizer's Research Report RR 720-04098 1008-011 (Page 51)

3.1.2.7 Reviewer's Results

Four out of the seven Pregabalin patients (1/1 150 mg/day and 3/6 600 mg/day) who became seizure free had 7 days or less of double blind seizure diary data. This reviewer noticed that the standard deviation of the RRatios was higher for the 600 mg/day group than the 150 mg/day and placebo groups. This may be attributable to the fact that although more of the 600 mg group patients improved than in the other groups there were also a few 600 mg/day patients near the worst part of the RRatio range, i.e., +100. Nevertheless, this reviewer verified that the 600 mg/day and 150 mg/day groups were significantly improved compared to the placebo group based on the primary analysis of the RRatio (both $p<0.0001$) in the ITT population. The 600 mg/day group was also significantly better than the 150 mg/day group ($p<0.0001$).

The primary analysis population was the ITT population - all randomized patients that had at least one day of double-blind seizure diary data. To check for sensitivity of the results to the effect of dropouts and incomplete diary data, analyses were also carried out on the Evaluable and Completers populations. The evaluable population excluded patients with less than 28 days of seizure diary data. This reviewer defined the completers population as all randomized patients that completed at least part of all 3 months of the double-blind phase. It appears that the sponsor's completers population included some patients that opted to enter the open label extension before the beginning of the third month. Nevertheless, the sponsor's and this reviewer's results were similar for their respectively defined completers populations. Although there were fewer 600 mg/day patients than 150 mg/day or placebo patients in the evaluable and completers populations the conclusions seem to be insensitive to the exclusion of incomplete diaries and dropouts.

Table 19 Study 0011: Primary Analysis Results for Primary Population (ITT) and Secondary Populations

POPULATION	RRATIO	PLACEBO	150 MG/DAY(TID)	600 MG/DAY(TID)
ITT	N	96	99	92
	Mean	0.88	-11.55	-31.41
	Std. Dev.	26.02	22.87	36.30
	Comparison with Placebo P-value	.	0.0005	<0.0001
Evaluable#	N	88	91	77
	Mean	-1.01	-11.54	-29.97
	Std. Dev.	25.20	21.10	33.05
	Comparison with Placebo P-value	.	0.0013	<0.0001
Completer*	N	85	89	71
	Mean	-0.97	-11.45	-31.85
	Std. Dev.	25.33	21.25	29.90
	Comparison with Placebo	.	0.0014	<0.0001

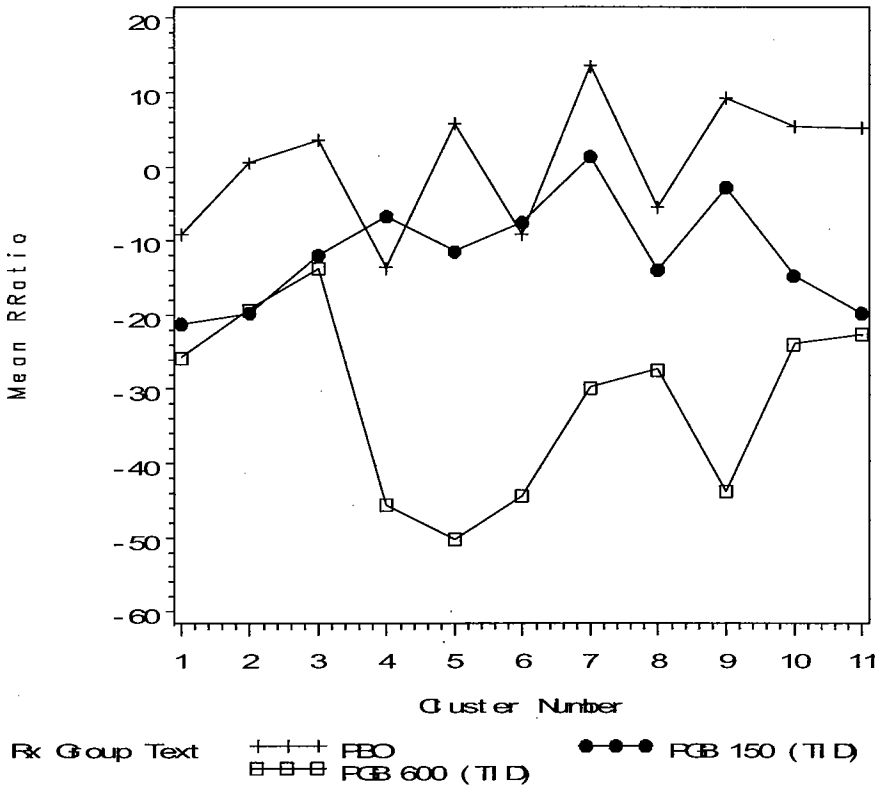
	P-value			

Had at least 28 days of seizure diary data in both baseline and double-blind periods
* Had double blind seizure diary data in all 3 months

Impact of Individual Sites and Clustered Sites

Clusters were formed by pooling sites according to geographic proximity until each cluster had at least 18 patients. The within cluster results were reasonably consistent across all clusters and the overall results and group comparisons were not excessively influenced by or dependent on any one cluster (or site).

Figure 5 Study 0011: Group Mean RRatios within each Cluster



Interim Analysis

In the protocol it was planned to randomize 240 total patients and to possibly conduct an interim analysis, for administrative purposes only, after the first 120 patients had either withdrawn or completed the study. A total of 288 patients were actually randomized. The sponsor opted not to conduct an interim analysis. This reviewer investigated what the interim analysis results would have been had it been conducted. The p-value for the 600 mg/day vs. placebo group comparison of the mean rank of the RRatios, <0.0001, was less than the planned significance level, 0.001, for the interim analysis, while the p-value for the 150 mg/day vs. placebo comparison was not (p=0.20). The subset of the first 120 randomized patients that were randomized to placebo did slightly better than those that were randomized to placebo later on:

Before N=44 Mean RRatio -4.78 (+/- 3.84 S.E.)
After N=52 Mean RRatio 5.67 (+/- 3.57 S.E.)

There was little difference in those randomized to the Pregabalin groups earlier as compared to later, but because later placebo patients did worse than earlier placebo patients, the treatment effects based on the last 168 patients were slightly larger (each about 8 points better compared to placebo).

The planned sample size, 240 total patients, was exceeded by 48 (20%). This reviewer carried out an additional analysis on the first 240 patients randomized. It was found that the additional 48 patients beyond the planned sample size of 240 had no effect on the significance of any of the group comparisons.

Analysis of Responder Rate (Secondary)

This reviewer also verified the sponsor's analysis of the responder rates, a secondary analysis. It was pre-specified that patients that had a double blind seizure rate less than or equal to 50% of the baseline seizure rate would be classified as responders. The 600 mg/day group had a significantly higher proportion of responders than either the placebo or the 150 mg/day groups (44%, 6%, and 14% respectively). Although there was a higher proportion of responders in the 150 mg/day group than in the placebo group the difference was not significant (14% vs. 6%, p=0.09). This was only a secondary analysis though and the result approached significance, so it shouldn't detract from the primary analysis comparison of the 150 mg/day and placebo groups. This reviewer notes also that the 150 mg/day group did have a higher proportion of patients than placebo with at least a 40% reduction in seizure rate (25% vs. 12% p=0.01), but this is admittedly a post-hoc analysis and therefore doesn't carry the weight of a pre-planned analysis. In summary, although the 600 mg/day group appeared significantly more efficacious than the 150 mg/day group it also was less well tolerated (18% compared to 10% dropped out because of an adverse event).

3.1.3 Study 1008-034

3.1.3.1 Objectives

To evaluate the efficacy of pregabalin administered BID as compared to placebo as add-on treatment in reducing seizure frequency in patients with partial seizures.

To evaluate the dose response relationship of pregabalin (50, 150, 300, and 600 mg/day) administered BID as add-on treatment in reducing seizure frequency in patients with partial seizures.

3.1.3.2 Study Design

A total of 400 patients with medically uncontrolled partial seizures will participate in this randomized, double-blind, parallel-group, multicenter study. Participants will be patients who are receiving 1 to 3 standard AEDs at doses within an acceptable therapeutic range. There will be approximately 80 sites with 5 to 24 patients per site.

The study comprises three phases: (1) an 8-week baseline phase; (2) a 12-week double-blind phase; and (3) a 6-day double-blind withdrawal phase for patients choosing to exit the study. Those patients choosing to proceed to open label pregabalin will be enrolled in a follow-on study (protocol 1008-035).

To qualify for the study patients must have at least 3 partial seizures during the 1 month preceding entry to baseline. Patients will continue their current AEDs at the same dosages throughout baseline. Seizures will be recorded by the patient, a family member, caregiver, or legal guardian and documented in a daily seizure diary. Patients return at 4-week intervals for 2 additional visits, one during baseline (Visit B2), and one at the end of baseline (Visit DB1), the first double-blind visit, at which time seizure counts will be assessed to determine a baseline seizure frequency and to confirm eligibility to be randomized. 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 12-week double-blind phase begins the day following Visit DB1. Patients will continue their current AEDs at the same dosages. Double blind treatment dosing will occur each morning and evening. Following randomization and initiation of DB medication, 4 visits follow in 2- or 4-week intervals (Visits DB2, DB3, DB4, and DB5/Termination).

3.1.3.3 Efficacy Assessments

Primary

The principal efficacy criterion will be the reduction in the frequency of all partial seizures during the double-blind treatment period as compared with the baseline period. Seizures will be recorded by the patients, a family member, or legal guardian and documented in a daily seizure

diary. The primary efficacy parameter is response ratio (RRatio or symmetrized percent change), a comparison of baseline seizure rate (B) with treatment seizure rate (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. RRatio = $[(T-B)/(T+B)] \times 100$. The primary comparison will be the 600 mg/day treatment group versus placebo.

Secondary
Secondary efficacy parameters are the response rate, defined as the proportion of patients who have 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 as compared to baseline.

3.1.3.4 Statistical Analysis Plan

Analysis Populations
The primary population will be the ITT population, defined as all patients randomized to treatment who receive at least one dose of study medication.

A secondary population will be the Evaluable (EVAL) population, defined as all patients who are randomized to study medication, receive 28 days of study medication, and have a minimum of 28 days of evaluable seizure diary data within both the baseline phase and the double-blind phase.

Sample Size
The sample size estimate is based on the primary efficacy parameter, response ratio, and the secondary parameter responder rate. Based on previous add-on trials with Neurontin (877-210P, 945-05, 945-06), assumptions for mean response ratio at the final visit are -15 (±25) for the pregabalin treatment and -3 (±25) the placebo treatment, with a 12 point difference between treatments. Assuming a 10% dropout rate, a total of 80 patients will be randomized to provide 70 patients per treatment group in the Evaluable (EVAL) population and provide at least 80% power ($\alpha = 0.05$, 2-sided) for both the primary ITT and secondary Evaluable populations.

Pooling of Centers
Centers will be managed by pooling small centers (n<18) of the same region. A cluster is a single center (at least 18 patients) or an aggregation of centers which are located in the same country or region. The nearest center is added to a cluster until a minimum of 18 patients is reached. The clustering will be done before the code breaking.

Primary Analysis
The primary efficacy variable will be the response ratio (RRatio or symmetrized percent change) for all partial seizures at the end point of the study (Week 20/Termination). ITT patients with no seizure diary will carry forward the baseline seizure rate for the double-blind seizure rate. The

primary population will be the ITT population using the value at Week 20 for those completing the study or the value at endpoint for those withdrawing prior to Week 20. The RRatio will be ranked across patients and analysis will be performed using an analysis of variance (ANOVA) model with treatment (as main effect) and center (cluster), and the ranking of the RRatio as the dependent variable ($\alpha = 0.05$, 2-sided).

The primary efficacy outcomes will be pairwise comparisons of 300 and 600 mg/day versus placebo. The comparisons will use a step down procedure starting with the 600 mg/day dose versus placebo as the primary comparison, followed by 300 mg/day versus placebo. Secondary pairwise treatment comparisons will be 150 and 50 mg/day versus placebo. In addition, 95% confidence intervals will be provided for all pairwise comparison differences versus placebo and all pregabalin treatment group pairwise comparisons.

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

The primary analysis (ANOVA) main model will be used with treatment x center (cluster) added to the model to test for significant interaction (α=0.15 as strong evidence against

Dose Response
Data from the 4 pregabalin groups and placebo will be used to develop a descriptive dose-response relationship.

Secondary Analysis
The responder rate will be compared between treatments using a Cochran-Mantel-Haenszel chi-square analysis stratified by center (cluster), at the Week 20/endpoint ($\alpha = 0.05$, 2-sided) with the ITT Population. Treatment comparisons will be done using the same pairwise stepdown procedure as in the primary analysis. Confidence intervals of 95% will be provided for all pairwise comparison differences.

Percent change in 28-Day Seizure Rate will be summarized by treatment group at the Week 20/endpoint. No inferential analysis will be performed as this endpoint is a direct transformation of the RRatio.

All 3 efficacy parameters will be summarized by treatment group for each seizure type. These include the following:
- All partial seizures;
- Simple partial;
- Complex partial;
- Partial seizures with secondary generalization; and
- Partial seizures without secondary generalization.

Re-Estimation of Sample Size

The withdrawal rate for patients not completing 28 days in either baseline or double-blind will be blindly monitored while the study is ongoing. Any trend in the rate to increase considerably from 10% may require a sample size adjustment upward.

Interim Analysis

An interim analysis may be conducted when 150 patients have been randomized and either completed 12 weeks in double-blind or withdrawn from the study. The interim analysis will evaluate only the primary efficacy parameter RRatio. The purpose of the interim analysis is administrative. A Haybittle-Peto method will be applied, using $\alpha = 0.001$ at the interim and $\alpha = 0.049$ at the final analysis.

Notable amendments to the original protocol

- The primary endpoint was changed from the RRatio to the rank over all ITT patients of the RRatio.
- Definition of clusters for pooling small centers and use of clusters instead of individual centers in the analyses.
- Primary population changed from Evaluable (all randomized patients with at least 28 days of diary data in both the baseline and double-blind periods) to ITT (all randomized patients who received at least one dose). ITT patients with no diary data will have baseline seizure rate carried forward.

3.1.3.5 Study Population

Of the 453 patients in the ITT population, 100 were randomized to the placebo group, 88 to 50 mg/day pregabalin, 86 to 150 mg/day pregabalin, 90 to 300 mg/day pregabalin, and 89 to the 600 mg/day pregabalin group.

Table 20 Study 0034: Patient Disposition

Population	Placebo	Pregabalin 50 mg/day (BID)	Pregabalin 150 mg/day (BID)	Pregabalin 300 mg/day (BID)	Pregabalin 600 mg/day (BID)	All Patients
Randomized to Treatment	100	88	88	90	89	455 (100%)
Total Excluded From ITT			2			
Did Not Take Study Medication			2			
Total Included in ITT	100 (100%)	88 (100%)	86 (97.7%)	90 (100%)	89 (100%)	453 (99.6%)
Total Excluded From Evaluable[b]	3	7	4	13	20	
<28 Days of Baseline Diary		1		1	1	
<28 Days of Double-Blind Diary	3	7	4	12	20	
<28 Days of Double-Blind Dosing	3	7	4	12	19	
Total Included in Evaluable	97 (97.0%)	81 (92.0%)	82 (93.2%)	77 (85.6%)	69 (77.5%)	406 (89.2%)

[a] Percentage of patients based on number of patients randomized to treatment

[b] A patient may have had more than one reason for his or her data being excluded.

Table copied from Table 4 of Pfizer's Research Report RR 720-04102 1008-034 (Page 35)

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.

Table 21 Study 0034: Baseline Demographics

Characteristic	Placebo	Pregabalin 50 mg/day (BID)	Pregabalin 150 mg/day (BID)	Pregabalin 300 mg/day (BID)	Pregabalin 600 mg/day (BID)	All Pregabalin	All Patients
	N = 100	N = 88	N = 86	N = 90	N = 89	N = 353	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 copied from Table 5 of Pfizer's Research Report RR 720-04102 1008-034 (Page 37)

All of the patients who entered the double-blind treatment phase had medically refractory partial seizures. Age at diagnosis, duration of epilepsy, etiology, and median baseline seizure rate were comparable among the treatment groups for the ITT population. The majority of patients were taking more than 1 AED at baseline.

Table 22 Study 0034: 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 copied from Table 6 of Pfizer's Research Report RR 720-04102 1008-034 (Page 39)

The incidences of different types of seizures were reasonably similar among the randomized treatment groups.

Table 23 Study 0034: Summary of History of Seizure Types : ITT population

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%)*	353 (100.0%)*	453 (100.0%)*
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%)*	323 (91.5%)*	411 (90.7%)*
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%)*	225 (63.7%)*	281 (62.0%)*
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							

* Includes seizure history data from 1 patient (Patient 027014) not entered in database

Table copied from Table 7 of Pfizer's Research Report RR 720-04102 1008-034 (Page 40)

3.1.3.6 Sponsor's Results

The proportions of patients who completed were similar among the placebo, 50 mg/day (BID), and 150 mg/day (BID) groups, but the proportion completing was smaller for the 300 mg/day (BID) group and smaller still for the 600 mg/day (BID) group. The most frequent reason given for withdrawal was adverse event (10.1 %). The proportion withdrawn because of an adverse event in the placebo group was less than the proportion in the 300 mg/day (BID) group which was less than the proportion in the 600 mg/day (BID) group.

Table 24 Study 0034: Patient Disposition II

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%)

Table copied from Table 10 of Pfizer's Research Report RR 720-04102 1008-034 (Page 45)

Primary Analysis

The primary analysis, an ANOVA of the ranks of the RRatios adjusted for clusters (pooled centers), showed that Pregabalin 150 mg/day (BID), 300 mg/day (BID), and 600 mg/day (BID) groups were superior to placebo in terms of efficacy ($p <= 0.0001$, $p <= 0.0001$, and $p <= 0.0001$). The 150 mg/day dose was a minimum effective dose. There was a significant linear trend in dose-response ($p < 0.0001$). A test for a quadratic dose-response relationship was also significant ($p=0.021$) when the placebo group was included, but was only marginally significant without the placebo group ($p=0.074$). Pairwise comparisons were also performed for the pregabalin groups and the results are contained in Table 26.

Table 25 Study 0034: Summary Statistics for RRatio (All Partial Seizures): ITT Population

Period	Placebo	Pregabalin 50 mg/day (BID)	Pregabalin 150 mg/day (BID)	Pregabalin 300 mg/day (BID)	Pregabalin 600 mg/day (BID)
	N = 100	N = 88	N = 86	N = 90	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

Table copied from Table 11 of Pfizer's Research Report RR 720-04102 1008-034 (Page 47)

Table 26 Study 0034: Group Comparisons of Mean RRatios (All Partial Seizures): ITT Population

Treatment Comparisons	N[b]	Treatment Differences[a] Mean (SE)	95% CI	Probability
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

Table copied from Table 12 of Pfizer's Research Report RR 720-04102 1008-034 (Page 48)

Secondary Analyses

A patient was classified as a responder if he or she had at least a 50% reduction in seizure rate compared to the baseline seizure rate. The proportions of responders in the 150 mg/day (BID), 300 mg/day (BID), and 600 mg/day (BID) groups were all significantly higher than the proportion in the placebo group. The increasing linear trend in the responder rate across all treatment groups was significant (p<=0.001).

Figure 6 Study 0034: Responder Rates (All Partial Seizures): ITT Population

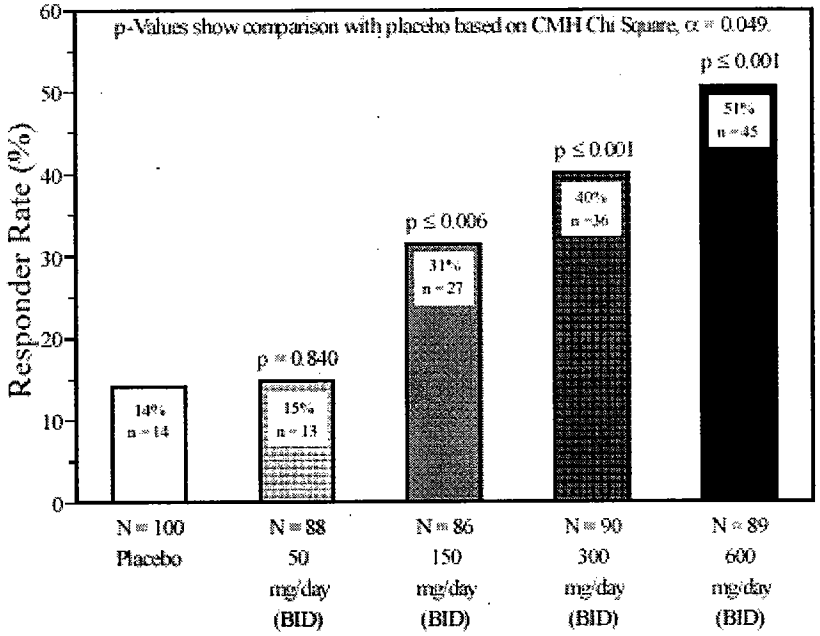


Figure copied from Figure 3 of Pfizer's Research Report RR 720-04102 1008-034 (Page 49)

3.1.3.7 Reviewer's Results

Thirteen of the seventeen 600 mg/day group patients who became seizure free had 7 days or less of double blind seizure diary data. Five of these had only 1 day of double blind diary data. In fact, the number of double-blind diary days completed decreased significantly with increasing dose. This reviewer also noticed that the standard deviations of the RRatios were significantly higher for the 300 mg/day and 600 mg/day groups than the other groups. In fact, both the observed RRatios and the ranks of the RRatios failed a test for equal group variances, thus violating an assumption of the primary analysis method (ANOVA). This reviewer employed several other methods which are more appropriate when group variances are not equal to check the robustness of the results. These alternative methods were the Van-Elteren test (a cluster stratified (nonparametric) Wilcoxon rank sum test) and Welch's ANOVA, which do not assume equal group variances, and an ANOVA with observations weighted according to the number of diary entries in the double-blind treatment period. Another problem with the ordinary unweighted ANOVA is that it does not account for the fact that seizure rates (and RRatios) based on less diary data are less reliable. The weighted ANOVA gives more weight to patients with more diary data than to those with less diary data. These alternative analysis methods all yielded the same conclusions so the results seem to be robust and the non-constancy of the variance does not seem to be a serious issue in this case.

The 300 mg/day and 600 mg/day groups also had fewer completers than the other groups. Nevertheless, the conclusions for the evaluable and completers populations were the same as for the ITT population. Therefore, the results do not seem to depend on the extent of dropouts or the completeness of the double-blind diary data.

Table 27 Study 0034: Primary Analysis Results for Primary Population (ITT) and Secondary Populations

Population	RRatio	RXGRP				
		Placebo	50 mg/day(BID)	150 mg/day(BID)	300 mg/day(BID)	600 mg/day(BID)
ITT	N	99	87	86	88	87
	Mean	-3.89	-6.25	-20.47	-28.43	-38.22
	Std. Dev.	25.74	23.88	29.56	36.63	44.49
	Comparison with Placebo P-value	.	0.5496	0.0001	<0.0001	<0.0001
Evaluable#	N	97	81	82	77	69
	Mean	-4.06	-7.25	-20.08	-24.05	-29.90
	Std. Dev.	25.91	21.37	28.23	31.43	37.20
	Comparison with Placebo P-value	.	0.5221	0.0001	<0.0001	<0.0001
Completers*	N	92	76	81	72	63
	Mean	-6.56	-7.08	-20.11	-26.91	-31.17
	Std. Dev.	23.54	19.91	28.41	30.99	36.36
	Comparison with Placebo P-value	.	0.9252	0.0003	<0.0001	<0.0001

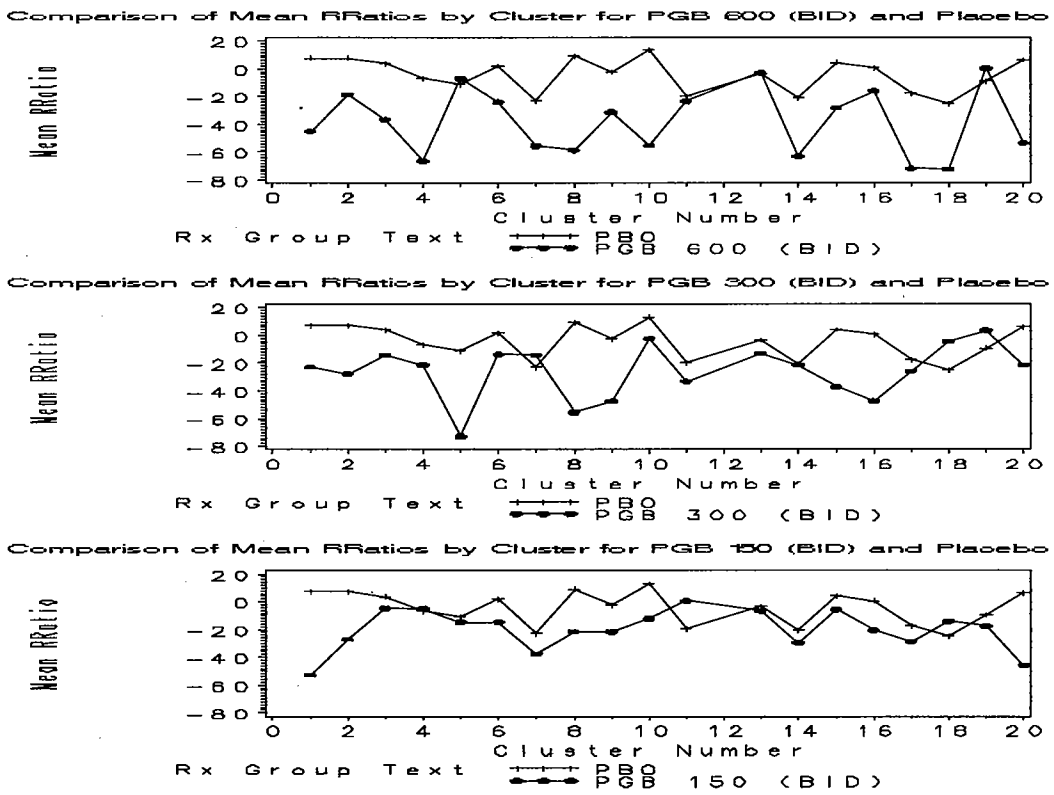
*# Had at least 28 days of seizure diary data in both baseline and double-blind periods
* Had double blind seizure diary data in all 3 months
P-values based on ranks of RRatios

The sponsor used step-down testing to control the type I error associated with comparing multiple dose groups with placebo. Specifically, first, the high dose was compared with placebo. If this test was significant at the 0.049 level (adjusted because of the interim analysis) then the next smaller dose was compared to placebo and so on. In addition to the pregabalin vs. placebo group comparisons the sponsor reported the results of pairwise comparisons between the different pregabalin groups, but the step-down procedure does not cover the pregabalin vs. pregabalin comparisons. For example, if the order of comparisons was 600 vs. PBO, 300 vs. PBO, 150 vs. PBO, 50 vs. PBO, 600 vs. 50, etc., then the 600 vs. 50 comparison could not be carried out without inflating the type I error because the 50 mg vs. placebo comparison was not significant at the 0.049 level. Therefore, the comparisons between the different pregabalin groups should be considered exploratory. The sponsor reported that the pairwise comparison between the 600 mg/day and 150 mg/day Pregabalin groups was significant in the ITT population (p=0.01) but it was not in the Evaluable population (p=0.11). Note that only 79% of the 600 mg/day group were evaluable compared to 95% of the 150 mg/day group.

Impact of Individual Sites and Clustered Sites

Clusters were formed by pooling sites according to geographic proximity until each cluster had at least 18 patients. The following figure shows the Mean RRatios for 600 (BID) and placebo in the top box, 300 (BID) and placebo in the middle box, and 150 (BID) and placebo in the bottom box. The within cluster results were reasonably consistent across all clusters and the overall results were not excessively influenced by or dependent on any one cluster (or site).

Figure 7 Study 0034: Group Mean RRatios within Clusters



Interim Analysis

In the protocol the sponsor planned an interim analysis which would include the first 150 randomized patients who completed or withdrew from the study. The interim analysis was described as for administrative purposes rather than for stopping early. A Haybittle-Peto approach was planned to adjust the significance levels so as not to inflate the type I error. In this approach the tests are conducted at α=0.001 significance level at the interim analysis and α=0.049 at the final analysis. The interim analysis plan stated that all patients randomized before Feb 20, 1999 would be included in the interim analysis. This amounts to 165 / 455 or 36% of all patients randomized.

After the interim analysis the completion rates in the Pregabalin groups dropped, especially for the 300 and 600 mg/day groups. In particular, the proportion of patients who completed at least part of all 3 months was smaller for patients who were not included in the interim analysis than for patients that were. For example, in the 600 mg/day group 86% of the early patients completed at least part of all 3 months compared to 60% for the later patients.

Table 28 Study 0034: Proportion of Patients completing part of first 1, 2, or 3 Months

INTERIM		PLACEBO	50 (BID)	150 (BID)	300 (BID)	600 (BID)	ALL
Before	1	.(.)	1(3.0)	.(.)	3(9.4)	4(11.1)	8(4.9)
	1/2	4(11.4)	1(3.0)	1(3.5)	1(3.1)	1(2.8)	8(4.9)
	1/2/3	31(88.6)	31(93.9)	28(96.6)	28(87.5)	31(86.1)	149(90.3)
After	1	3(4.6)	7(12.7)	4(7.0)	10(17.2)	17(32.1)	41(14.2)
	1/2	1(1.5)	3(5.5)	.(.)	4(6.9)	4(7.6)	12(4.2)
	1/2/3	61(93.9)	45(81.8)	53(93.0)	44(75.9)	32(60.4)	235(81.6)

This reviewer carried out a Rank ANOVA analysis of the RRatios from patients randomized before Feb 20, 1999, who were to be included in the interim analysis, and patients randomized after this date. These results are shown in the following table. The primary comparison, 600 mg vs. placebo, was close to but exceeded the 0.001 significance level prescribed for the interim analysis.

It is notable that the 150 mg/day patients randomized later did worse than the 150 mg/day randomized early and the opposite is true for the 300 mg/day and 600 mg/day groups. Nevertheless, the overall ITT results indicated that the 150, 300, and 600 groups were all better than placebo in terms of efficacy and the interim analysis seems to have predicted this.

Table 29 Study 0034: Mean RRatios by Interim analysis inclusion status

		Level of RXGRP				
		PBO	50(BID)	150(BID)	300(BID)	600(BID)
Interim		35	33	29	32	36
Before	N					
	Mean RRatio	-2.76	-7.66	-27.31	-23.95	-31.31
	StdErr	4.70	3.63	4.54	6.07	6.39
	P-value	.	0.929	0.005	0.037	0.002
After	N	64	54	57	56	51
	Mean RRatio	-4.50	-5.38	-16.99	-31.00	-43.09
	StdErr	3.09	3.50	4.17	5.07	6.74
	P-value	.	0.326	0.008	<0.001	<0.001

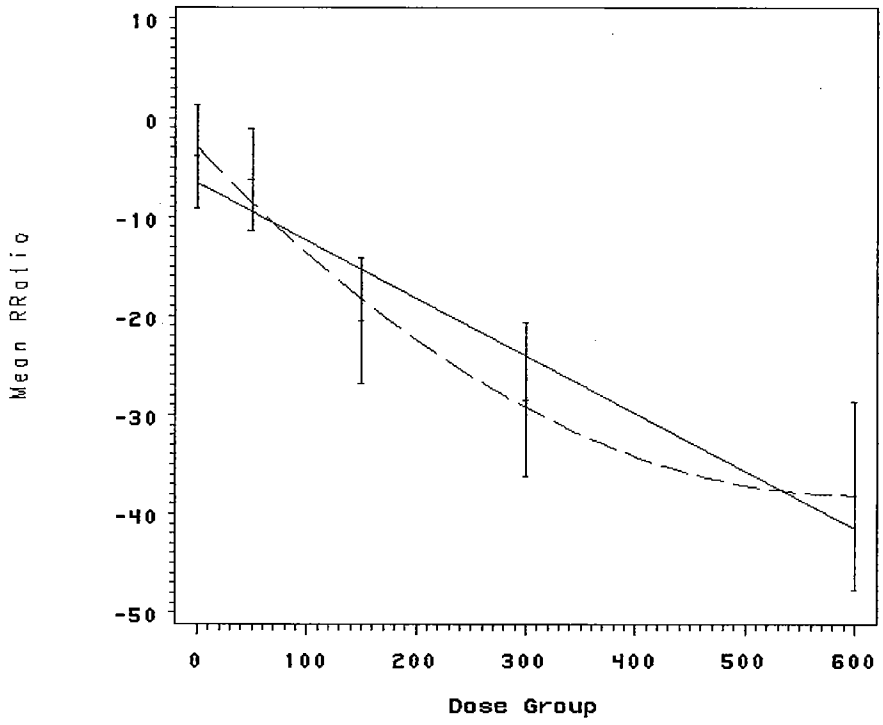
The sponsor randomized 55 patients more than the originally planned number, 400. Therefore, this reviewer conducted a Rank ANOVA of the RRatios based on the first 400 patients

randomized. This yielded the same conclusions for the pregabalin vs. placebo comparisons as for all 455 randomized patients. One small difference was that the pregabalin 600 mg vs. pregabalin 150 mg comparison based on only the first 400 patients was not significant (p=0.12).

Dose Response

Figure 8 displays the Mean RRatios +/- 2 standard errors by dose. Also displayed are the fitted linear and quadratic regression models. Both the linear and quadratic dose effects were statistically significant and the quadratic model has noticeably better agreement with the observed means. The fitted quadratic model suggests that the RRatio decreases (i.e., improves) more rapidly as the dose is increased in the lower dose range and less rapidly as the dose is increased in the higher dose range than for the fitted linear model. While the study was not powered to detect differences between the different Pregabalin doses and no multiplicity adjustments were made for the pregabalin vs. pregabalin comparisons, pairwise comparisons between the 150, 300, and 600 mg/day (BID) dose groups suggested that the 600 mg/day dose was more effective than the 150 mg/day dose (p=0.01), but the differences between the 150 mg/day and 300 mg/day and 300 mg/day and 600 mg/day doses were not statistically significant. While the RRatio improved with increasing dose, the proportions of withdrawals for any reason and withdrawals due to an adverse event also increased with dose so the 300 mg/day dose may be preferred over the 600 mg/day dose after considering both risks and benefits.

Figure 8 Study 0034: Mean RRatio as a function of Dose



3.2 Evaluation of Safety

See clinical safety review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 Gender

The Mean RRatios suggest that the 600 mg/day doses (BID) and (TID) were more efficacious for females than males in studies 9 and 11, but in study 34 males and females at 600 mg (BID) had equivalent efficacy compared to placebo. Therefore, the evidence for a treatment by gender effect is inconclusive. Gender differences in the treatment effect for the 150 mg/day groups were small and thus did not support the gender differences seen for the 600 mg/day groups. Finally, it is important to note that even though the 600 mg/day doses appeared to be less efficacious for the males than for females they were still significantly better than placebo despite the smaller size of the groups.

Table 30 Mean RRatios by Gender and Treatment Group

		Dose Group						
		Placebo	50 mg/day BID	150 mg/day BID	150 mg/day TID	300 mg/day BID	600 mg/day BID	600 mg/day TID
Study/Gend								
9 / Female	N	48	.	.	.	.	52	53
	Mean RRatio	5.68	.	.	.	.	-34.72	-40.89
	StdDev	31.46	.	.	.	.	39.88	45.93
	P-value	.	.	.	.	.	<0.001	<0.001
9 / Male	N	50	.	.	.	.	49	57
	Mean RRatio	-4.32	.	.	.	.	-22.80	-32.31
	StdDev	25.47	.	.	.	.	32.58	33.58
	P-value	.	.	.	.	.	0.006	<0.001
11 / Female	N	42	.	.	55	.	.	45
	Mean RRatio	-0.42	.	.	-11.20	.	.	-38.65
	StdDev	30.41	.	.	22.95	.	.	30.37
	P-value	.	.	.	0.061	.	.	<0.001
11 / Male	N	54	.	.	44	.	.	47
	Mean RRatio	1.90	.	.	-11.98	.	.	-24.48
	StdDev	22.26	.	.	23.03	.	.	40.31
	P-value	.	.	.	0.010	.	.	<0.001

		Dose Group						
		Placebo	50 mg/day BID	150 mg/day BID	150 mg/day TID	300 mg/day BID	600 mg/day BID	600 mg/day TID
34 / Female	N	48	48	50	.	41	44	.
	Mean RRatio	-5.19	-3.45	-21.01	.	-27.01	-41.08	.
	StdDev	26.86	23.36	33.27	.	41.15	48.83	.
	P-value	.	0.455	0.020	.	0.024	<0.001	.
34 / Male	N	51	39	36	.	47	43	.
	Mean RRatio	-2.66	-9.69	-19.72	.	-29.68	-35.29	.
	StdDev	24.85	24.36	23.92	.	32.58	39.94	.
	P-value	.	0.054	<0.001	.	<0.001	<0.001	.

4.1.2 Race

Although the studies provided limited data on non-white ethnicities it does not appear that the efficacy of Pregabalin depends on ethnicity. The observed differences are not significant and are consistent with the greater variability and imprecision associated with small samples.

Table 31 Mean RRatios by Race Group

	White		Black		Hispanic		Other		All	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Placebo	259	-1.1 (26.5)	12	3.4 (32.8)	12	1.5 (33.4)	10	-1.1 (24.4)	293	-0.8 (27.0)
50 mg/day BID	75	-7.3 (25.2)	5	-1.3 (13.6)	3	3.3 (13.6)	4	1.1 (9.0)	87	-6.2 (24.0)
150 mg/day BID	73	-19.6 (30.5)	8	-19.9 (12.6)	4	-46.4 (26.7)	1	13.9 (.)	86	-20.5 (29.1)
150 mg/day TID	93	-10.7 (22.4)	2	-3.1 (23.8)	2	-43.4 (29.2)	2	-27.0 (33.1)	99	-11.5 (22.5)
300 mg/day BID	76	-27.0 (36.8)	4	-41.3 (32.2)	7	-32.6 (42.1)	1	-54.3 (.)	88	-28.4 (36.8)
600 mg/day TID	173	-33.8 (39.0)	6	-39.0 (33.1)	13	-33.4 (38.0)	10	-38.3 (35.9)	202	-34.2 (38.6)
600 mg/day BID	161	-32.3 (41.4)	11	-26.8 (40.3)	12	-47.1 (35.3)	4	-46.4 (27.5)	188	-33.2 (40.7)

4.1.3 Age

Overall, the mean age was 38 and ages ranged from 12 to 82. There was very limited data on patients under the age of 18. In studies 9 and 11 the lowest age was 17 with only 1 patient at that age. Study 34 had several more patients under 18 (patients aged

). Thus, the three add-on studies provided little direct evidence to support the efficacy of pregabalin as adjunctive therapy in epilepsy patients under the age of 18.

Table 32 Study 0034: RRatios for Age<=18 adjusted for cluster

Dose	Placebo	50 mg	150 mg	300 mg	600 mg
N					
Base SzRate					
P-value					
RRatio					
P-value					

In study 9 there is a suggestion that the treatment differences based on the RRatios increase with age. However, studies 11 and 34 do not seem to support this. Therefore, overall, there do not appear to be any significant age differences in the efficacy of pregabalin.

Table 33 Mean RRatios by Age Group

AgeGrp	12-18		19-29		30-44		>=45		All	
	N	RRatio Mean (SD)	N	RRatio Mean (SD)	N	RRatio Mean (SD)	N	RRatio Mean (SD)	N	RRatio Mean (SD)
Placebo	12		58	3.5 (23.5)	125	-2.3 (30.5)	98	-1.9 (24.6)	293	-0.9 (26.9)
50 mg/day BID	2		16	0.0 (29.8)	38	-7.1 (24.5)	31	-7.9 (20.4)	87	-6.2 (23.9)
150 mg/day BID	7		15	-31.0 (28.0)	42	-17.1 (29.5)	22	-23.7 (25.6)	86	-20.4 (29.2)
150 mg/day TID	1		30	-4.0 (19.7)	46	-14.4 (25.9)	22	-15.9 (18.5)	99	-11.6 (22.5)
300 mg/day BID	4		18	-38.0 (35.1)	40	-19.5 (34.9)	26	-33.1 (37.4)	88	-28.4 (36.0)
600 mg/day TID	3		49	-25.2 (34.3)	95	-33.0 (39.3)	55	-45.7 (38.5)	202	-34.2 (37.7)
600 mg/day BID	6		37	-24.4 (40.9)	86	-34.8 (39.6)	59	-36.5 (42.7)	188	-33.2 (40.7)

4.2 Other Special/Subgroup Populations

4.2.1 Analysis of RRatio by Seizure Type

Note that analyses by seizure type were planned as secondary analyses but it is risky to draw conclusions in subgroups for many reasons. First, within the subgroup the groups may no longer be balanced with respect to important predictors of outcome so the treatment effect may be confounded with other predictors. Also, when the observed difference is small one can argue that there was insufficient power to detect a difference. On the other hand when an observed difference is large one has to consider how many tests were conducted since the chance of a false positive increases with the number of tests. Although analyses by seizure type were planned in the protocol they were secondary analyses not involved in the determination of the success or failure of the study in demonstrating efficacy. Therefore, to avoid inflating the type I error the following p-values should be considered exploratory, i.e., used for hypothesis generation rather than hypothesis confirmation.

4.2.1.1 Simple Seizures

For partial seizures classified as simple the 600 mg/day TID pregabalin group appeared to be better than both placebo ($p<0.01$) and the 600 mg/day BID pregabalin group ($p=0.02$). However, the latter result was not supported by the other studies. After pooling the data from all three studies it appeared that both 600 mg/day regimens were superior to placebo for simple partial seizures and not significantly different from each other.
Both the 150 mg/day (TID) and (BID) groups were numerically better than placebo for simple seizures in studies 11 and 34 respectively. The differences were not statistically significant but this may be a matter of low power since a smaller number of patients had simple partial seizures.

Table 34 Mean RRatios for Partial Seizures classified as Simple

Simple Seizures		Randomized Group						
		Placebo	50 mg/day BID	150 mg/day BID	150 mg/day TID	300 mg/day BID	600 mg/day BID	600 mg/day TID
Study		56	.	.	.	.	48	58
9	N							
	Mean RRatio	8.39	.	.	.	.	-10.66	-38.42
	StdDev	59.28	.	.	.	.	71.23	62.83
	P-value	.	.	.	.	.	0.155	<0.001
11	N	40	.	.	32	.	.	30
	Mean RRatio	-6.09	.	.	-11.40	.	.	-26.00
	StdDev	59.40	.	.	54.23	.	.	60.49
	P-value	.	.	.	0.734	.	.	0.105
34	N	47	43	42	.	44	45	.
	Mean RRatio	2.21	0.34	-10.65	.	-24.52	-46.52	.
	StdDev	59.18	55.23	61.31	.	49.22	58.23	.
	P-value	.	0.916	0.234	.	0.041	<0.001	.

4.2.1.2 Complex Seizures

All 150 mg/day and higher dose groups were better than placebo for partial seizures classified as complex and for partial seizures classified as either simple or complex.

Table 35 Mean RRatios for Partial Seizures classified as Complex

Complex Seizures		Randomized Group						
		Placebo	50 mg/day BID	150 mg/day BID	150 mg/day TID	300 mg/day BID	600 mg/day BID	600 mg/day TID
Study								
9	N	85	.	.	.	.	92	97
	Mean RRatio	-5.87	.	.	.	.	-31.81	-35.95
	StdDev	35.52	.	.	.	.	42.68	44.58
	P-value	.	.	.	.	.	<0.001	<0.001
11	N	85	.	.	88	.	.	83
	Mean RRatio	-3.11	.	.	-14.34	.	.	-37.00
	StdDev	37.31	.	.	37.38	.	.	42.35
	P-value	.	.	.	0.016	.	.	<0.001
34	N	89	82	75	.	77	78	.
	Mean RRatio	0.50	-5.77	-17.97	.	-26.20	-37.62	.
	StdDev	38.20	37.82	41.34	.	47.83	53.03	.
	P-value	.	0.295	0.001	.	<0.001	<0.001	.

4.2.1.3 Simple and Complex Seizures

Analyses of RRatios specific to all seizures that were either simple or complex led to conclusions similar to those for all partial seizures. In particular, all dose groups above 50 mg/day were significantly better at the 0.05 level than placebo in terms of efficacy.

Table 36 Mean RRatios for Partial Seizures classified as Simple or Complex

Simple + Complex Seizures		Randomized Group						
		Placebo	50 mg/day BID	150 mg/day BID	150 mg/day TID	300 mg/day BID	600 mg/day BID	600 mg/day TID
Study								
9	N	97	.	.	.	.	96	108
	Mean RRatio	2.37	.	.	.	.	-23.84	-34.15
	StdDev	33.35	.	.	.	.	40.21	44.56
	P-value	.	.	.	.	.	<0.001	<0.001
11	N	92	.	.	96	.	.	88
	Mean RRatio	1.94	.	.	-10.57	.	.	-30.74
	StdDev	30.65	.	.	30.57	.	.	40.79
	P-value	.	.	.	0.003	.	.	<0.001
34	N	99	86	84	.	85	87	.
	Mean RRatio	-0.73	-5.12	-21.40	.	-29.01	-36.15	.
	StdDev	30.72	27.75	35.29	.	38.10	50.23	.
	P-value	.	0.395	<0.001	.	<0.001	<0.001	.

1 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Statistical- 1

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The sponsor seeks an indication for adjunctive therapy of partial seizures in patients but only a small number of patients (20/1056 ≈ 2%) in the three randomized, double-blind, placebo-controlled studies of Pregabalin as adjunctive therapy were between the ages of 12 and 17, so no definitive conclusions can be reached on efficacy in this subgroup. While the three add-on studies demonstrated the efficacy of 150, 300, and 600 mg/day doses for individuals age 18 and above, there is little direct evidence and no independent verification that pregabalin is effective as adjunctive therapy for partial seizures in individuals under 18 years of age.

A concern for the efficacy of the 600 mg/day doses is that in the majority of cases the number of days with diary entries was less for the 600 mg/day group than for placebo which means that there was less chance for seizures to be recorded in the 600 mg/day group and is a possible source of bias. This effect was most dramatic in study 0034 where the amount of double-blind diary data was significantly less for the 600 mg/day BID and 300 mg/day BID groups than for the placebo group (Wilcoxon rank sum p=0.0005 and p=0.0158, respectively). The 600 mg/day group(s) also tended to have less diary data than placebo in studies 009 and 011, but the differences were smaller. It is important to note that there was no titration in study 0034 whereas in studies 0009 and 0011 there was one week of titration. Thus, the absence of a week of upward titration may have led to the greater number of high dose dropouts in study 0034.

Since the ANOVA method assumes equal group variances but the variability of the RRatios was larger for the 600 mg/day pregabalin group than for placebo, the estimate of the mean RRatio is less precise for the 600 mg/day group and the 95% confidence interval reported by the sponsor for the difference in mean RRatios between the 600 mg/day and placebo groups may be too narrow, i.e., the confidence that the interval contains the true mean difference is actually slightly

less than 95%. The ANOVA based estimate of variability is a weighted average of the group variances. In study 0034, since the 50 and 150 mg/day groups had variances that were closer to placebo than to the 600 mg/day group the ANOVA based estimate of the variability is considerably smaller than the variability in the 600 mg/day group. Still, while the confidence may be slightly overstated, the difference is clearly significant ($p<0.0001$). This reviewer also verified that several alternative analyses to the (Rank) ANOVA that do not require the equal group variances assumption yielded the same conclusions as the Rank ANOVA.

The primary (ITT) results were complimented by the results in the evaluable population (patients with at least 28 days of double blind seizure diary data) and the completers population. Patients with very limited double-blind diary data were excluded from these populations and, yet, the analyses specific to these populations yielded the same conclusions for the pregabalin vs. placebo group comparisons. Most of the 600 mg/day patients who were not evaluable withdrew because of adverse events but still had very good efficacy results. Excluding these non-evaluable patients did not affect the conclusions regarding the efficacy of the 600 mg/day groups. The 150 mg/day groups were more comparable to placebo in terms of the amount of double blind seizure diary data provided, so the placebo vs. 150 mg/day group comparisons are fairer and more reliable than the 600. The 150 mg/day groups also had fewer withdrawals due to adverse events and still demonstrated efficacy.

In study 0034 which explored the dose-response relationship most fully it appeared that the dose-response relationship had both a linear and a quadratic term. The fitted quadratic model suggests that the RRatio decreases (i.e., improves) more rapidly as the dose is increased in the lower dose range and less rapidly as the dose is increased in the higher dose range than it would for a purely linear dose-response. Therefore, considering the higher number of withdrawals due to adverse events at the 600 mg/day doses, the optimal dose may be lower than 600 mg/day.

5.2 Conclusions and Recommendations

The data support the efficacy of pregabalin as adjunctive therapy in the treatment of partial seizures. Doses of 150 mg/day, 300 mg/day, and 600 mg/day were identified as effective. There was evidence of increasing benefit with increasing dose but withdrawals due to adverse events increased with increasing dose also. The 600 mg/day groups tended to have more patients with less than 28 days of double blind diary data and therefore less chance to experience seizures. Sensitivity analyses still supported the efficacy of the 600 mg/day doses and the differences between 600 mg/day and placebo were larger than the differences between 150 mg/day and placebo but they were also less reliable, i.e., the differences between 600 mg/day and placebo had wider confidence intervals.

APPENDIX

Outlying Seizure Rates and Percent Changes

Several patients had double blind seizure rates that were very large compared to the majority of the other rates. For example, the double blind seizure rate for patient 35010 in study 0009 may not be reliable because it is extremely large compared to most others and the patient had only 12 non-missing diary entries in the double-blind phase. Because RRatio values must lie between -100 and 100, analysis of the RRatio is less sensitive to outliers than the analysis of the percent change in seizure rates, which has no upper limiting value. In fact, although the majority of percent change values are better for the 600 mg/day (TID) group than placebo, the significance of the 600 mg/day (TID) vs. placebo comparison based on an ANOVA of the percent change values, hinges on the inclusion of this patient because of the extreme value. Significance of the ANOVA of percent change was also susceptible to a single outlier in studies 0011 and 0034. This is an undesirable statistical property and part of the reason why the RANK ANOVA was planned for the primary analysis instead of the ordinary ANOVA. Because the patients have the same ranks for the RRatio and Percent Change (i.e., the same order when the values are arranged from smallest to largest) the Rank ANOVAs of the RRatio and Percent change are identical. The Rank ANOVA results are preferable because they better reflect the majority of patients. They do hide the presence of outlying percent changes in seizure rates though.

Table 39 Study 0009: Means and ANOVA Results for Pct Change, RRatio, and their Ranks

DOSE	PLACEBO	600 MG/DAY (TID)	600 MG/DAY (BID)
N	98.0	110.0	101.0
Pct Chg	37.1 (179.2)	303.0(3583)*	-29.8 (58.3)
P-value	0.7974	0.4222	0.7314
RRatio	0.6 (28.8)	-36.4 (40.1)	-28.9 (36.8)
P-value	<0.0001	<0.0001	<0.0001
Rank of PctChg/RRatio	210.2 (68.9)	120.8 (85.3)	138.7 (86.6)
P-value	<0.0001	<0.0001	<0.0001

*without patient 35010 the Mean (SD) Pct Chg in 600 mg/day (TID) is -38.5 (78.2)

Table 40 Percent Change Outliers and the Three largest (worst) RRatios in each study

STUDY	PTID	GROUP	BSZRT	DBSZRT	DBDAYS	PCHGSZ	RRATIO	RANK
009	42003	600 mg/day TID	11	80	93	625	76	307.0
009	26005	Placebo	4	56	1	1500	88	308.0
009	35010	600 mg/day TID	7	2634	12	37533	99	309.0
011	93002	Placebo	4	24	84	492	71	285.0
011	94004	600 mg/day TID	10	73	5	666	77	286.0
011	37005	600 mg/day TID	13	561	35	4386	96	287.0
034	13001	Placebo	6	38	47	535	73	445.0
034	40020	50 mg/day BID	13	120	7	860	81	446.0
034	78003	600 mg/day BID	15	350	4	2314	92	447.0

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