CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-216

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#:	21-216
DRUG COMPANY:	Parke Davis
NAME OF DRUG:	Neurontin (Gabapentin)
INDICATION:	[redacted]
STUDIES REVIEWED:	Study 86/186 and Study 305/405
DOCUMENTS REVIEWED:	Sponsor's original NDA submission, Vol. 1, 104-125
MEDICAL REVIEWER	Mani, Ranjit, M.D.

1. Introduction

Gabapentin [GBP, 1-(aminomethyl) cyclohexaneacetic acid, Neurontin] has been approved as an adjunctive therapy in patients 12 years of age and above with refractory partial epilepsy. The purpose of the studies in this NDA submission was to confirm the efficacy of gabapentin in children under 12 years of age.

Two clinical studies are included in this NDA submission: Study 86/186 and Study 305/405. Study 86/186 was a 12-week study conducted in patients of age 3 years to 12 years old, and Study 305/405 was a 3-day lab study conducted in patients of age one month to 3 years old.

2. Specifications and Findings of Study 86/186

The purpose of study 86/186 was to confirm the efficacy of GBP in children under 12 years of age. Study 945-86 was initiated in June 1993; it was to be conducted exclusively at sites in the United Kingdom. The sponsor stated that due to slow enrollment, sites were initiated a year later in Europe, South Africa, and the United States. For administration reasons, these additional sites were given a different protocol number (945-186). Protocol 945-186 stipulated that data from both studies were to be pooled and a combined analysis was to be performed. The studies are thus referred to as a single study (945-86/186).

2.1 Objectives

The objectives of the study were as follows:

- To evaluate the efficacy of gabapentin compared to placebo as add-on therapy in the treatment of pediatric patients with medically uncontrolled partial seizures;
- To examine the safety profile of gabapentin compared with placebo as add-on therapy in this population; and
- To compare the global effects of gabapentin with placebo as add-on therapy on patients' seizures and wellbeing.

2.2 Study Management

Study 945-86 was performed at 23 centers in the UK and the study 945-186 was performed at 31 centers in Europe, South Africa, and the US. The first patient in study 945-86 entered baseline on June 6, 1993, and the last patient completed the double-blind phase of the study on September 24, 1996. The first patient in study 945-186 entered baseline on November 18, 1994, and the last patient completed double-blind phase of the study on November 20, 1996.

2.3 Study Design

Study 945-86/186 was a 12-week, randomized, double-blind, parallel-group comparison of gabapentin versus placebo as add-on therapy in children. The study comprised two phases:

- Baseline: During the 6-week baseline phase, patients' concurrent AED therapies were maintained. Patients' seizures were recorded by their parents/legal guardians in a daily diary.
- Double-blind: Patients who had experienced a minimum of four seizures (with at least one in each 2-week period of the baseline phase) were randomly assigned to add-on therapy with either gabapentin or placebo for a 12-week double-blind treatment period. The randomization was to provide equal allocation of patients to gabapentin and placebo treatment. Gabapentin dosage was dependent upon patient weight at entrance into this phase. A final dose of 23.2 to 35.3 mg/kg/day (600-1800 mg/day), administered as TID regimen, was to be achieved. Existing AED therapy was continued.

To achieve the targeted dosage range, patients were assigned one of the two sets of study medication based on their weight. Patients weighing 17 to 36.9 kg received medication Set A (100-mg gabapentin or placebo capsules), whereas patients weighing 37 to 72 kg received medication Set B (200 mg gabapentin or placebo capsules). Medication was titrated to the largest dosage by the third day of dosing.

To response to an adverse event (AE), investigators were allowed to reduced the study medication dosage from 3 to 2 times a day (eliminating the midday dose) for no more than 2 consecutive days during the double-blind phase. If the adverse event had not resolved after 2 days so that 3 times a day dosing could be reinstituted, patients were to be withdrawn.

2.4 Main Inclusion Criteria

Patients were required to meet the following criteria to be enrolled in the study:

- Boys or girls, 12 years of age or younger, who weighed between 17 and 72 kg and were able to swallow study medication capsules;

- Had seizures classified as simple partial, complex partial, or partial becoming secondarily generalized;
- Were currently receiving 1, 2, or 3 standard AEDs but not achieving satisfactory seizure control.

2.5 Concurrent Antiepileptic Drug Treatment

Patients were required to maintain current AED therapy at constant dosages during both the baseline and double-blind phases of the study. AEDs given to *pro re nata* (prn) were permitted.

2.6 Efficacy Variables

2.6.1 Primary Efficacy Variables

The protocol specified that seizure reduction would be measured using two primary efficacy variables, Response Ratio (R-Ratio) and Responder rate. The sponsor stated that the inferential analysis plan, which was finalized before blind was broken, further stipulated that R-Ratio was to be considered more important of these parameters, with responder rate considered to be complementary. It was stated in the analysis plan that study results were to be interpreted as demonstrating a significant difference between gabapentin and placebo if R-Ratio for all partial seizures were significantly different between the two groups as $p<0.05$.

Response Ratio

Seizure frequency was expressed as the number of seizures per 28 days:

$$\text{Seizure Frequency} = (\text{Number of seizures}/\text{Number of days}) \, 28$$

R-Ratio compares seizure frequency per 28 days during baseline (B) with seizure frequency per 28 days during treatment (T). R-Ratio is defined as R-Ratio= (T-B)/(T+B).

The R-Ratio is always between –1 and +1. Negative values indicate a reduction in seizure frequency during treatment relative to baseline, whereas positive values indicate an increase.

Responder Rate

A patient with a 50% or greater reduction in the number of seizures per 28 days during treatment compared with baseline was classified as a responder. Responder rate is the percent of patients in each treatment group who were responders.

2.6.2 Secondary Efficacy Variables

Secondary efficacy variables were percent change (PCH) from baseline to treatment in partial seizure frequency, PCH and R-Ratio for individual types of partial seizures (simple partial seizure, complex partial seizure, and partial seizures secondarily generalized), and global assessments by the investigator and the parent/guardian.

At the end of double-blind phase, the parent/guardian and physician each made a global assessment of the patient's seizure frequency and well-being as compared with before treatment (significant improvement, slight improvement, no change, worse, significantly worse).

2.6.3 Efficacy Population

The primary efficacy variables, R-Ratio and Responder rate, were based on seizure frequency per 28 days. The sponsor stated in the protocol that the primary efficacy analyses would utilize data from a modified intend-to-treat (MITT) patient population, including only those patients who had at least 28 days of seizure data in baseline phase and 28 days of seizure diary in the double-blind phase.

2.7 Statistical Method

2.7.1 Primary Analysis: R-Ratio for All Partial Seizures

The primary analysis of R-Ratio for all partial seizures evaluated data for the MITT (modified intent-to-treat) population. R-Ratio was evaluated by analysis of variance (ANOVA), including effects of treatment and center. Generalizability of results among centers was tested by repeating the ANOVA including a treatment-by-center interaction term. If an interaction was suggested ($p<0.20$), then the treatment effect within each center was examined. The assumption of normality was tested by examining the residuals from the model. If there was evidence of non-normality, ANOVA on rank-transformed data was performed.

2.7.2 Complementary Analysis: Responder Rate for All Partial Seizures

The primary analysis of responder rate for all partial seizures evaluated data for the MITT population. Responder rates were calculated for the gabapentin and placebo treatment groups and treatment difference was analyzed using the Cochran-Mantel-Haenszel (CMH) test, adjusting for center. Homogeneity among centers was evaluated using the Breslow-Day test.

2.7.3 Analysis of Secondary Efficacy Variables

No inferential testing were specified for variables of response ratio for individual types of partial seizures and percent change in seizure frequency. Only descriptive statistics were computed for those variables for the MITT population. Analyses of global assessments were performed using data for the ITT population only. Global assessment by physician

and parent/guardian were compared between the two treatment groups using the center adjusted Cochran-Mantel-Haenszel (CMH) test.

2.7.4 Center Grouping

The sponsor stated that after study was completed and before the blind was broken, the groupings were specified: 6 small centers in Study 945-86 were pooled into one larger center, and 13 small centers in Study 945-186 were pooled to form 3 larger centers.

2.8 Protocol Amendments

Amendment 3 changed duration of baseline period from 12 weeks to 6 weeks. Accordingly, the minimum number of seizures required for entering double-blind treatment phase was changed from 8 seizures to 4 seizures with at least one seizure in each 2-week, instead of 4-week, period (Amendment 4).

In Amendment 5, the inclusion criteria for the age of the pediatric patients was changed from 5-12 years to any age under 12 years, allowing children under age 5 to be included. The criteria for the weight were maintained.

In Amendment 6, the inclusion criteria for current AEDs were changed from 2 AEDs to 3 AEDs.

The following differences in protocols 945-86 and 945-186 were reported:

- Patients aged 2-12 years were included. This was amended on March 24, 1994, to allow patients aged up to and including 12 years to enter the study.
- Weight >= 17 kg. There was no upper limit in Protocol 945-86.
- Patients were to be currently receiving 1 or 2 anticonvulsant drugs. This was amended on March 25, 1994, to allow patients receiving 1, 2, or 3 standard anticonvulsant drugs to enter the study.

2.8 Results: Sponsor's Analysis

2.8.1 Patient Baseline and Demographic Characteristics

A total of 247 patients entered the double-blind treatment phase of the study (sponsor's Table 2). Of those, 119 patients were randomly assigned to the gabapentin group, and 128 patients were assigned to the placebo group. The sponsor reported that the treatment groups were comparable at screening with respect to demographic variables.

Spnsor's table

TABLE 2. Characteristics of the MITT and ITT Populations: Study 945-86/186

Characteristic	MITT Population		ITT Population	
	Placebo N = 120	Gabapentin N = 113	Placebo N = 128	Gabapentin N = 119
Gender, N (%)				
Males	68 (56.7)	54 (47.8)	75 (58.6)	59 (49.6)
Females	52 (43.3)	59 (52.2)	53 (41.4)	60 (50.4)
Age, years				
Mean ± SD	8.5 (2.8)	8.5 (2.4)	8.4 (2.7)	8.5 (2.4)
Range	3 - 12	3 - 12	3 - 12	3 - 12
Race, N (%)				
White	112 (93.3)	103 (91.2)	118 (92.2)	108 (90.8)
Black	1 (0.8)	3 (2.7)	1 (0.8)	3 (2.5)
Asian	3 (2.5)	2 (1.8)	4 (3.1)	2 (1.7)
Other	4 (3.3)	5 (4.4)	5 (3.9)	6 (5.0)
Height, cm	N = 118	N = 109	N = 126	N = 115
Mean ± SD	131.9 (16.8)	131.2 (14.9)	131.3 (16.7)	131.3 (14.7)
Range	96 - 175	99 - 170	96 - 175	99 - 170
Weight, kg	N = 118	N = 109	N = 126	N = 115
Mean ± SD	32.4 (11.7)	31.3 (11.1)	32.1 (11.7)	31.6 (11.1)
Range	15.5 - 73.1	15.9 - 67.5	15.5 - 73.1	15.9 - 67.5
Baseline Partial Seizure Frequency per 28 Days				
Mean ± SD	64.6 (106.3)	76.6 (275.1)	63.3 (103.8)	74.5 (268.3)
Median	28.0	25.4	28.0	24.1
Range	1.3 - 698.0	2.7 - 2893.3	1.3 - 698.0	2.7 - 2893.3

SD = standard deviation, ITT = intent-to-treat, MITT = modified intent-to-treat.

The sponsor stated that all of the patients who entered double-blind treatment phase had medically refractory partial seizures. Age at onset, duration, and etiology of epilepsy were similar between the two treatment groups. The treatment groups were also similar with respect to both the types of seizures that patients had experienced at any time prior to screening and median baseline seizure frequency. The sponsor reported that the seizures experienced by this patient population were highly refractory to treatment. At screening, 46% of all patients had tried and failed more than 4 AEDs, and the majority of patients (70%) were currently taking 2 or 3 AEDs. A summary of disease characteristics is provided in the following table.

Sponsor's table

TABLE 3. Summary of Disease Characteristics (Randomized Patient Population): Study 945-86/186

Characteristic	Placebo N = 128	Gabapentin N = 119	Total N = 247
Age at Epilepsy Onset, years			
Mean ± SD	3.0 (2.5)	2.7 (2.6)	2.9 (2.6)
Median	2.5	2.0	2.3
Range	<1 - 10.7	<1 - 9.5	<1 - 10.7
Duration of Epilepsy, years			
Mean ± SD	5.4 (3.1)	5.7 (3.0)	5.6 (3.0)
Median	5.3	5.9	5.6
Range	<1 - 11.9	<1 - 11.3	<1 - 11.9
Etiology of Epilepsy[a], N (%)			
Birth Complications	15 (11.7)	12 (10.1)	27 (10.9)
Infection	14 (10.9)	8 (6.7)	22 (8.9)
Family History of Epilepsy	11 (8.6)	11 (9.2)	22 (8.9)
Head Trauma	1 (0.8)	4 (3.4)	5 (2.0)
Unknown	72 (56.3)	60 (50.4)	132 (53.4)
Other	27 (21.1)	34 (28.6)	61 (24.7)
Types of Seizures Experienced (History at Screening)[a]			
Simple Partial	58 (45.3)	54 (45.4)	112 (45.3)
Complex Partial	112 (87.5)	99 (83.2)	211 (85.4)
Partial Secondarily Generalized	70 (54.7)	73 (61.3)	143 (57.9)
Myoclonic	12 (9.4)	16 (13.4)	28 (11.3)
Tonic-Clonic	13 (10.2)	15 (12.6)	28 (11.3)
Tonic	11 (8.6)	8 (6.7)	29 (11.7)
Atonic	9 (7.0)	8 (6.7)	17 (6.9)
Atypical Absence	7 (5.5)	7 (5.9)	14 (5.7)
Clonic	2 (1.6)	2 (1.7)	4 (1.6)
Absence	2 (1.6)	0 (0.0)	2 (0.8)
Unclassified	4 (3.1)	5 (4.2)	9 (3.6)

SD = standard deviation.

[a] Patients could have more than 1 category of epilepsy etiology and more than 1 seizure type.

2.8.2 Patient Disposition

The sponsor reported that 25 of the 272 children who entered baseline withdrew, so that 247 were randomized (128 to the placebo group and 119 to gabapentin treatment). During the study 49 patients (20%) withdrew. More patients in the placebo group than in the gabapentin group withdrew due to lack of efficacy (15% versus 9%), while the rate for adverse event withdrawals was higher for gabapentin (5% versus 2%). Completion rate was similar in the two groups (78%, placebo versus 82%, gabapentin).

Sponsor's Table

TABLE 5. Patient Disposition: Study 945-86/186
[Number (%) of Patients]

	Placebo		Gabapentin		Total	
Entered Baseline	NA		NA		272	
Withdrawn During Baseline	NA		NA		25	
Randomized	128		119		247	
MITT	120		113		233	
Withdrawals Due to:						
Lack of Efficacy	19	(14.8)	11	(9.2)	30	(12.1)
Adverse Events	3	(2.3)	6	(5.0)	9	(3.6)
Change in Current AED	2	(1.6)	0	(0.0)	2	(0.8)
Other	4	(3.1)	4	(3.4)	8	(3.2)
Total Withdrawn	28	(21.9)	21	(17.6)	49	(19.8)
Total Completed	100	(78.1)	98	(82.4)	198	(80.2)
Entered Open-Label (945-87/187)	120	(93.8)	112	(94.1)	232	(93.9)

NA = not applicable, MITT = modified intent-to-treat.

2.8.3 Number of Patients in Efficacy Populations

Patients with one or more reasons for exclusion from the MITT population (<28 days of seizure diary in baseline or double-blind, <28 days of study medication) are detailed in Table 11. The sponsor reported that 14 patients listed in the table (8 placebo, 6 gabapentin) were excluded from the MITT population, resulting in 120 placebo patients and 113 gabapentin patient included in the MITT population.

Sponsor's Table 11. Details of patients excluded from the MITT population

Protocol-center-patient	Treatment Group	Number of Days of Seizure Diary During Baseline	Number of Days of Seizure Diary During Double-Blind	Number of Days of Study Medication
086-17-1	Placebo		18	
086-20-4	Placebo		0	6
186-2-3	Placebo		6	6
186-2-6	Placebo		3	4
186-7-4	Placebo	10		
186-12-4	Placebo		1	1
186-13-3	Placebo		10	10
186-18-3	Placebo		14	14
086-11-1	Gabapentin		9	8
086-17-11	Gabapentin		20	20
186-18-1	Gabapentin	15		
186-24-3	Gabapentin		26	26
186-29-11	Gabapentin		0	1
186-30-11	Gabapentin		14	14

The sponsor stated that the ITT and MITT populations had similar demographic profiles. Exclusion of patients from MITT population did not appear to select for any specific characteristics and did not affect the overall profile of the patient population.

2.8.4 Efficacy Results

2.8.4.1 Primary Efficacy Variable: Response Ratio for All Partial Seizures

The sponsor reported that gabapentin was significantly better than placebo in controlling partial seizures based on the primary analysis of R-Ratio (MITT population) with a p-value of 0.0407. It was also reported that the results of the supplemental analysis (ITT population) did not show a significant difference in R-Ratio between the treatment groups. Results of the primary analysis of R-Ratio with MITT and ITT populations are shown in sponsor's Table 9 and Table 10, respectively.

TABLE 9. Primary Analysis of Response Ratio for All Partial Seizures (MITT Population): Study 945-86/186

Treatment Group	N	Least Squares Mean[a]	Standard Error	Treatment Comparison (Gabapentin - Placebo) Difference	95% CI[b]	p-Value
Placebo	120	-0.072	0.031			
Gabapentin	113	-0.161	0.031	-0.089	(-0.174, -0.004)	0.0407

MITT = modified intent-to-treat, CI = confidence interval.
[a] Analysis of Variance, main effects model
[b] CI = confidence interval; 2-sided with 95% probability.

TABLE 10. Supplemental Analysis of Response Ratio for All Partial Seizures (ITT Population): Study 945-86/186

Treatment Group	N	Least Squares Mean[a]	Standard Error	Treatment Comparison (Gabapentin - Placebo) Difference	95% CI[b]	p-Value
Placebo	127	-0.079	0.031			
Gabapentin	118	-0.146	0.032	-0.067	(-0.153, -0.019)	0.1246

ITT = intent-to-treat, CI = confidence interval.
[a] Analysis of Variance, main effects model
[b] CI = Confidence interval; 2-sided with 95% probability.

The sponsor stated that examination of the residuals from the model revealed evidence of non-normality in the distribution of the data. Therefore, an ANOVA was performed on rank transformed data for each population. Results of the analyses showed that mean R-Ratio was significantly lower (better) for the gabapentin treatment group than for the placebo group in both the MITT (p=0.0103) and ITT (p=0.0299) populations (Table 11).

TABLE 11. Analysis of Response Ratio for All Partial Seizures Using ANOVA With Rank Transformation: Study 945-86/186

Population	Treatment Comparison	Estimate	Standard Error	95% Confidence Interval[a]	p-Value
MITT	Gabapentin - Placebo	-23.0	8.9	(-40.4, -5.5)	0.0103
ITT	Gabapentin - Placebo	-19.8	9.0	(-37.6, -1.9)	0.0299

MITT = modified intent-to-treat, ITT = intent-to-treat, ANOVA = analysis of variance.
[a] 2-sided with 95% probability

2.8.4.2 Primary Efficacy Variable: Responder Rate for All Partial Seizures

The sponsor reported that results of the CMH analysis of responder rate for all partial seizures showed no significant difference between treatment groups for both the MITT (p=0.355) and ITT (p=0.500) populations (Table 12). The Breslow-Day test indicated homogeneity among centers (MITT, p=0.101; ITT p=0.227).

TABLE 12. Responder Rate for all Partial Seizures (MITT and ITT Populations): Study 945-86/186

Population	Treatment Group	N	Number of Responders	Responder Rate	CMH p-Value
MITT	Placebo	120	21	17.5%	
	Gabapentin	113	24	21.2%	0.335
ITT	Placebo	127	23	18.1%	
	Gabapentin	118	25	21.2%	0.500

MITT = modified intent-to-treat, ITT = intent-to-treat, CMH = Cochran-Mantel-Haenszel.

2.8.4.3 Secondary Efficacy Analysis

Secondary efficacy variables of Response Ratio by Seizure Type and Percentage Change from Baseline for All Partial Seizures were designated as for descriptive purpose only. The following tables present the descriptive statistics of those secondary efficacy variables.

Sponsor's Table 17. 95% Confidence Intervals for the Difference in Mean R-Ratio by Seizure Type: MITT population

Seizure Type	Difference in Mean R-Ratio	95% CI
Simple Partial	-0.035	(-0.235, 0.165)
Complex Partial	-0.062	(-0.192, 0.069)
Secondarily Generalized	0.154	(-0.346, 0.039)

Sponsor's Table 18. Percent Change from Baseline for All Partial Seizures and by Seizure Type: MITT Population

	Placebo		Gabapentin	
	N	Median	N	Median
All Partial	120	-6.5	113	-17.0
Simple Partial	48	-14.0	41	-15.0
Complex Partial	94	-12.0	83	-35.0
Secondarily Generalized	43	13.2	51	-28.0

Global Assessment

Global assessments of the patients' seizure frequency and well-being during the double-blind phase as compared to baseline were made by both physician and the parent/guardian at the end of the double-blind treatment phase. The sponsor reported that the only assessment that differed significantly between the gabapentin and placebo treatment groups was the evaluation of seizure frequency by the parent/guardian (CMH test, p=0.046). The parent/guardians of children receiving gabapentin felt there was more improvement and less worsening of their seizure frequency than did the parent/guardian of children treated with placebo.

2.10 Reviewer's Analysis

2.10.1 Efficacy Results for Study 86/186

2.10.1.1 Primary Efficacy Analysis

The efficacy analyses specified and performed by the sponsor were replicated and the results reported by the sponsor were confirmed to be correct.

The protocol specified two primary efficacy variables, the R-Ratio and responder rate. The primary analysis for the R-Ratio was ANOVA with treatment and center as factors. The analysis was performed, and the residuals from the ANOVA model were examined by the Shapiro-Wilk test and graphic method for the normal assumption to be met. It was found that the p-value from the Shapiro-Wilk test was 0.0272 using the MITT population and 0.0024 using the ITT population. Therefore, the normal assumption for the ANOVA model was considered as being violated. According to the protocol, the same ANOVA model was performed on the rank-transformed data. The p-values from the ANOVA model on the rank-transformed data were found to be 0.0299 for the ITT population and 0.0103 for the MITT population.

The primary analysis for responder rate was CMH test controlling for center. The analysis was performed and no evidence of efficacy was found. The p-value obtained from the center controlled CMH test was 0.369 using MITT population and 0.5000 using ITT population. These p-values were the same as obtained by the sponsor.

Descriptive statistics for R-Ratio and responder rate with respect to gender and age are presented in the following table.

Reviewer's Table 1. Descriptive statistics of primary efficacy variables by gender and age.

			Protocol 086/186	
			Placebo	Gabapentin
R-Ratio				
Sex	Male	n	74	59
		Mean (SD)	-0.078 (.366)	-0.127 (.272)
		Median	-0.056	-0.072
	Female	n	53	59
		Mean (SD)	-0.101 (.343)	-0.181 (.345)
		Median	-0.015	-0.109
Age	< 9	n	62	58
		Mean (SD)	-0.091 (.400)	-0.188 (.303)
		Median	-0.046	-0.114
	>= 9	n	65	60
		Mean (SD)	-0.085 (.310)	-0.121 (.317)
		Median	-0.015	-0.083
Responder Rate (%)				
Sex	Male		17.57	20.34
	Female		18.87	22.03
Age	< 9		19.35	25.86
	>= 9		16.92	16.67

2.10.1.2 Analysis of Secondary Efficacy Variables

Results from analysis of Global Assessment and descriptive statistics of other secondary efficacy variables reported by the sponsor have been verified by this reviewer. The results obtained by this reviewer agree with the results obtained by the sponsor (see Section 2.8.4.3).

3. Specifications and Findings of Study 305/405

3.1 Objectives

The objectives of the study were as follows:

- To evaluate the effect of gabapentin treatment on the frequency of partial seizures in pediatric patients 1 to 36 months of age with epilepsy;
- To evaluate the short term safety gabapentin treatment; and
- To assess the pharmacokinetics of gabapentin treatment using a population approach.

3.2 Study Management

Protocol 945-305 was conducted at 73 centers in the United States and Canada, and Protocol 945-405 was conducted at 15 international centers.

The first patient in study 945-305 entered baseline on April 11, 1999 and the last patient completed the double-blind phase of the study on August 19, 1999. The first patient in study 945-405 entered baseline on June 3, 1999 and the last patient completed double-blind phase of the study on August 19, 1999.

3.3 Study Design

This randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluated gabapentin as adjunctive therapy in pediatric patients with partial seizures. The study consisted a 3-day baseline phase, a 3-day double-blind treatment phase, and a 2-day withdrawal phase.

Patients were eligible for study entry if they had a confirmed diagnosis of partial seizures that are not adequately controlled by concurrent therapy with at least one AED. Following the screening, eligible patients entered a 3-day baseline phase, which included a target of 48 hours of video-EEG monitoring. At the end of the baseline phase, patients were randomized to receive gabapentin (40 mg/kg/day given TID) or placebo treatment to enter the 3-day double-blind phase, during which video-EEG monitoring (target 72 hours of recording) was conducted.

3.4 Main Inclusion Criteria

Eligible pediatric patients met the following entry criteria:

- Male or female one month to 36 months of age, who weighed between 3.5 and 20 kg;
- Were receiving at least one marketed AED;
- Ceased taking gabapentin (if previously on gabapentin treatment) at least one week prior to the start of the screening period;
- Had at least one partial seizure during the screening period (within two weeks prior to baseline).

3.5 Efficacy Variables

The sponsor stated that efficacy parameters were defined in the Inferential Analysis Plan, which was finalized before the study medication blind was broken. The primary criterion to establish the efficacy of gabapentin was the reduction in the 28-day all partial seizure rate during treatment with study medication compared to baseline. A 28-day all partial seizure rate was calculated for each phase by dividing the number of all partial seizures (PS) observed during the video-EEG monitoring by the total hours of recordable time for that phase in accordance with the following formula:

28-day all PS rate = (# of all PS in phase)/(total recordable hours in phase) * 24 * 28

3.5.1 Primary Efficacy Parameter

The primary efficacy parameter was the response ratio (R-Ratio or symmetrized proportional change) for all partial seizures (simple partial + complex partial + SGTC).

3.5.2 Secondary Efficacy Variables

The protocol defined two secondary efficacy parameters: responder rate and percent change in the 28-day all partial seizure rate between the double-blind and baseline phase. In addition, the sponsor included another parameter in the inferential analysis. This parameter was defined as the proportion of patients who exhibited a decrease in each treatment group as measured by the ratio of the 28-day SGTC seizure rate to the 28-day partial seizure rate (total of simple and complex partial seizures).

Details about response ratio and responder rate were described previously in study 945-86/186. The intent-to-treat population was defined as the primary efficacy population.

3.6 Statistical Method

3.6.1 Analysis of Primary Efficacy Variables

The primary analysis of the R-Ratio for all partial seizures was performed on the ITT population. For patients with no video-EEG record during the baseline or during both the baseline and double-blind phases, the R-Ratio was defined as zero. For patients missing double-blind seizure data, their baseline all partial seizure rates were carried forward, which resulted in an R-Ratio zero. Patients with no seizures in both the baseline and double-blind phase were defined to have an R-Ratio of zero.

The statistical comparison of R-Ratio between the two treatment groups was based on analysis of covariance (ANCOVA) using the rank transformation approach adjusting for patient's gender.

3.6.2 Analysis of Secondary Efficacy Variables

The primary analysis of the responder rate for all partial seizures was performed on the ITT population. Patients with no seizures at the baseline and the double-blind phases were defined as non-responders. Responder rates were calculated for each treatment group, and were analyzed using Fisher's exact test.

No inferential testing was performed for the percentage change in seizure frequency. The analysis of the proportion of patients exhibiting a decrease in the ratio of the 28-day SGTC seizure rate to the 28-day partial seizure rate was performed using the secondarily generalized seizure population. The proportion of patients exhibiting a decrease in SGTC seizures between the two treatment groups was compared using Fisher's exact test.

3.7 Results: Sponsor's Analysis

3.7.1 Patient Baseline and Demographic Characteristic

A total of 76 pediatric patients were randomly assigned to treatment (ITT patient population): 38 patients to placebo and 38 patients to gabapentin. Of the 76 patients, there were more male (approximately 60%) than female (approximately 40%) pediatric patients. Most patients in each treatment group were white. The sponsor stated that the median 28-day all partial seizure rate during the baseline phase was similar between the 2 treatment groups and demographic variables were similarly distributed between the 2 treatment groups (Table 6).

TABLE 6. Characteristics of the ITT and Evaluable Populations: Study 945-305/405

Characteristic	ITT Population		Evaluable Population	
	Placebo N = 38	Gabapentin N = 38	Placebo N = 25	Gabapentin N = 22
Gender, N (%)				
Males	22 (57.9)	24 (63.2)	15 (60.0)	14 (63.6)
Females	16 (42.1)	14 (36.8)	10 (40.0)	8 (36.4)
Race, N (%)				
White, Non-Hispanic	23 (60.5)	22 (57.9)	15 (60.0)	13 (59.1)
Black, Non-Hispanic	7 (18.4)	7 (18.4)	5 (20.0)	3 (13.6)
Hispanic	7 (18.4)	8 (21.1)	4 (16.0)	5 (22.7)
Other	1 (2.6)	1 (2.6)	1 (4.0)	1 (4.5)
Age, months				
N	38	38	25	22
Mean ±SD	17.9 (8.1)	19.0 (8.7)	15.9 (7.7)	18.4 (10.5)
Median	17.6	18.4	14.8	18.1
Range	2.0 – 33.3	1.9 – 36.0	2.0 – 29.0	1.9 – 36.0
Age Categories, months, N (%)				
<3	2 (5.3)	2 (5.3)	2 (8.0)	2 (9.1)
3 to <6	1 (2.6)	1 (2.6)	1 (4.0)	1 (4.5)
6 to <12	5 (13.2)	6 (15.8)	5 (20.0)	5 (22.7)
12 to <24	20 (52.6)	17 (44.7)	11 (44.0)	5 (22.7)
24 to 36	10 (26.3)	12 (31.6)	6 (24.0)	9 (40.9)
Weight, kg				
N	38	38	25	22
Mean ±SD	10.4 (3.0)	11.1 (3.0)	9.7 (3.0)	10.5 (3.2)
Median	10.2	10.9	10.1	10.2
Range	3.0 – 17.5	3.5 – 18.6	3.0 – 15.0	3.5 – 15.9
Height/Length, cm				
N	37	37	24	21
Mean ±SD	78.9 (11.6)	81.3 (11.1)	75.6 (11.6)	79.9 (12.4)
Median	80.0	83.0	78.9	83.5
Range	47.5 – 99.6	53.5 – 101.0	47.5 – 90.0	53.5 – 95.0
Baseline Partial Seizure Frequency per 28 Days				
N	38	38	25	22
Mean ±SD	291.7 (621.6)	266.1 (537.1)	443.4 (725.0)	459.6 (644.3)
Median	24.1	22.5	56.0	142.1
Range	0.0 – 2790.5	0.0 – 2302.2	0.0 – 2790.5	0.0 – 2302.2

SD = standard deviation, ITT = intent-to-treat.

The mean age of epilepsy onset was 5.8 ±5.2 months for patients treated with placebo and 4.1 ±4.0 months for patients treated with gabapentin (Table 7). All patients were diagnosed with partial seizures and had a history of either partial seizures (71.1%, placebo; 78.9%, gabapentin), SGTC seizures (63.2%, placebo; 65.8%, gabapentin), or

both. At baseline, all patients in each treatment group were taking concurrent AEDs. The sponsor stated that the most frequently used AED was carbamzepine in the placebo group and phenobarbital in the gabapentin group.

TABLE 7. Summary of Disease Characteristics (ITT and Evaluable Populations): Study 945-305/405

	ITT Population		Evaluable Population	
	Placebo N = 38	Gabapentin N = 38	Placebo N = 25	Gabapentin N = 22
Age at Onset, months				
N	38	38	25	22
Mean (SD)	5.8 (5.2)	4.1 (4.0)	3.7 (3.6)	3.0 (3.4)
Median	3.8	3.1	2.7	1.8
Range	0.00 – 17.60	0.03 – 14.18	0.00 – 12.14	0.03 – 11.91
Etiology of Epilepsy, N (%) [a]				
Birth Complications	5 (13.2)	6 (15.8)	4 (16.0)	3 (13.6)
Infections	7 (18.4)	4 (10.5)	3 (12.0)	2 (9.1)
Family History of Epilepsy	4 (10.5)	6 (15.8)	2 (8.0)	4 (18.2)
Unknown	19 (50.0)	12 (31.6)	13 (52.0)	6 (27.3)
Other	7 (18.4)	13 (34.2)	7 (28.0)	9 (40.9)
Types of Seizures Experienced (History at Screening), N (%) [a]				
Partial (Simple or Complex)	27 (71.1)	30 (78.9)	20 (80.0)	18 (81.8)
Partial Secondarily Generalized	24 (63.2)	25 (65.8)	14 (56.0)	12 (54.5)
Myoclonic	0 (0.0)	1 (2.6)	0 (0.0)	1 (4.5)
Clonic	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)
Tonic	2 (5.3)	5 (13.2)	1 (4.0)	3 (13.6)
Tonic-Clonic	0 (0.0)	5 (13.2)	0 (0.0)	3 (13.6)
Atonic	0 (0.0)	2 (5.3)	0 (0.0)	0 (0.0)
Other (Infantile Spasms)	2 (5.3)	11 (28.9)	1 (4.0)	7 (31.8)
Prior AED Therapy[b]				
N (%) of Patients	38 (100.0)	38 (100.0)	25 (100.0)	22 (100.0)

SD = standard deviation, ITT = intent-to-treat, AED = antiepileptic drug.

[a] Patients could have more than 1 category of epilepsy etiology and more than 1 seizure type.

[b] Includes concurrent AEDs taken at start of baseline (Day B1).

3.7.2 Concurrent Medications

Overall, 22 patients (28.9%) took one or more concurrent non-antiepileptic medications during the study. A greater proportion of placebo-treated patients (39.5%) used non-antiepileptic medications than gabapentin-treated patients (18.4%). The sponsor stated that no concurrent non-antiepileptic medications taken by these patients were considered likely to impact study results.

3.7.3 Patient Disposition

Of the 114 pediatric patients who were screened, 76 (66.7%) entered the baseline phase of the study (Table 8). The sponsor reported that no patients withdrew during the baseline phase and all 76 patients were randomly assigned to study treatment (38 patients to each group). Thirty-six (94.7%) placebo-treated patients and 38 (100%) gabapentin treated patients completed the double-blind phase. One placebo-treated patient withdrew early due to lack of efficacy and one placebo-treated patient withdrew due to other administrative reasons.

TABLE 8. Patient Disposition: Study 945-305/405
[Number (%) of Patients]

	Placebo		Gabapentin		Total	
Entered Screening	NA		NA		114	
Withdrawn During Screening						
No Seizures Recorded	NA		NA		7	
No Partial Seizures Recorded	NA		NA		16	
Other/Administrative	NA		NA		15	
Entered Baseline	NA		NA		76	
Withdrawn During Baseline	NA		NA		0	
Randomized	38		38		76	
Withdrawn During Double-Blind						
Lack of Efficacy	1	(2.6)	0	(0.0)	1	(1.3)
Other/Administrative	1[a]	(2.6)	0	(0.0)	1	(1.3)
Completed Double-Blind Treatment Phase	36	(94.7)	38	(100.0)	74	(97.4)
Entered Open-Label (945-301/401)	38	(100.0)	37	(97.4)	75	(98.7)

NA = not applicable, EEG = electroencephalogram.
[a] Patient could not tolerate continual video-EEG monitoring.

3.7.4 Efficacy Results

3.7.4.1 Primary Efficacy Analysis

The sponsor reported that the mean R-Ratio was -0.048 for gabapentin-treated patients and 0.018 for placebo-treated patients (Table 17). The difference in R-Ratio between treatment groups (-0.066) was not statistically significant ($p = 0.369$).

Both male and female pediatric patients in the gabapentin group had a decrease in their double-blind rate from the baseline rate with a mean R-Ratio of -0.032 and -0.072,

respectively. Placebo-treated patients did not show a corresponding decrease as indicated by their R-Ratios (0.013 for males and 0.026 for females).

TABLE 17. Primary Analysis of Response Ratio for All Partial Seizures in ITT Population: Study 945-305/405

			Treatment Comparisons (Gabapentin – Placebo)	
Treatment Group	N	Mean (SE)	Difference	p-Value[b]
All Patients[a]				
Placebo	38	0.018 (0.071)	-0.066	0.369
Gabapentin	38	-0.048 (0.071)		
Males[c]				
Placebo	22	0.013 (0.117)	NA	NA
Gabapentin	24	-0.032 (0.070)		
Females[c]				
Placebo	16	0.026 (0.121)	NA	NA
Gabapentin	14	-0.072 (0.078)		

ITT = intent-to-treat, SE = standard error, NA = not applicable.
[a] Least squares means from ANCOVA using raw data, adjusted for gender.
[b] ANCOVA using rank transformation, adjusted for gender.
[c] Raw means.

3.7.4.2 Analysis of Secondary Efficacy Variables

Responder Rate for All Partial Seizures

The responder rate, i.e., the proportion of patients whose partial seizure rate declined by 50% or more, was 13.2% for both gabapentin-treated and placebo-treated patients (Table 19).

TABLE 19. Analysis of Responder Rate for All Partial Seizures: Study 945-305/405

Population	Treatment Group	N	Number of Responders	% Responders	p-Value[b]
ITT[a]	Placebo	38	5	13.2%	>0.999
	Gabapentin	38	5	13.2%	

ITT = intent-to-treat.
[a] Patients with no seizures in the baseline and double-blind phases were defined as non-responders.
[b] Fisher's exact test.

Percent Change in 28-day All Partial Seizure Rate

The sponsor reported that the mean percent changes in 28-day all partial seizure rates for gabapentin-treated and placebo-treated patients were –0.7% and 14%, respectively. Seizure rates declined in 26 patients (31.6% placebo-treated and 36.8% gabapentin-

treated) and increased in 50 patients (68.4% placebo-treated and 63.2% gabapentin-treated). No p-value was reported.

Proportion of Patients Exhibiting a Decrease in the Ratio of SGTC Seizure Rate to Partial Seizure Rate

The sponsor reported that this analysis was carried out using the SGTC seizure population, which include only 6 patients, equally distributed between the 2 treatment groups. Two of the 3 placebo-treated patients (66.7%) exhibited a decrease in the ratio of 28-day SGTC seizure rate to 28-day day partial seizure rate. None of the gabapentin-treated patients exhibited a decrease using the same ratio.

3.8 Reviewer's Analysis

The primary analysis specified by the protocol was ANOVA on R-Ratio adjusted by gender. It was found that the p-value from the analysis was 0.5079. The normal test on the residual of the ANOVA model suggested that the normal assumption was violated (p=0.0001, Shapiro-Wilk test). The same ANOVA model was then applied to the rank-transformed data of R-Ratio. The results from the ANOVA on rank-transformed data agree with the results from the sponsor (p=0.369).

For the secondary efficacy variable of responder rate, it was found that both treatment groups have the same responder rates (13.16%). Therefore, the analysis resulted in a p-value of 1.000. Descriptive statistics of other secondary efficacy variables reported by the sponsor were verified to be correct (see Section 3.7.4.2). No inferential analysis was planned on other secondary efficacy variables.

Based on the protocol specified efficacy variables and their corresponding analyses, this reviewer concluded that there is no evidence shown in this study that GBP is efficacious as an adjunctive therapy for treatment of epilepsy in this pediatric patient population.

4. Reviewer's Summary

In this submission of NDA two studies of GBP as adjunctive therapy for treatment of epilepsy in pediatric patient population were reviewed. Study 86/186 was conducted on patients of age 3 to 12 years old and study 305/405 was conducted on patients of age one month to 3 years old.

Study 305/405 designated response ratio as the primary efficacy variable. There was no significant difference between the gabapentin group and placebo group with respect to response ratio.

The following is a summary for study 86/186

Study 86/186 designated two primary efficacy variables, R-Ratio and Responder Rate. The designation of the primary efficacy variables was not changed in any of the six amendments. In a separate Inferential Analysis Plan, the sponsor stated that R-Ratio was to be considered most important of the parameters with Responder Rate considered to be complementary, and the study would be considered successful if R-Ratio was significantly different between the two treatment (favoring gabapentin) at $p<0.05$. The Inferential Analysis Plan, which was finalized 5 months after the trials had been completed but before the blind was broken, was not submitted to the agency. The results from analyses showed that the p-values of the difference between gabapentin-treated patients and placebo-treated patients at the end of the double-blind treatment were 0.0299 for the R-Ratio and 0.5000 for the responder rate.

Due to the conflicting efficacy results from the R-Ratio and responder rate, the issue of acceptability of the decision rule change, which was made in a document not submitted, has to be considered. The disparity between the results of R-Ratio and responder rate was examined. The following table displays the percentage in seizure reduction for the two treatment groups.

Reviewer's Table 2. Percentage of Seizure Reduction by Treatment Group (Study 86/186; ITT Population)

Percentage of seizure reduction	Placebo N=127	Gabapentin N=118
No reduction or increasing	54 (42.52%)	29 (24.58%)
0% - 10%	12 (9.45%)	16 (13.56%)
10% - 20%	12 (9.45%0	20 (16.95%)
20% - 30%	9 (7.09%)	9 (7.63%)
30% - 40%	6 (4.72%)	9 (7.63%)
40% - 50%	11 (8.66%)	10 (8.47%)
50%+ (Responder)	23 (18.11%)	25 (21.19%)

Although the responder rates for the two treatment groups were close (18.11% for the placebo group and 21.19% for gabapentin group), there were more patients in the gabapentin group who had seizure reduction compared to placebo group. There were generally more patients in the gabapentin group than in the placebo group who had seizure reduction across all categories except the category of 40% - 50% seizure reduction.

Recall that a patient who had 50% or more seizure reduction was categorized as a responder. In other words, responder rate is the percentage of patients who had seizure reduction of 50% or more. Since the percentage change of seizure frequency is a monotone function of the R-Ratio, the responder rate, obtained from the percentage change of seizure frequency, is not an independent variable of R-Ratio, but rather a derived variable from the R-Ratio. It appears that the loss of significance of responder rate is partly contributed by the loss of information in categorizing. On the other hand,

the R-Ratio is a continuous variable that measures overall seizure reduction across all levels. Table 2 suggests that gabapentin reduces seizures consistently across all levels.

In summary, although the acceptability of the inferential analysis plan is questionable, the disparity in efficacy results between the R-Ratio and the responder rate can be explained. This reviewer would recommend the agency to accept the R-Ratio to be the primary efficacy variable in study 86/186.

/S/

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Mathematical Statistician

Concur:

/S/

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HFD-710/Dr. Jin
HFD-710/Dr. Yan
This review consists of 22 pages. 10/3/00