

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number 21-216**

**MEDICAL REVIEW(S)**

## **MEMO TO FILE**

**Subject:           Supervisory Review, NDA 21-216**

**Date:               October 6, 2000**

### **Introduction**

The following formulations of Neurontin are currently approved: capsule, tablet, and oral solution. The oral solution was approved based on bioequivalence in NDA 21-129, but has not been marketed. The current NDA provides the results of controlled add-on trials in pediatric patients with partial seizures from 1 month to 12 years. In these trials, the capsule and oral solution formulations were used. Because the oral solution NDA was still under review when the sponsor wanted to submit these pediatric results, the pediatric studies were submitted under a new NDA (as opposed to a labeling supplement). Dr. Mani has reviewed the clinical data. Dr. Yan has provided the statistical review. And Dr. Sunzel has performed the biopharm review.

### **Efficacy**

#### **Study 86/186**

Study 86 was a randomized, double-blind, placebo-controlled, add-on trial of Neurontin in the treatment of partial seizures in patients aged up to 12 years of age. A lower age limit was not specifically stated; rather patients had to weigh 17 kg and be able to swallow capsules. The study was conducted entirely in the U.K. The study included a 6-week baseline and a 12-week treatment period.

Study 186 followed an identical protocol, but was conducted in Europe, South Africa, and the U.S. Protocol 186 stated that the results of 186 were to be pooled with the results of 86. The 2 studies can be considered a single study, referred to as Study 86/186.

The inclusion/exclusion criteria were standard, allowing patients to be on a maximum of 3 standard AEDs at stable doses.

To be randomized, a patient was required to have at least 4 seizures during baseline and at least 1 seizure during each 2-week segment of baseline.

Daily diaries were to be kept by the patient's parent or guardian.

The primary outcome measure was the response ratio, defined as  $(T - B)/(T + B)$ , where T = seizure frequency per 28 days during treatment and B = seizure frequency per 28 days during baseline.

The primary analysis was ANOVA, including effects of treatment and center. If there was evidence of non-normality, from examining the residuals from the model, then ANOVA on rank-transformed data was to be performed.

Patients were dosed with Neurontin capsules at a dose of 24-35 mg/kg/day divided into 3 doses. Dose titration took place over a 3 day period.

### Results

A total of 247 patients were randomized, 119 to Neurontin and 128 to placebo. The patients ranged in age from 3-12 years. Roughly 70% were currently taking 2-3 other AEDs. Of note, roughly 1/3 of patients was on either concomitant clobazam or vigabatrin, drugs not currently marketed in the US. Fourteen patients, 8 placebo and 6 Neurontin, had less than 28 days of either baseline seizure diary days, treatment period seizure diary days, or treatment period days of medication. These 14 patients were excluded from the sponsor's modified intent-to-treat or MITT population. The MITT included 120 placebo patients and 113 Neurontin patients.

Because non-normality was demonstrated by the protocol-specified test, the ANOVA was performed on rank-transformed data (as per protocol). For both the MITT population and the ITT population, a statistically significant difference in favor of Neurontin was found ( $p = 0.01$  for MITT;  $p = 0.03$  for ITT). Dr. Yan has repeated the sponsor's analyses and confirmed these results.

For the MITT population, the median percent change from baseline in all partial seizures was a 6.5% reduction for placebo and a 17% reduction for Neurontin.

The sponsor performed an analysis of secondarily generalized seizures, reporting the proportion of patients with them who experienced a reduction in the percent of total partial seizures that secondarily generalized. There was a slight trend in favor of Neurontin with 49% of patients showing such a change versus 40% for placebo. The difference was not statistically significant however.

Because clobazam and vigabatrin are not currently marketed in the US, Dr. Yan has performed an additional analysis exploring the effect of Neurontin only in patients on neither clobazam nor vigabatrin. The results of this analysis are essentially the same as the results for all patients combined.

## **Study 305/405**

Study 305 was a randomized, double-blind, placebo-controlled, add-on study of Neurontin in partial seizures in patients age 1 month to 3 years. Centers were located in the U.S. and Canada. The baseline phase consisted of 48 hours of video-EEG. The treatment period consisted of 72 hours of video-EEG.

Study 405 was identical in design to Study 305, but centers were located in other international locations.

By protocol, results from the 2 studies were to be pooled and analyzed together.

During the treatment period, patients were given Neurontin oral solution, 40mg/kg/day in divided doses. There was no dose titration.

The primary outcome was again the response ratio.

According to Dr. Mani's review, the planned sample size was 40, with 20/group.

## **Results**

A total of 76 patients were randomized, 38 gabapentin and 38 placebo. The discrepancy between the planned enrollment and the final enrollment is not addressed in the sponsor's submission and was not pursued in the clinical and statistical reviews. The difference in response-ratio between the treatment groups was not statistically significant,  $p = 0.369$ .

## **Safety**

The safety data has been reviewed by Dr. Mani. Safety data was included with the NDA and a subsequent 4-month safety update submitted in April, 2000.

For patients ages 3-12 years, the total exposure is 445 patient-years. Roughly 300 patient-years of exposure comes from the monotherapy experience, while the rest comes from adjunctive therapy experience. For patients ages 1 month-3 years, the exposure is only 13 patient-years, all from adjunctive studies.

A total of 645 patients 1 month – 12 years were treated. Of these 392 received adjunctive Neurontin and 205 received monotherapy.

For adjunctive therapy ages 3-12 years, there were 277 patients treated altogether; 127 were treated for 6 months and only 1 was treated for a year.

For monotherapy ages 4-13 years, there were 205 patients treated altogether; 174 were treated for 6 months and 146 were treated for a year.

## ***Deaths***

There were 2 deaths. Neither can be reasonably attributed to Neurontin.

## ***Serious Adverse Events and Dropouts***

Dr. Mani lists all serious events for all 645 pediatric patients on page 58 of his review. Many represent background events in the pediatric population.

Dr. Mani lists all dropouts on page 60 of his review. The most common events in these patients were emotional lability (8), hostility (6), hyperkinesia (6), convulsions, and somnolence (4).

Dr. Mani's review of these cases is summarized on page 60 of his review.

## ***Common Adverse Events***

The table of adverse events from Study 86/186 is presented on page 43 of Dr. Mani's review. The events reasonably attributed to Neurontin are nausea, vomiting, somnolence, hostility, and emotional lability. Hostility was reports for 7.6% of Neurontin patients and 2.3% of placebo patients.

Dr. Mani has specifically addressed behavioral adverse events on page 77 of his review.

## ***Other Issues***

The biopharm group has performed modeling of PK data collected in pediatric studies. Based on this analysis, they have recommended that 3 and 4 year-old patients receive a higher maintenance dose, 40 mg/kg/day, than patients 5 years of age and older (30 mg/kg/day).

In Study 86/186, 3 and 4 year-old patients were not dosed differently than the others. However, only 8 patients, ages 3 and 4 years, were randomized to Neurontin in this study.

Additionally, the sponsor has made a Phase 4 Commitment to perform tox studies in younger animals.

## **Conclusions**

Study 86/186 has demonstrated the efficacy of Neurontin in the treatment of partial seizures in patients 3-12 years of age. An effect in preventing secondary generalization was not demonstrated in that same study. Based on pharmacokinetic models, it seems reasonable to conclude that patients, age 3 and 4 years, should be dosed at 40 mg/kg/day while patients 5 years and older are dosed according to the same regimen utilized in Study 86/186.

Study 305/405 does not support the efficacy of Neurontin in pediatric populations < 3 years of age.

The safety profile of Neurontin in the 3-12 year group demonstrates a higher incidence of hostility in Neurontin treated patients, which sometimes led to withdrawal of the medication. Because caregivers may not intuitively recognize such neuropsychiatric adverse events as side effects to a medication, it is reasonable to place information in the WARNINGS section of labeling describing their occurrence. The sponsor has agreed to do this.

## **Recommendation**

The sponsor should be issued an Approval Letter with the mutually agreed upon labeling.

  
John Feeney, M.D.  
Neurology Team Leader

cc:  
NDA 21-216  
NDA 20-235  
NDA 20-882  
NDA 21-129  
Katz/Feeney/Mani/Ware

J. Wane  
SEP 28 2000

## Review and Evaluation of Clinical Data

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<b>NDA</b>	<b>21216</b>
<b>Sponsor:</b>	<b>Parke-Davis</b>
<b>Drug:</b>	<b>Gabapentin</b>
<b>Proposed Indication:</b>	
<b>Material Submitted:</b>	<b>Original NDA</b>
<b>Correspondence Date:</b>	<b>12/14/99</b>
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<b>Date Review Completed:</b>	<b>9/28/00</b>
<b>Reviewer:</b>	<b>Ranjit B. Mani, M.D.</b>

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**APPEARS THIS WAY  
ON ORIGINAL**

## 1. Background

This submission contains an original NDA for the use of gabapentin (Neurontin®) — in the treatment of partial seizures in pediatric patients. Enclosed also are supplemental NDAs for Neurontin® capsules (NDA 20235/S-014) and tablets (NDA-20882/S-002), to which the pediatric safety and efficacy data contained in NDA 21216 is cross-referenced.

These applications are each accompanied by requests for a pediatric exclusivity determination for Neurontin®. These are in response to a formal Written Request from the Agency, the final version of which was dated October 18, 1999. Earlier a Written Agreement, between the Agency and sponsor, was drafted in response to a request from the sponsor which was seeking to confirm that the studies they were conducting would meet the terms of the Written Request. However this Written Agreement was never finalized.

Gabapentin (Neurontin®) is an anticonvulsant approved since 12/30/93 for marketing in this country as adjunctive therapy for partial seizures, with or without secondary generalization, in adults. The original NDA, # 20235, was for the hard gelatin capsules in strengths of 100 mg, 300 mg and 400 mg; this is the only dosage form currently marketed in this country. Subsequently 2 additional NDAs for alternate dosage forms for the same indication were approved: NDA 20882 for 600 mg and 800 mg film-coated tablets was approved on 10/9/98; and NDA 21129 for a 250 mg/5 ml syrup formulation was approved on 3/2/00. The sponsor proposes that, upon approval of the current application, a common package insert be used for all 3 formulations of the drug.

The Pediatric Use subsection of the approved package insert for Neurontin® states that "Safety and effectiveness in children below the age of 12 years have not been established".

**The original NDA submission was followed by a 4-Month Safety Update that had a correspondence date of 4/14/00. The Safety Update is being reviewed together with the original NDA submission.**

## 2. Tabular Summary Of Studies in NDA

Studies included in the Integrated Summary of Safety are listed under the following categories

### 2.1 Combined Adjunctive Therapy Studies

#### 2.1.1 Efficacy And Safety Studies

Both protocols in this category were intended to assess the efficacy and safety of gabapentin as adjunctive therapy for partial seizures

Study #	945-86/186	945-305/405
Design	Randomized, double-blind, placebo-controlled, parallel-arm	Randomized, double-blind, placebo-controlled, parallel-arm
Dosage	23.2 to 35.3 mg/kg/day in 3 divided doses* (Capsule)	40 mg/kg/day in 3 divided doses (Syrup)
Duration of double-blind treatment	12 weeks	3 days
Randomized population	Gabapentin: 119 patients Placebo: 128 patients	Gabapentin: 38 patients Placebo: 38 patients
Main inclusion criteria	<ul style="list-style-type: none"> <li>• Age: 3-12 years</li> <li>• Weight: 17-72 kg</li> <li>• At least 4 partial seizures during 6-week baseline period with at least one in each 2-week period</li> <li>• Receiving at least one marketed anti-epileptic drug</li> </ul>	<ul style="list-style-type: none"> <li>• Age: 1-36 months</li> <li>• Weight: 3.5-20 kg</li> <li>• At least 1 partial seizure during screening (within 2 weeks prior to baseline)</li> <li>• Receiving at least one marketed anti-epileptic drug</li> </ul>
Primary efficacy measure****	Response Ratio** for all-partial seizures	Response Ratio** for all partial seizures
Results of primary efficacy analysis***	Gabapentin superior to placebo Difference: -0.089 p-value: 0.0407	Gabapentin superior to placebo Difference: -0.066 p-value: 0.369

\*Doses used were 600, 900, 1200 or 1800 mg per day used so as to fall into the 23.2 to 35.3 mg/kg/day dose range

\*\* Response Ratio was calculated from the following formula:

$$\frac{(T - B)}{(T + B)}$$

where

T = 28 day adjusted partial seizure rate for double-blind phase

B = 28 day adjusted partial seizure rate for baseline phase

\*\*\* The primary efficacy analyses were on the following populations

In Protocol 945-86/186 the primary efficacy analysis was on the "modified intent-to-treat" population. This population was defined as all those randomized, excluding those who had fewer than 28 days of seizure data recorded in their seizure diaries in either the baseline or double-blind phase. The "modified intent-to-treat" population comprised 113 patients who received gabapentin and 120 patients who received placebo

In Protocol 945-305/405 the primary efficacy analysis was on the intent-to-treat population comprising all those randomized. Note that a supplementary analysis was performed on the "evaluable" population comprising all those randomized who had at least one partial seizure during the baseline or double-blind phase; this population comprised 22 patients who received placebo and 25 patients who received gabapentin; while gabapentin appeared to be superior to placebo in this analysis with a treatment difference of -0.110 on the Response Ratio, this difference was not statistically significant (p=0.428)

\*\*\*\*While the original protocol for Study 945-86/186 stipulated that the Response Ratio and Responder Rate were both primary efficacy measures for this study without either measure being pre-eminent, the Inferential Analysis Plan formulated before the blind was broken, designated the Response Ratio as being the main primary efficacy measure and the Responder Rate as complementary

### 2.1.2 Long-Term Safety Studies

Both studies were ongoing at the time of the submission

Study #	945-87/187	945-301/401
Design	Open-label extension to 945-86/186	Open-label extension to 945-305/405
Dosage	23-60 mg/kg/day (Capsules)	40 mg/kg/day (Syrup)
Duration	Upto 26 weeks	Upto 1 year
Number enrolled	237 patients	145 patients

### 2.2 Pharmacokinetic Studies

Study #	945-202	945-296
Design	Single-dose, open-label study	Single-dose, open-label study
Dosage	10 mg/kg/day (approx) (Capsules)	10 mg/kg/day (approx) (Syrup)
Number enrolled	24 healthy subjects Ages 4 to 12 years	26 healthy subjects Ages 1 to 47 months

### 2.3 Monotherapy Studies

These were studies conducted in pediatric patients with benign childhood epilepsy with centrotemporal spikes (BECTS). They have been included in the NDA to provide further information regarding the safety of gabapentin in pediatric patients. The efficacy data for these studies are not pertinent to this review.

Study #	945-94
Design	Randomized, double-blind, placebo-controlled, parallel-arm
Dosage	30 mg/kg/day (Capsules)
Duration of double-blind treatment	36 weeks
Randomized population	Gabapentin: 113 patients Placebo: 112 patients

Study #	945-95
Design	Open-label extension to 945-94
Dosage	30-60 mg/kg/day (Capsules)
Duration	Upto 96 weeks
Number enrolled	191 patients

### 2.4 Additional Studies

Studies Submitted In NDA 20-235

Study #	Duration of Exposure	Number of Pediatric Patients
877-034, 877-034X 945-11, 945-11X 945-16 945-19, 945-19X 945-20, 945-20X 945-49 945-50	Upto 1352 days	42 patients* exposed to gabapentin capsules in various doses

\*ages 3 to 12 years

### Prematurely terminated study

Study #	Design	Duration of Exposure	Number of Patients	Dose
945-08	Initial randomized, double-blind, placebo-controlled, parallel-arm study followed by open-label extension. Assessment of safety and efficacy of gabapentin as add-on therapy in the treatment of pharmacotherapy-resistant childhood epilepsies. Age 3 to 12 years	102 – 505 days	6 exposed to gabapentin capsules*	16-24 mg/kg/day (Capsules)

## 3. Summary of Pediatric Pharmacokinetics

### 3.1 Summary Of Clinical Pharmacokinetics In Adults

The pharmacokinetics of gabapentin have been studied extensively in healthy adults and are summarized below:

- After oral administration peak plasma gabapentin concentrations occur approximately 3-4 hours post-dose. The oral bioavailability from 300 mg capsule and solution formulations is about 60%. The absolute amount of drug absorbed increases with increasing dose with percentage of dose absorbed decreasing with increasing dose. Food does not influence the bioavailability of gabapentin
- Gabapentin is not bound to plasma proteins and is not metabolized.
- Gabapentin is eliminated in an unchanged form, largely through the renal route
- The elimination half-life of gabapentin is independent of dose and averages between 5 and 7 hours; plasma clearance and renal clearance are linearly correlated with creatinine clearance and in patients with impaired renal function dose adjustment may be made on the basis of creatinine clearance
- Gabapentin does not induce or inhibit hepatic enzymes responsible for drug metabolism
- No interactions have been noted between gabapentin and phenytoin, phenobarbital, valproic acid and carbamazepine; or between gabapentin and an estrogen-progestin oral contraceptive

### 3.2 Pediatric Pharmacokinetics

The pediatric pharmacokinetic data are derived from 2 sources:

- The 2 single-dose pharmacokinetic studies in healthy children summarized in the table below

Study #	945-202	945-296
Design	Single-dose, open-label study	Single-dose, open-label study

Dosage	10 mg/kg/day (approx) (Capsules)	10 mg/kg/day (approx) (Syrup)
Number enrolled	24 healthy subjects Ages 4 to 12 years	26 healthy subjects Ages 1 to 47 months

- Sparse pharmacokinetic data from 5 Phase II/III studies: 945-94, -95, -86/186, 305/405 and 301/401

The 2 data sources were combined to yield a population pharmacokinetic model; this analysis was based on non-linear mixed effects modeling.

Based on the 2 single-dose pharmacokinetic studies, the sponsor has concluded that:

- In children  $\geq 5$  years old exposure, based on  $C_{max}$  and  $AUC_{0-\infty}$ , is similar to that in adults when dosed on a mg/kg basis
- In children  $< 5$  years old exposure, based on  $C_{max}$  and  $AUC_{0-\infty}$ , is about 30 % less than in children  $\geq 5$  years old, when dosed on a mg/kg basis.
- Children  $< 5$  years old require a 30% higher daily dose (40 mg/kg/day) than children  $\geq 5$  years old (30 mg/kg/day) to achieve an exposure similar to that of a 70 kg adult receiving therapeutic doses
- Elimination half-life values for subjects  $< 5$  years old and those  $\geq 5$  years old were similar

Using the population pharmacokinetic model the sponsor has concluded that:

- A linear relationship between gabapentin oral clearance and creatinine clearance was observed in children. Metabolism does not appear to be a significant pathway for gabapentin metabolism in children
- A linear relationship between creatinine clearance and gabapentin renal clearance was observed in children similar to that in adults
- Creatinine clearance is a good predictor of gabapentin renal clearance for both children and adults

#### 4. Efficacy

The evidence for the efficacy of gabapentin as add-on therapy in treating refractory partial seizures in pediatric patients is provided by 2 sets of pooled identical studies: 945-86/186 and 945-305/405. Each of these sets of studies is reviewed below as a single item.

#### 5. Study 945-86/186

- Study 945-86 was conducted exclusively in the United Kingdom (27 centers). A total of 96 patients entered the double-blind phase of this study. The largest number of patients entering the double-blind phase at any single center was 15 (C. Kennedy, Southampton, England)
- Study 945-186 was conducted at 33 centers in the following countries: France, Belgium, Italy, the Netherlands, Germany, Spain, Switzerland, Finland, the Czech Republic, Hungary, Yugoslavia, South Africa and the United States. A total of 151 patients entered the double-blind phase of this study. The largest number of patients entering the double-blind phase at any single center was 15 (M. Djuric, Belgrade, Yugoslavia)

Note that Study 945-86 was initiated prior to, but was ongoing, at the time Study 945-186 was initiated. The protocol for 945-186 clearly stipulated that for analysis purposes both studies were to be combined

### **5.1 Title**

A double-blind, parallel-group comparison of gabapentin versus placebo as add-on therapy for epilepsy in children

### **5.2 Objective**

- To compare the efficacy of gabapentin and placebo as add-on therapy to existing anti-epileptic therapy
- To examine the safety profile of gabapentin and placebo by adverse event monitoring and regular tests
- To compare the global effects of gabapentin and placebo on the patients' seizures and well-being

### **5.3 Design**

Randomized (1:1), double-blind, placebo-controlled, parallel-arm study at multiple centers

### **5.4 Duration**

Following screening, the study was to consist of 2 phases:

- A baseline phase of 6 weeks on current (i.e., established) anti-epileptic drug therapy
- A double-blind treatment phase lasting 12 weeks
- A withdrawal phase lasting 1 week for patients not entering the subsequent open-label extension study (Protocol # 945-87/187)

Randomization occurred at entry into the double-blind phase of the study

### **5.5 Dosage**

Gabapentin 24-35.3 mg/kg/day as 100/200 mg capsules in 3 divided doses (patients were to be titrated to that dose over 3 days, beginning with a dose ranging from 8-17.6 mg/kg/day).

OR

Matching placebo capsules

Doses were to be administered at 8AM, 2PM and 8PM daily

Individual dosing regimes were pre-specified for each of 4 different weight intervals (within a weight interval dosing regimes were consistent)

17-25 kg

26-36 kg

37-50 kg

51-72 kg

In response to adverse events investigators were allowed to reduce the study medication from 3 to 2 times a day, eliminating the midday dose for not more than 2 consecutive days. If the adverse event had not resolved within 2 days so that 3 times a day dosing could be re-instituted, patients were to be withdrawn from the study

### **5.6 Sample Size**

230 patients (both studies combined) were to be enrolled

### **5.7 Main Inclusion Criteria**

- Male or female
- Age: upto and including 12 years\*  
\*Note that Protocol 945-86 originally stipulated that only children aged between 5 and 12 years would be enrolled; a subsequent amendment allowed the recruitment of children less than 5 years old without a lower age limit being specified. Protocol 945-186 allowed the recruitment of children "upto and including 12 years" but again never specified a lower age limit. In the Integrated Summary of Efficacy the sponsor states that "although the protocol did not dictate a lower limit for age, the weight restrictions and the requirement that patients be able to swallow capsules meant that the youngest patient enrolled was 3 years of age."
- Weight: 17 to 72 kg
- Able to swallow capsules
- Currently receiving one, two or three anticonvulsant drugs without satisfactory control
- Seizures that are simple partial, complex partial, or partial becoming secondarily generalized, as defined in the ILEA classification of seizures (1981)
- Patients with a structural central nervous system lesion or encephalopathy should have had a head CT or magnetic resonance imaging within 2 years prior to screening
- Compliant and reliable parent/legal guardian
- Written informed consent from parent/legal guardian

Note that to continue into the double-blind period patients must have experienced

- a minimum of 4 seizures in the baseline period and
- at least one seizure during each 2-week period of the baseline period

### **5.8 Main Exclusion Criteria**

- Female patients who are pregnant, lactating or sexually active, and not using a barrier or hormonal method of contraception
- Seizures related to drugs, alcohol or acute medical illness
- Typical absence epilepsy
- Known progressive structural central nervous system disease or a progressive encephalopathy
- Known or suspected chronic hematological, hepatic or renal disease (criteria specified)
- Total white blood cell counts  $< 3 \text{ K}/\mu\text{L}$  or absolute neutrophil counts  $< 1 \text{ K}/\mu\text{L}$  within the previous 6 months. History of previous bone marrow suppression
- Any serious medical or psychiatric disorder within the previous 6 months
- Structural lesion in central nervous system or encephalopathy, shown to be progressive and demonstrated by magnetic resonance imaging or CT scanning done within the previous 2 years
- Use of any investigational drug within the previous 3 months
- Withdrawal of any anti-epileptic drug within the previous 4 weeks
- Use of high-dose amino acid therapies or central nervous system active compounds that could interfere with patient evaluation

- Use of any non-anticonvulsant medication that could alter the effectiveness of the patient's medication, response, seizure frequency or characterization
- Patients not reasonably expected to complete the trial

### **5.9 Concomitant Medications**

#### **5.9.1 Prohibited Medications**

Maalox®

#### **5.9.2 Permitted Medications**

A full list is not provided but oral contraceptives are permitted.

### **5.10 Efficacy Outcome Measures**

Seizure counts were based on daily diaries recorded by the patient's parent or legal guardian.

#### **5.10.1 Primary Efficacy Measures**

- Response Ratio (RRatio), also referred to as symmetrized proportional change.

This ratio would be used to compare the partial seizure frequency between the baseline phase and the double-blind treatment phase.

This ratio was to be calculated from the following formula:

$$\frac{(T - B)}{(T + B)}$$

where

T = 28 day adjusted partial seizure rate for double-blind phase

B = 28 day adjusted partial seizure rate for baseline phase

The Response Ratio was to be calculated for each patient

- Responder Rate, defined as the proportion of patients with a 50 % or greater reduction in partial seizure frequency during double-blind treatment compared with the baseline phase

**In the Inferential Analysis Plan, finalized prior to the breaking of the study blind, the sponsor stated that the Response Ratio was to be considered the more important of these parameters with the Responder Rate being complementary. However, neither in the original protocols for Studies 945-86 and 945-186, nor in subsequent protocol amendments was there any indication that the Response Ratio would be considered a more important primary efficacy variable than the Responder Rate.**

For two key efficacy studies (945-5 and 945-6) submitted with the "adult" NDA (# 20235) for Neurontin® as adjunctive treatment for refractory partial seizures, the Division accepted that the Response Ratio could be the key primary efficacy variable and the Responder Rate a complementary primary efficacy variable. For another key efficacy study in NDA 20235 (877-210P) the Responder

Rate was the primary efficacy variable; the Response Ratio was not originally an efficacy variable at all, but an analysis of the latter was eventually performed.

#### **5.10.2 Secondary Efficacy Measures**

- Percentage change from baseline in partial seizure frequency (all partial seizures and partial seizure subtypes)
- Global assessment by investigator and parent/guardian. A scale ranging from 1 ("Significant Improvement") to 5 ("Much Worse") was to be used. 4 different assessments were to be performed
  - Investigator's Assessment of Seizure Frequency
  - Investigator's Assessment of Well-Being
  - Parent/Guardian's Assessment of Seizure Frequency
  - Parent/Guardian's Assessment of Well-Being
  
- Change in frequency (Response Ratio) of partial seizure subtypes

#### **5.10.3 Safety Measures**

Adverse events, and safety laboratory tests

### **5.11 Analysis Plan**

#### **5.11.1 General Considerations**

- All hypothesis testing was to be 2-sided and at the 0.05 level of significance
- Partial seizures were to be categorized in the Case Report Forms as simple partial, complex partial or secondarily generalized
- The number of seizures per 28 days were to be computed as follows: the total number of seizures in a phase was to be divided by the total number of days in the phase and then multiplied by 28
- Days on which no seizure diary was kept were to be subtracted from the number of days in the phase (i.e., it would not be assumed that patients would not have 0 seizures on each of those days)

#### **5.11.2 Demographic And Baseline Characteristics**

Baseline clinical characteristics and demographic data were to be summarized and examined to see if the 2 treatment groups were well-matched

#### **5.11.3 Primary Efficacy Parameters**

- The primary population to be analyzed was a modified intent-to-treat population comprising all patients randomized who had at least 28 days of seizure data in each phase. A separate intent-to-treat analysis would then be performed on all patients randomized: if less than 28 days of seizure data were available the data would be extrapolated (i.e., carried forward)
- The Responder Rate was to be compared between treatment groups using the Cochran-Mantel-Haenszel test adjusting for center. Homogeneity among centers was to be evaluated using the Breslow-Day test.
- The Response Ratio was to be analyzed using ANOVA; the primary model would include effects of treatment and center. Adjusted means for each treatment group would be obtained from this model and 95% confidence

intervals on the difference between gabapentin and placebo would also be computed. The generalizability of the results among centers would be tested by repeating the analysis using a treatment-by-center interaction term; if an interaction was suggested ( $p < 0.20$ ) the treatment effect within each center would be examined. For the ANOVA model the assumptions of normality would be checked by examining the residuals from the model to ensure that they were approximately normally distributed; if clear evidence of non-normality was present, an ANOVA on rank-transformed data might have to be performed.

- As indicated above the Response Ratio was to be considered the more important of these parameters with the Responder Rate being complementary
- The study was to be considered successful if the Response Ratio was significantly different between gabapentin and placebo and favoring gabapentin ( $p < 0.05$ )

#### 5.11.4 Secondary Efficacy Parameters

- Only descriptive statistics would be provided for the Response Ratios for partial seizure subtypes: the primary display would be for the modified intent-to-treat population with a supplemental display for the pure intent-to-treat population.
- The percentage change in partial seizure frequency (total partial seizures and partial seizure subtypes) would not be subjected to an inferential analysis. Instead descriptive statistics including the mean, standard error, 25<sup>th</sup> and 75<sup>th</sup> percentiles and the median for each treatment group and between treatment groups would be calculated. The number and percentage of patients with percentage change of specific categories (increase or decrease) would also be provided. Patients with zero seizure frequency during the baseline phase for a particular seizure type would not have the percentage change for that type computed. These displays would be provided for the modified and pure intent-to-treat populations
- Each of the 4 global assessments would be analyzed separately using a center-stratified Cochran-Mantel-Haenszel test with modified Ridit scores. Only the pure intent-to-treat population would be analyzed

#### 5.11.5 Sample Size Rationale

- The sample size calculation was based on the responder rate from clinical trials of gabapentin in adults
- The assumptions underlying the sample size calculation were as follows
  - Type 1 error of 0.05 (2-sided)
  - Power of 80 %
  - Responder rates of 25 % and 10 % in those treated with gabapentin and placebo respectively
- A total sample size of 230 patients was estimated to be needed for the combined studies

### 5.11.6 Safety Parameters

- The incidence of adverse events would be summarized using COSTART preferred terms
- Laboratory data would be summarized by comparing the baseline and final values for each treatment group. The incidence of clinically important changes would also be summarized

### 5.12 Protocol Amendments

These have been incorporated into the above.

### 5.13 Actual Analyses Performed

The analyses were performed according to the above plan.

Note that the report for this study was issued November 20, 1997. In the Written Request, finalized October 18, 1999, the Agency stated that for a claim for using gabapentin in the treatment of secondarily generalized tonic-clonic seizures, an appropriate conditional analysis should be performed. A summary of this conditional analysis has been included in the Integrated Summary of Efficacy, and in a separate report (RR-Memo 720-0417; date 10/14/99) included in this submission, but not in the body of the main study report.

### 5.14 Efficacy Results

#### 5.14.1 Patient Disposition

247 patients were randomized: their disposition is indicated in the following table. As the sponsor's table below indicates the proportion of patients completing the study was similar in both groups

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.

**5.14.2 Baseline Demographic And Disease Characteristics**

Baseline demographic characteristics and partial seizure frequency are summarized in the following table, provided by the sponsor. As the table indicates, the placebo group had a higher male: female ratio and a lower partial seizure frequency at baseline.

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.

Additional disease characteristics at baseline are summarized in the next table, provided by the sponsor. The treatment groups were comparable in regard to age of onset of epilepsy, duration of epilepsy and percentage with simple and partial complex seizures. The percentage with partial seizures with secondary generalization was higher in those treated with gabapentin than in those treated with placebo.

Summary of Disease Characteristics (Randomized Patient Population): Study 945-86/186			
Characteristic	Placebo N = 128	Gabapentin N = 119	Total N = 247
<b>Age at Epilepsy Onset, years</b>			
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
<b>Duration of Epilepsy, years</b>			
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
<b>Etiology of Epilepsy<sup>a</sup>, N (%)</b>			
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)
<b>Types of Seizures Experienced (History at Screening)<sup>b</sup></b>			
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.  
<sup>a</sup> Patients could have more than 1 category of epilepsy etiology and more than 1 seizure type.

The groups were not strictly comparable in regard to their history of anti-epileptic drug use at screening as indicated by the next table, provided by the sponsor:

History of Antiepileptic Drug Use at Screening (Randomized Patient Population): Study 945-86/186			
	[Number (%) of Patients]		
	Placebo N = 128	Gabapentin N = 119	Total N = 247
<b>Total Number of AEDs Tried and Failed</b>			
0	5 (3.9)	2 (1.7)	7 (2.8)
1-2	33 (25.8)	26 (21.8)	59 (23.9)
3-4	29 (22.7)	38 (31.9)	67 (31.2)
>4	61 (47.7)	53 (44.5)	114 (46.2)
<b>Number of Concurrent AEDs at Screening</b>			
1	44 (34.4)	31 (26.1)	75 (30.4)
2	57 (44.5)	58 (48.7)	115 (46.6)
3	27 (21.1)	30 (25.2)	57 (23.1)

AEDs = antiepileptic drugs.

### 5.14.3 Duration

The duration of treatment was comparable in both treatment groups as indicated by the following (sponsor's) table

Exposure (Weeks)	Duration of Treatment [Number (%) of Patients]	
	Placebo N = 128	Gabapentin N = 119
At least one dose	128 (100.0)	119 (100)
≥1	124 (96.9)	118 (99.2)
≥2	123 (96.1)	117 (98.3)
≥4	122 (95.3)	114 (95.8)
≥6	113 (88.3)	110 (92.4)
≥8	109 (85.2)	106 (89.1)
≥10	102 (79.7)	99 (83.2)
≥12	86 (67.2)	84 (70.6)
≥14	6 (4.7)	5 (4.2)

### 5.14.4 Primary Efficacy Analysis

#### 5.14.4.1 Response Ratio

The main primary efficacy analysis using the original ANOVA model (without rank transformation) revealed a statistically significant superiority of gabapentin over placebo using the modified intent-to-treat population as indicated in the next table, provided by the sponsor.

Primary Analysis of Response Ratio for All Partial Seizures (MITT Population): Study 945-86/186						
Treatment Group	N	Least Squares Mean <sup>a</sup>	Standard Error	Treatment Comparison (Gabapentin - Placebo)		
				Difference	95% CI <sup>b</sup>	p-Value
Placebo	120	-0.072	0.031			
Gabapentin	113	-0.161	0.031	-0.089	(-0.174, -0.004)	0.0407

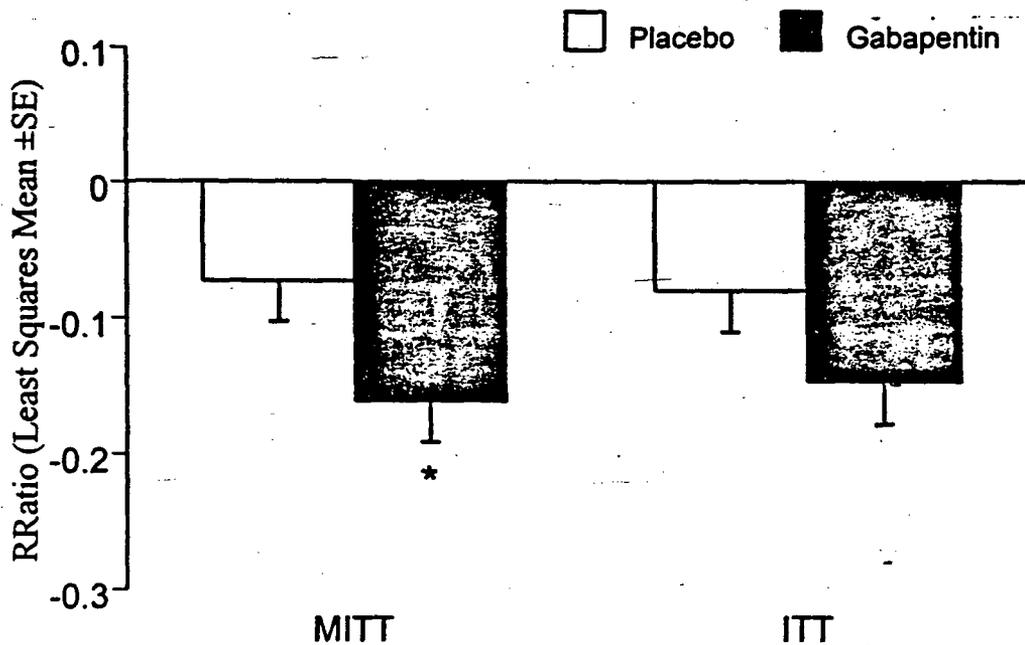
MITT = modified intent-to-treat, CI = confidence interval.  
<sup>a</sup> Analysis of Variance, main effects model  
<sup>b</sup> CI = confidence interval; 2-sided with 95% probability.

A supplemental analysis on the main primary efficacy parameter using the original ANOVA model (without rank transformation) on the intent-to-treat population showed a greater treatment effect in those treated with gabapentin than in those treated with placebo, but the treatment difference did not reach statistical significance as shown in the next table, provided by the sponsor.

Supplemental Analysis of Response Ratio for All Partial Seizures (ITT Population): Study 945-86/186						
Treatment Group	N	Least Squares Mean <sup>a</sup>	Standard Error	Treatment Comparison (Gabapentin - Placebo)		
				Difference	95% CI <sup>b</sup>	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.  
<sup>a</sup> Analysis of Variance, main effects model  
<sup>b</sup> CI = Confidence interval; 2-sided with 95% probability.

The above analyses are graphically represented below, the figure is provided by the sponsor.



VLAMP/CLC/101097  
 945/86-186/RRatio\_MITT & ITT

Least-Squares Mean Response Ratio (RRatio) for All Partial Seizures: Study 945-86/186

\*Statistically significant difference between gabapentin and placebo treatments (p = 0.0407).

SE = standard error, MITT = modified intent-to-treat, ITT = intent to treat.

The sponsor further states that examination of the residuals from the original model showed that the data were not normally distributed. Therefore an ANOVA was then performed on rank-transformed data for each population, as stipulated in the protocol. Using rank-transformed data, gabapentin was superior to placebo at a statistically significant level for both the modified intent-to-treat and the intent-to-treat datasets as indicated in the next table, provided by the sponsor.

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 <sup>a</sup>	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.  
<sup>a</sup> 2-sided with 95% probability

**5.14.4.2 Responder Rate**

The responder rates (complementary efficacy variable) for the 2 treatment groups did not differ at a statistically significant level for either the modified intent-to-treat or the intent-to-treat populations, using the Cochran-Mantel-Haenszel test. The results are as displayed in the next (sponsor's) table. The sponsor attributes the lack of a statistically significant difference to what the sponsor believes is an unusually high placebo responder rate.

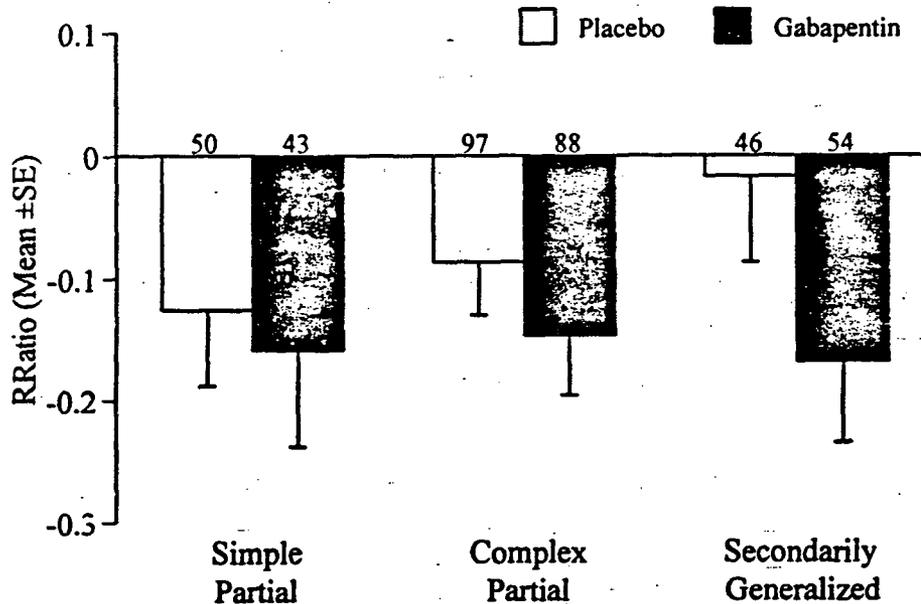
Responder Rate for all Partial Seizures (MITT and ITT Populations): Study 945-86/186					
Population	Treatment Group	N	Number of Responders	Responder Rate	CMH p-Value
MITT	Placebo	120	21	17.5%	0.335
	Gabapentin	113	24	21.2%	
ITT	Placebo	127	23	18.1%	0.500
	Gabapentin	118	25	21.2%	

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

**5.14.5 Analysis Of Secondary Efficacy Measures**

**5.14.5.1 Response Ratio By Seizure Type**

For the modified intent-to-treat and intent-to-treat to treat populations the mean Response Ratio was lower for the gabapentin treatment group than for the placebo group for each of the 3 seizure types (simple partial, complex partial and secondarily generalized). Data for the modified intent-to-treat population is displayed graphically in the next figure, provided by the sponsor.



VLAMP/CLC/102997  
 945/86-186/ITT Response

**Mean Response Ratio (RRatio) by Seizure Type for the MITT Population: Study 945-86/186**

The numbers above each bar represent the number of patients with that seizure type. SE = standard error, MITT = modified intent-to-treat.

However the 95% confidence intervals for the difference in mean Response Ratio for each of 3 seizure types included zero as indicated in the next table, provided by the sponsor.

Seizure Type	Difference in Mean RRatio	95% CI <sup>a</sup>
Simple Partial	-0.035	(-0.235, 0.165)
Complex Partial	-0.062	(-0.192, 0.069)
Secondarily Generalized	-0.154	(-0.346, 0.039)

MITT = modified intent-to-treat, RRatio = response ratio, CI = confidence interval.  
<sup>a</sup> CI = confidence interval; 2-sided with 95% probability.

**5.14.5.2 Percentage Change From Baseline For All Partial Seizures And By Seizure Type**

For the modified intent-to-treat population median percentage change for all partial seizures and for each partial seizure type was better for gabapentin-treated patients than for those who received placebo as indicated in the next (sponsor's) table: however the gabapentin-placebo difference for simple partial seizures was minimal

	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

MITT = modified intent-to-treat.

The 95% confidence intervals for difference in median percentage change for all partial seizures and by seizure type included zero only for simple partial seizures as shown in the next (sponsor's) table

Seizure Type	Median Difference	Confidence Interval
All Partial	-13.3	(-25.2, -2.1)
Simple Partial	-3.9	(-32.3, 23.1)
Complex Partial	-16.5	(-33.1, -1.3)
Secondarily Generalized	-31.1	(-53.8, -5.4)

MITT = modified intent-to-treat.

**5.14.5.3 Proportion Of Patients Exhibiting A Decrease In The Ratio Of Secondarily Generalized Tonic-Clonic Seizure Rate To Partial Seizure Rate**

Although the proportion of gabapentin-treated patients was higher than the proportion of placebo-treated patients, the difference between treatment groups was not statistically significant. This difference is illustrated in the next table provided by the sponsor.

Analysis of Proportion of Patients Exhibiting a Decrease From Baseline to Double-Blind Treatment in the Ratio of SGTC Seizure Rate to Partial Seizure Rate (Secondarily Generalized Seizures Population): Study 945-86/186				
Treatment Group	N	Number (%) of Patients Exhibiting a Decrease		p-Value <sup>a</sup>
Placebo	35	14	(40%)	0.435
Gabapentin	43	21	(49%)	
SGTC = secondarily generalized tonic-clonic. <sup>a</sup> Pearson's chi-square test.				

**5.14.5.4 Global Assessments**

As the protocol indicates global assessments of patients' seizure frequency and well being during the double-blind phase as compared with the baseline phase were made by both the physician and the parent/guardian at the end of the double-blind treatment phase. The results for the intent-to-treat population are summarized in the table below, which I have adapted from one provided by the sponsor.

The only assessment that differed significantly between the gabapentin and placebo groups was the evaluation by the parent/guardian; the parents/guardians of children receiving gabapentin felt there was more improvement and less worsening of their seizure frequency than did the parents/guardians of children treated with placebo (CMH test; p=0.046).

	Placebo	Gabapentin
Evaluated by Parent/Guardian	N=127	N=117
Significant Improvement (%)	22.8	30.8
Slight Improvement (%)	29.1	30.8
No Change (%)	33.1	28.2
Worse (%)	12.6	8.5
Much Worse (%)	2.4	1.7
Evaluated by Physician	N=127	N=116
Significant Improvement (%)	19.7	27.6
Slight Improvement (%)	26.8	29.3
No Change (%)	41.7	37.1
Worse (%)	10.2	5.2
Much Worse (%)	1.6	0.9

**5.15 Safety Results**

These are reviewed as part of the Integrated Summary of Safety

**5.16 Sponsor's Conclusions Regarding Efficacy**

- Gabapentin is effective as adjunctive therapy in the treatment of refractory partial seizures in pediatric patients between 3 and 12 years of age; this conclusion is based on the primary analysis that used the Response Ratio
- The sponsor has attributed the lack of a statistically significant superiority of gabapentin over placebo when the Responder Rate was analyzed to the unusually high placebo responder rate: in 3 adult studies reported in the approved NDA and package insert, the percentage of placebo responders ranged from 8% to 10%.

**5.17 Agency Statistician's Analysis Of Efficacy**

Dr Sharon Yan, Biometrics Reviewer

- Confirms that the residuals for the ANOVA model for the Response Ratio were not normally distributed (based on the Wilk-Shapiro test)
- Has performed separate analyses on the 945-86 and 945-186 studies using the same statistical methods as the sponsor. Based on her analyses, 945-186 is a "negative" study: a statistically significant result on the Response Ratio and Responder Rate were seen only in the 945-86 study which had a smaller enrollment. Her results are in the following table

Efficacy Variable	MITT			ITT		
	Placebo	Gabapentin	p-value	Placebo	Gabapentin	p-value
<b>Protocol 086</b>						
Response Ratio						
N	50	42		51	44	
Mean	-0.038	-0.198	0.0089	-0.057	-0.177	0.0670
SD	0.340	0.282		0.362	0.294	
Median	-0.014	-0.101		-0.014	-0.088	
Responder Rate	18.00%	23.81%	0.319	19.61%	22.73%	0.562
<b>Protocol 186</b>						
Response Ratio						
N	70	71		76	74	
Mean	-0.121	-0.145	0.5792	-0.108	-0.139	0.6125*
SD	0.326	0.320		0.352	0.321	(.2448)
Median	-0.058	-0.090		-0.046	-0.091	
Responder Rate	17.14%	19.72%	0.674	17.11%	20.27%	0.694

\*The p-value for the test of normality is 0.0111

**5.18 Reviewer's Comments**

- Although the original protocol designated both the Response Ratio and the Responder Rate as co-eminent primary outcome measures, an Inferential Analysis Plan formulated prior to the breaking of the study blind designated the Response Ratio as the main primary efficacy measure with the Responder Rate being complementary; the Division has previously accepted the Response Ratio as the sole primary efficacy measure in 2 key adult efficacy studies and in the pediatric protocol 945-305/405 (see below)
- While the protocol-designated main primary efficacy analysis (ANOVA) using untransformed data, for the modified intent-to-treat dataset, on the Response Ratio did show a statistically significant superiority for gabapentin over placebo, although the effect size was small, the p-value borderline (p=0.0407), and the effect not seen on the slightly larger intent-to-treat population. Nevertheless the protocol did stipulate that should normality not be demonstrated when the residuals for the ANOVA on untransformed data were examined, the ANOVA should be performed on rank-transformed data. Using rank-transformed data, the ANOVA was positive for both the modified intent-to-treat and the intent-to-treat populations
- Protocol 945-186 specified that for analysis purposes the results of Studies 945-86 and 945-186 would be pooled. Thus the results of each study

analyzed separately should not, at least for regulatory purposes, negate the results of the pooled 945-86/186 study

- Considering that a statistically significant superiority was demonstrated for gabapentin over placebo on an analysis plan specified prior to the study blind being broken\*, 945-86/186 should be considered a positive study

\*While the approval signatures on the Inferential Analysis Plan for this study all bear dates for the second half of April 1997, internal Parke-Davis documents confirm that the breaking of the randomization code for the above study was authorized June 5, 1997

- There was no evidence from this study that gabapentin had efficacy in the treatment of secondarily generalized tonic-clonic seizures.

## 6. Study 305/405

- Study # 945-305 was conducted in the United States and Canada at 73 centers. 54 patients entered the double-blind phase of the study (39 centers did not enter any patients into this phase). The largest number of patients entering the double-blind phase at any single center was 5 (J. Pina-Garza; Nashville, Tennessee)
- Study # 945-405 was conducted at 15 centers in the following countries: Mexico, Brazil, South Africa, Italy, Hungary, Belgium, Spain and the United Kingdom. 22 patients entered the double-blind phase of the study (4 centers did not enter any patients into this phase of the study). The largest number of patients entering the study at any single center was 5 (R. Guerra; Monterrey, Mexico)
- During discussion of both protocols with this Division it was stipulated that for analysis purposes the results of both studies would be combined.

### 6.1 Title

Gabapentin pediatric add-on trial: a randomized, double-blind, placebo-controlled, parallel-group, multicenter study in patients with partial seizures

### 6.2 Objective

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

### 6.3 Design

Randomized, double-blind, placebo-controlled, parallel-group, multicenter study

Following screening, the study is to consist of 3 phases:

- A baseline phase consisting of a 48 hour video-electroencephalogram monitoring period
- A double-blind treatment phase consisting of a 72 hour video-electroencephalogram monitoring period
- A withdrawal phase lasting 2 days for patients not entering the subsequent open-label extension study (Protocol # 945-301)

Randomization occurred at entry into the double-blind phase of the study

### 6.4 Duration

The duration of the double-blind treatment phase was to be 72 hours

### **6.5 Dosage**

During the double-blind treatment phase the dosage of study medication was to be as follows:

Gabapentin syrup in a dose of 40 mg/kg/day in 3 equal divided doses orally (without titration)

OR

Matching placebo syrup

### **6.6 Sample Size**

40 patients (both studies combined) were to be enrolled at a total of 80-120 centers

### **6.7 Key Inclusion Criteria**

- Male or female
- Age: 1 to 36 months
- Weight: 3.5 to 20 kg
- Currently receiving at least 1 marketed anti-epileptic drug at the time of randomization
- Those who have previously been treated with gabapentin may be included in the study provided they cease taking gabapentin at least one week prior to the start of the screening period
- At least 1 partial seizure, as defined in the ILEA classification of seizures, during screening period within 2 weeks prior to baseline
- Partial seizures diagnosed in either of 2 ways
  - Clinical observation of partial seizure with focal semiology confirmed by and consistent with the localization of either focal epileptiform abnormality on electroencephalogram within the last 2 years or focal abnormality on brain imaging
  - Seizure recorded by electroencephalogram monitoring which fulfils the ILEA criteria for seizure type
- Patients with infantile spasms may be included if they are also experiencing partial seizures as noted above
- 12-lead electrocardiogram at screening without significant abnormalities
- Head CT or magnetic resonance imaging at any time that demonstrates no progressive structural abnormalities
- Compliant and reliable parent/legal guardian
- Written informed consent from parent/legal guardian

### **6.8 Main Exclusion Criteria**

- Diagnosis of febrile seizures or seizures related to acute medical illness
- Primary (e.g., absence epilepsy) or secondary generalized (e.g., Lennox-Gastaut syndrome) epilepsy
- Known progressive structural central nervous system disease or a progressive encephalopathy
- Known or suspected chronic hematological, hepatic or renal disease (criteria specified)

- Total white blood cell counts  $< 3 \text{ K}/\mu\text{L}$  or absolute neutrophil counts  $< 1 \text{ K}/\mu\text{L}$  within the previous 6 months for infants  $> 6$  months old, or at any prior period for infants  $< 6$  months old. History of previous bone marrow suppression
- Use of any investigational drug within 2 weeks prior to screening
- Use of any non-anticonvulsant medication that could alter the effectiveness of the patient's medication, response, seizure frequency or characterization
- Patients not reasonably expected to complete the trial

#### **6.9 Concomitant Medications**

- Administration of central nervous system-active compounds is prohibited during the trial
- Benzodiazepines and phenobarbital are considered anti-epileptic drugs regardless of indication or frequency of usage
- Emergency benzodiazepine usage will be permitted during the double-blind phase on a single occasion only
- Metoclopramide, cisapride and ranitidine are permitted

#### **6.10 Outcome Measures**

Note that all video-EEGs were to be read by a single central reader.

##### **6.10.1 Primary Efficacy Measures**

Response Ratio (RRatio), also referred to as symmetrized proportional change.

This would be used to compare the partial seizure frequency between the baseline phase and the double-blind treatment phase.

This ratio was to be calculated from the following formula:

$$\frac{(T - B)}{(T + B)}$$

where

T = 28 day adjusted partial seizure rate for double-blind phase

B = 28 day adjusted partial seizure rate for baseline phase

The Response Ratio would be calculated for each patient

##### **6.10.2 Secondary Efficacy Measures**

Four secondary efficacy measures were to be used

- Responder rate, defined as the proportion of patients with a 50 % or greater reduction in partial seizure frequency during double-blind treatment compared with the baseline phase
- Percentage change in partial seizure frequency comparing double-blind treatment compared with the baseline phase
- Proportion of patients exhibiting a decrease in the ratio of secondarily generalized tonic-clonic seizure rate to partial seizure rate  
$$\frac{\text{Rate of secondarily generalized tonic-clonic seizures}}{\text{Rate of simple plus complex partial seizures}}$$
- 28-day partial seizure rate and partial seizure frequency counts

All 4 secondary efficacy measures were to be based on the 28-day adjusted seizure rate

### 6.10.3 Safety Measures

Adverse events, vital signs, physical and neurological examinations, weight, 12-lead electrocardiogram, antiepileptic drug concentrations, and safety laboratory tests

### 6.11 Analysis Plan

#### 6.11.1 Primary Efficacy Parameter

- The primary efficacy parameter was to be the Response Ratio for all partial seizures
- The Response Ratio was to be calculated for each patient using the formula noted under "Outcome Measures"
- The population for the primary efficacy analysis was to be the intent-to-treat population defined as all patients who were randomized to either of the 2 treatments.
- Patients with zero seizure frequency in both the baseline and double-blind phase were to be defined as having a Response Ratio of zero; for patients missing double-blind seizure data all partial seizures were carried forward which resulted in a Response Ratio of zero. For patients with no video-EEG record during the baseline phase or baseline and double-blind phase were also defined as having a Response Ratio of zero.
- The primary efficacy analysis was to be an ANCOVA: The approach used rank transformation adjusting for the patient's gender only. For descriptive purposes, the mean, standard error and 95 % confidence intervals, as well as the median and the 25<sup>th</sup> and 75<sup>th</sup> percentiles of the Response Ratio were to be computed in the 2 treatment groups, and in the subgroups of male and female infants. The mean treatment difference and 95 % confidence interval for the difference between treatment groups was also to be calculated. Also a scatter plot display of seizure frequency counts and 28-day all partial seizure rates per treatment group were to be computed. Testing was to be 2-sided and was to be performed at the 0.05 level of significance
- A secondary population for the efficacy analysis was to be the Observed Cases population. This was to be composed of all patients who were randomized to treatment, received placebo or gabapentin, and had any video-EEG data in the baseline and double-blind treatment phases. Patients without video-EEG data during the baseline or double-blind phase were to be excluded. The analysis of this population was to be similar to the primary efficacy analysis and is referred to as a supplementary analysis
- Other secondary populations for the analysis of the primary efficacy parameter were to be as follows:
  - A steady-state population defined as all intent-to-treat patients who had any data beyond the first day of the double-blind phase
  - An evaluable patient population defined as all intent-to-treat patients who had at least 1 partial seizure during the baseline or double-blind phase
- An interim analysis was originally planned but was later canceled

### 6.11.2 Secondary Efficacy Parameters

- The population for the analysis of all secondary efficacy parameters was to be the intent-to-treat population defined as above
- The responder rate would be analyzed using Fisher's Exact Test. Patients with no seizures in the baseline and double-blind phases would be defined as non-responders
- The percentage change in partial seizure frequency would not be subjected to an inferential analysis. Instead descriptive statistics including the mean, standard error, 25<sup>th</sup> and 75<sup>th</sup> percentiles and the median for each treatment group and between treatment groups would be calculated. The number and percentage of patients with percentage change of specific categories (increase or decrease) would also be provided. Patients with zero seizure frequency during the baseline and double-blind treatment phase and those with no video-EEG record during the baseline or double-blind phase would be defined as having a percentage change of zero
- The proportion of patients exhibiting a decrease in the ratio of secondarily generalized tonic-clonic seizure rate to partial seizure rate would be analyzed (conditional analysis of secondarily generalized tonic-clonic seizures) on the following population: secondarily generalized tonic-clonic seizures population defined as all intent-to-treat patients who had at least one secondarily generalized tonic-clonic seizure during the study. Fisher's exact chi-square test would be used to compare the treatment groups. A statistically significant difference between treatment groups would be declared if the p-value for the comparison (2-sided) was less than 0.05 ( $p < 0.05$ )
- The 28-day partial seizure rate and partial seizure frequency counts would be assessed on the intent-to-treat population: only descriptive statistics would be provided.

### 6.11.3 Safety Parameters

- The intent-to-treat population would be used for all safety analyses
- No inferential analyses were planned
- Frequencies of patients experiencing at least one adverse event would be tabulated by body system and COSTART preferred term
- Vital signs at baseline and changes in vital signs from baseline to the end of the double-blind phase would be summarized using descriptive statistics
- Abnormal laboratory results would be summarized according to treatment group

### 6.11.4 Sample Size Rationale

- The sample size estimate was based on data from add-on studies of gabapentin in adults and children aged 3 to 12 years with partial seizures
- The primary efficacy analysis was a comparison of mean Response Ratio for gabapentin and placebo, as noted above
- Assuming a mean gabapentin treatment effect of 0.14 (standard deviation = 0.15), a sample size of 20 patients per treatment group (total = 40 patients;

both studies combined) would be needed at 80 % power and at an  $\alpha = 0.05$  (2 – sided)

**6.11.5 Pharmacokinetic Analysis**

The pharmacokinetics of gabapentin would be characterized using a population approach with nonlinear mixed effects modeling

**6.12 Protocol Amendments**

These are incorporated in the above which includes the final Inferential Analysis Plan developed before the blind was broken.

**6.13 Actual Analyses Performed**

The analyses were performed as planned. Note that the plan for pooling the results of both studies was per protocol.

**6.14 Efficacy Results**

**6.14.1 Patient Disposition**

76 patients were randomly assigned to treatment: 38 patients were assigned to gabapentin and 38 patients were assigned to placebo. Their disposition is summarized in the following table. As the next (sponsor's) table indicates, with the exception of 2 patients randomized to placebo, all patients completed the double-blind phase.

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*	(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.  
 \* Patient could not tolerate continual video-EEG monitoring.

**6.14.2 Baseline And Other Demographic Characteristics**

Baseline demographic characteristics and partial seizure frequency are summarized in the following (sponsor's) table. Demographic variables were evenly distributed across the treatment groups as was mean baseline partial seizure frequency.

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		
<b>Gender, N (%)</b>									
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)	
<b>Race, N (%)</b>									
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)	
<b>Age, months</b>									
N	38		38		25		22		
Mean $\pm$ 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		
<b>Age Categories, months, N (%)</b>									
<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)	
<b>Weight, kg</b>									
N	38		38		25		22		
Mean $\pm$ 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		
<b>Height/Length, cm</b>									
N	37		37		24		21		
Mean $\pm$ SD	78.9	(11.6)	81.3	(11.1)	75.6	(11.6)	79.9	(12.4)	
Median	83.0		83.0		78.9		83.5		
Range	47.5 - 99.6		53.5 - 101.0		47.5 - 90.0		53.5 - 95.0		
<b>Baseline Partial Seizure Frequency per 28 Days</b>									
N	38		38		25		22		
Mean $\pm$ 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.

Disease characteristics are summarized in the next (sponsor's) table. As the table indicates, age at seizure onset was slightly earlier in placebo-treated patients in both populations.

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		
<b>Age at Onset, months</b>									
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 (%) <sup>a</sup>									
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 (%) <sup>a</sup>									
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 <sup>b</sup>									
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.  
<sup>a</sup> Patients could have more than 1 category of epilepsy etiology and more than 1 seizure type.  
<sup>b</sup> Includes concurrent AEDs taken at start of baseline (Day B1).

### 6.14.3 Primary Efficacy Analysis

The main primary efficacy analysis was on the intent-to-treat population. The Response Ratio was greater (i.e., more negative) for gabapentin-treated patients than for those treated with placebo. The difference was not statistically significant as indicated by the following (sponsor's) table

Primary Analysis of Response Ratio for All Partial Seizures in ITT Population: Study 945-305/405					
Treatment Group				Treatment Comparisons (Gabapentin - Placebo)	
	N	Mean	(SE)	Difference	p-Value <sup>b</sup>
All Patients <sup>a</sup>					
Placebo	38	0.018	(0.071)	-0.066	0.369
Gabapentin	38	-0.048	(0.071)		
Males <sup>c</sup>					
Placebo	22	0.013	(0.117)	NA	NA
Gabapentin	24	-0.032	(0.070)		
Females <sup>c</sup>					
Placebo	16	0.026	(0.121)	NA	NA
Gabapentin	14	-0.072	(0.078)		

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

As the table above indicates the male and female patient populations receiving gabapentin had an increase in Response Ratio, whereas those receiving placebo did not.

Supplementary analyses of the primary efficacy measure using the observed cases, steady-state and evaluable patients populations did not reveal any statistically significant differences between the 2 treatment groups. In all 3 populations declines were greater in those treated with gabapentin than in those

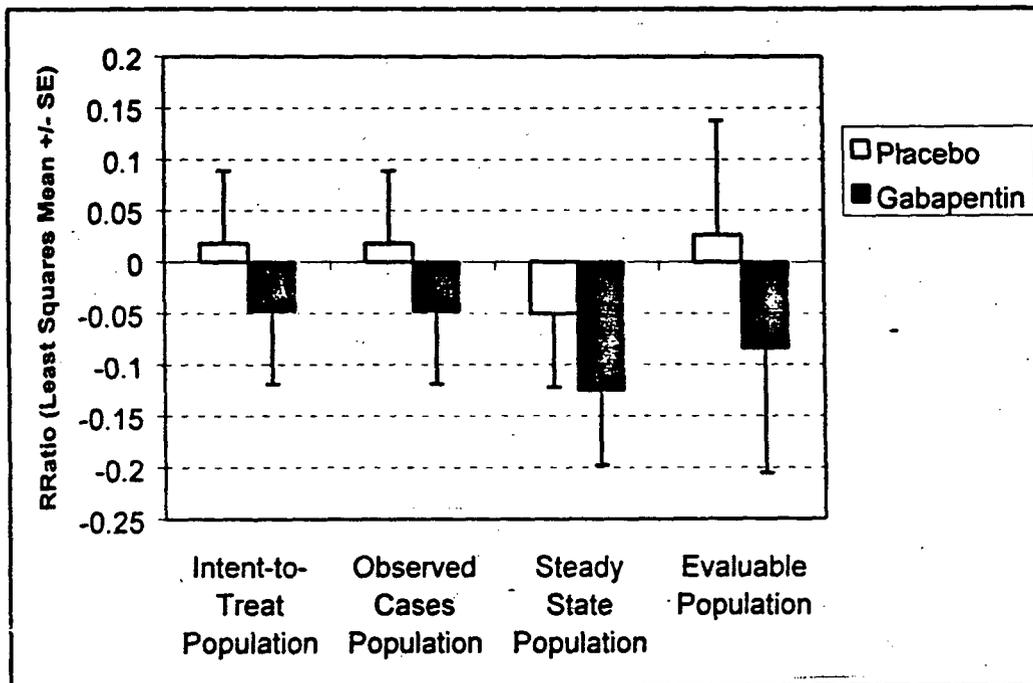
treated with placebo. These analyses are illustrated in the following table, provided by the sponsor.

Primary Analysis of Response Ratio for All Partial Seizures in Supplementary Populations: Study 945-305/405					
Treatment Group				Treatment Comparisons (Gabapentin - Placebo)	
	N	Mean (SE)		Difference	p-Value <sup>b</sup>
<b>Observed Cases Population<sup>a</sup></b>					
Placebo	38	0.018	(0.071)	-0.066	0.369
Gabapentin	38	-0.048	(0.071)		
<b>Steady State Population<sup>a</sup></b>					
Placebo	38	-0.050	(0.072)	-0.075	0.444
Gabapentin	38	-0.125	(0.073)		
<b>Evaluable Population<sup>a</sup></b>					
Placebo	22	0.026	(0.112)	-0.110	0.428
Gabapentin	25	-0.084	(0.121)		
SE = standard error.					
<sup>a</sup> Least squares means from ANCOVA using raw data, adjusted for gender.					
<sup>b</sup> ANCOVA using rank transformation, adjusted for gender.					

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Response Ratio changes in all 4 datasets are graphically displayed in the following figure, provided by the sponsor.

Least Squares Mean Response Ratio (RRatio) for All Partial Seizures:  
 Study 945-305/405



**6.14.4 Analysis Of Secondary Efficacy Measures**

These analyses were performed on the intent-to-treat population only, since with the primary efficacy analysis the results on that dataset matched those on the supplementary datasets

**6.14.4.1 Responder Rate**

The Responder Rate was similar for both groups, as illustrated in the (sponsor's) table below

Analysis of Responder Rate for All Partial Seizures: Study 945-305/405					
Population	Treatment Group	N	Number of Responders	% Responders	p-Value <sup>b</sup>
ITT <sup>a</sup>	Placebo	38	5	13.2%	>0.999
	Gabapentin	38	5	13.2%	

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

**6.14.4.2 Percentage Change From Baseline In 28-Day All Partial Seizure Rate**

The mean percentage change from baseline in 28-day all partial seizure rate represented virtually no change in the gabapentin group and an increase in the placebo group as indicated by the following table, provided by the sponsor.

Percent Change in 28-day All Partial Seizure Rate <sup>a</sup> (ITT Population): Study 945-305/405			
Percent Change	Placebo		Gabapentin
N	38		38
Mean (SE)	14.0	(18.2)	-0.7 (9.5)
25 <sup>th</sup> Percentile	-13.4		-23.6
Median	0.0		0.0
75 <sup>th</sup> Percentile	0.0		0.0

ITT = intent-to-treat, SE = standard error.  
<sup>a</sup> Patients with no seizures in the baseline and double-blind phases were defined as having a percent change of zero (0).

The number and percentage of patients in each group with increases or decreases in seizure rate are in the next table

Change In Seizure Rate	Placebo N (%)	Gabapentin N (%)	Total N (%)
Decline	12 (31.6)	14 (36.8)	26 (100)
Increase	26 (68.4)	24 (63.2)	50 (100)

**6.14.4.3 Proportion Of Patients Exhibiting A Decrease In The Ratio Of Secondly Generalized Tonic-Clonic Seizure Rate To Partial Seizure Rate**

Only 6 patients had secondarily generalized tonic-clonic seizures during the baseline phase: they were equally distributed between the 3 treatment groups. 2 of the 3 placebo-treated patients experienced a decline in the ratio of secondarily generalized tonic-clonic seizure rate to partial seizure rate from baseline to double-blind. None of the gabapentin-treated patients experienced a decline over the same period. The comparison of these proportions in the 2 treatment groups did not yield a statistically significant difference as indicated in the next table, provided by the sponsor

Analysis of Proportion of Patients Exhibiting a Decrease From Baseline to Double-Blind Treatment in the Ratio of SGTC Seizure Rate to Partial Seizure Rate (Secondarily Generalized Seizures Population): Study 945-305/405			
Treatment Group	N	Number (%) of Patients Exhibiting a Decrease	p-Value <sup>a</sup>
Placebo	3	2 (66.7)	0.400
Gabapentin	3	0 (0.0)	

SGTC = secondarily generalized tonic-clonic.  
<sup>a</sup> Pearson's chi-square test.

**6.15 Safety Results**

These are reviewed as part of the Integrated Summary of Safety

**6.16 Sponsor's Conclusions Regarding Efficacy**

The difference between placebo-treated patients and gabapentin-treated patients in Response Ratio between the baseline and double-blind phases suggested a positive effect of gabapentin but was not statistically significant. The sponsor notes that the magnitude of the effect was similar to that in the intent-to-treat population in the 945-86/186 study which was statistically significant when the ANOVA was performed on rank-ordered data.

The sponsor has suggested the following possible explanations for the "negative" results of the 945-305/405 study when viewed against the "positive" results of the 945-86/186 study

- Patients in the 945-305/405 study had a higher mean baseline partial seizure rate, an earlier age of seizure onset, a more common history of secondarily generalized tonic-clonic seizures,

and a higher rate of birth complications and infections as seizure etiologies; all these factors, the sponsor believes, point to more severe underlying disease and therefore seizures more resistant to medical treatment

- Patients in the 945-305/405 study were exposed to gabapentin for too short a period of time. The sponsor cites the greater gabapentin-placebo difference on the Response Ratio for the steady-state dataset than for the intent-to-treat population as evidence that might support this possibility
- The 945-305/405 study was underpowered. The sample size estimate was based on the drug effect seen in previous add-on trials of gabapentin in older children and adults, and on a variance that was assumed to be smaller (since video-EEG was to be used) than in previous trials in older children and adults. In actual fact the drug effect seen in Study 945-305/405 was smaller and the variance larger than in 945-86/186. The large variance in the former study was in turn attributed at least in part to the short period of observation during which 29/76 (38%) of patients had no seizures at all.

### 6.17 Reviewer's Comments

- Regardless of the explanation offered, the efficacy of gabapentin as add-on treatment in partial seizures occurring in the 0-36 month age group has not been established to a sufficient degree to meet current regulatory standards
- As the sponsor too indicates, the abbreviated duration of this study was based on ethical and practical considerations which were discussed with this Division prior to the study being instituted

## 7. Integrated Summary of Safety

### 7.1 Cut-Off Dates

The cut-off dates for safety data in the original NDA 21216 submission are summarized in the following table, provided by the sponsor

	Integrated Summary of Safety (ISS) Database	Serious Adverse Events and Deaths <sup>a</sup>
Cut-off Dates	August 13, 1999	November 10, 1999
<sup>a</sup> Includes all serious adverse events and deaths reported to Parke-Davis Clinical Safety database by November 10, 1999.		

### 7.2 Exposure Summary

Exposure to gabapentin in patients  $\leq$  12 years old with epilepsy in each of the groups of studies included is outlined in the following table, provided by the sponsor:

Studies	Ages 1 month to < 3 years	Ages 3 to 12 years	Combined
Combined Adjunctive Therapy Studies	13.2 patient-years	128.8 patient-years	142.0 patient-years
Monotherapy Studies	0	292.7 patient-years	292.7 patient-years
Studies Included in NDA 20-235	0	19.4 patient-years	19.4 patient-years
Prematurely-Terminated Study	0	3.7 patient-years	3.7 patient-years
<b>TOTAL</b>	<b>13.2 patient-years</b>	<b>444.6 patient-years</b>	<b>457.8 patient-years</b>

The number of pediatric patients with epilepsy exposed to gabapentin for specific durations is outlined in the following table, provided by the sponsor.

Studies	Any exposure	≥ 12 weeks	≥ 26 weeks	≥ 52 weeks
Combined Adjunctive Therapy Studies Monotherapy Studies Studies Included in NDA 20-235	639	451	315	148
Prematurely-Terminated Study	6	Data unavailable		

### 7.3 Studies Included In Integrated Summary Of Safety

The studies included in the Integrated Summary of Safety are all those included in the NDA: they are listed in Section 2 ("Tabular Summary Of Studies In NDA")

### 7.4 Study Pools In Integrated Summary Of Safety

The study pools used to analyze adverse events in the Integrated Summary of Safety are as follows:

- Clinical pharmacology studies
- Combined adjunctive therapy studies
- Monotherapy studies
- Combined adjunctive therapy and monotherapy studies
- Approved NDA pediatric experience
- Other pediatric experience

Deaths, serious adverse events, adverse events leading to study discontinuation, all study discontinuations and clinical laboratory data are discussed in separate sections distinct from the above pools.

All adverse events described below are treatment-emergent

## 8. Adverse Events In Clinical Pharmacology Studies

### 8.1 Demographics

These are summarized in the following table.

Study	Number Enrolled	Number Completing	Mean Age (years)	Mean Weight (kg)
945-202	24 (17 M, 7 F)	24	8.7 (Range: 4-12)	33.8 (Range: 16.4-52.1)
945-296	26 (12 M, 14 F)	24*	1.2	4.9
			7.0	7.7
			20.0	11.8
			36.0	13.9

\*one subject discontinued on account of vomiting (which later resolved) and another subject discontinued on account of an inability to maintain an intravenous infusion

### 8.2 Adverse Events

Adverse events occurring in all Clinical Pharmacology studies are summarized in the following table, provided by the sponsor. No deaths or serious adverse events occurred.

Adverse Events: Clinical Pharmacology Studies Number (%) of Patients										
Body System/ Preferred Term	Gabapentin									
	Study 945-202 Total Dose <sup>a</sup>						Study 945-296 1x10 mg/kg in Syrup N = 26		All Studies Combined N = 50	
	200 mg N = 7		300 mg N = 8		400 mg N = 9					
Body Area Whole	1	(14.3)	0	(0.0)	1	(11.1)	2	(7.7)	4	(8.0)
Abdominal Pain	1	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.0)
Asthenia	0	(0.0)	0	(0.0)	1	(11.1)	0	(0.0)	1	(2.0)
Infection	0	(0.0)	0	(0.0)	0	(0.0)	2	(7.7)	2	(4.0)
Digestive System	0	(0.0)	1	(12.5)	0	(0.0)	1	(3.8)	2	(4.0)
Vomiting	0	(0.0)	1	(12.5)	0	(0.0)	1	(3.8)	2	(4.0)
Hemic and Lymphatic System	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.8)	1	(2.0)
Ecchymosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.8)	1	(2.0)
Nervous System	0	(0.0)	0	(0.0)	1	(11.1)	4	(15.4)	5	(10.0)
Dizziness	0	(0.0)	0	(0.0)	1	(11.1)	0	(0.0)	1	(2.0)
Somnolence	0	(0.0)	0	(0.0)	0	(0.0)	4	(15.4)	4	(8.0)
Ataxia	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.8)	1	(2.0)
Respiratory System	0	(0.0)	0	(0.0)	0	(0.0)	4	(15.4)	4	(8.0)
Rhinitis	0	(0.0)	0	(0.0)	0	(0.0)	4	(15.4)	4	(8.0)
Special Senses	0	(0.0)	0	(0.0)	0	(0.0)	2	(7.7)	2	(4.0)
Otitis Media	0	(0.0)	0	(0.0)	0	(0.0)	2	(7.7)	2	(4.0)
Urogenital System	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.8)	1	(2.0)
Hematuria	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.8)	1	(2.0)
Any Adverse Event	1	(14.3)	1	(12.5)	2	(22.2)	10	(38.5)	14	(28.0)

TESS = Treatment-emergent signs and symptoms.  
<sup>a</sup> 200 mg = 2x100-mg Capsules; 300 mg = 1x300-mg Capsules; 400 mg = 1x400-mg Capsules.

Clinical laboratory abnormalities were considered sporadic, transient, unremarkable for this age group, and unrelated to gabapentin.

## 9. Adverse Events In Combined Adjunctive Therapy Studies

### 9.1 Demographics

These are summarized in the following table, provided by the sponsor. As the table indicates, and as might be expected there were considerable differences between the 2 sets of studies represented by

- 945-86/186 and 945-87/187
- 945-305/405 and 945-301/401

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Characteristic	Placebo-Controlled Adjunctive Therapy Studies								Open-Label Extension Studies				Gabapentin-Treated Patients in Combined Studies* N = 392	
	Study 945-86/186				Study 945-305/405				Study 945-87/187		Study 945-301/401			
	Placebo N = 128		Gabapentin N = 119		Placebo N = 38		Gabapentin N = 38		N = 237		N = 145			
Sex N (%)														
Males	75	(58.6)	59	(49.6)	22	(57.9)	24	(63.2)	126	(53.2)	76	(52.4)	207	(52.8)
Females	53	(41.4)	60	(50.4)	16	(42.1)	14	(36.8)	111	(46.8)	69	(47.6)	185	(47.2)
Age, years														
Mean (SD)	8.4	(2.7)	8.5	(2.4)	1.5	(0.7)	1.6	(0.7)	8.6	(2.5)	2.1	(1.1)	6.1	(3.8)
Median	9.0		9.0		1.5		1.5		9.0		1.9		6.0	
Range	3.0-12.0		3.0-12.0		0.2-2.8		0.2-3.0		3.0-12.0		0.2-4.9		0.2-12.0	
Race N (%)														
White	118	(92.2)	108	(90.8)	23	(60.5)	22	(57.9)	217	(91.6)	92	(63.4)	318	(81.1)
Black	1	(0.8)	3	(2.5)	7	(18.4)	7	(18.4)	4	(1.7)	20	(13.8)	25	(6.4)
Hispanic	0	(0.0)	0	(0.0)	7	(18.4)	8	(21.1)	0	(0.0)	27	(18.6)	27	(6.9)
Asian	4	(3.1)	2	(1.7)	0	(0.0)	0	(0.0)	6	(2.5)	0	(0.0)	6	(1.5)
American Indian	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.3)
Other	5	(3.9)	6	(5.0)	1	(2.6)	1	(2.6)	10	(4.2)	5	(3.4)	15	(3.8)
Weight, kg														
Mean (SD)	32.0	(11.7)	31.6	(11.1)	10.4	(3.0)	11.1	(3.0)	32.5	(11.7)	11.8	(3.7)	24.6	(13.7)
Median	29.4		29.0		10.2		10.9		29.8		12.0		22.0	
Range	15.5-73.1		15.9-67.5		3.0-17.5		3.5-18.6		15.5-73.1		3.0-23.8		3.0-73.1	
Height, cm														
Mean (SD)	131.3	(16.7)	131.3	(14.7)	78.9	(11.6)	81.3	(11.1)	132.1	(15.7)	83.7	(12.4)	113.8	(27.5)
Median	132.0		133.0		80.0		83.0		133.5		85.0		117.0	
Range	96.0-175.0		99.0-170.0		47.5-99.6		53.5-101.0		96.0-175.0		47.5-112.0		47.5-175.0	
Duration of Epilepsy, years														
Mean (SD)	5.4	(3.1)	5.7	(3.0)	1.0	(0.7)	1.2	(0.7)	5.7	(3.1)	1.4	(1.1)	4.0	(3.2)
Median	5.3		5.9		0.8		1.2		5.8		1.2		3.1	
Range	<1-11.9		<1-11.3		<1-2.4		<1-2.7		<1-11.9		<1-4.8		<1-11.9	
Concurrent AEDs, N (%)														
0	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
1	44	(34.4)	32	(26.9)	16	(42.1)	11	(28.9)	76	(32.1)	57	(39.3)	133	(33.9)
2	57	(44.5)	57	(47.9)	10	(26.3)	19	(50.0)	107	(45.1)	55	(37.9)	169	(43.1)
3	27	(21.1)	30	(25.2)	10	(26.3)	7	(18.4)	54	(22.8)	27	(18.6)	84	(21.4)
4	0	(0.0)	0	(0.0)	2	(5.3)	1	(2.6)	0	(0.0)	6	(4.1)	6	(1.5)

AED = Antiepileptic drug; SD = Standard deviation.

\* Studies that were combined: 945-86/186, 945-305/405, 945-87/187, and 945-301/401.

## 9.2 Exposure Data

Detailed exposure data as a function of patient age are in the following table, provided by the sponsor. For each patient exposure is represented by the total accumulated during double-blind and open-label studies

Duration of Gabapentin Exposure <sup>a</sup>	Patient Age					
	1 month to <3 years N = 115		3 to 12 years N = 277		Combined - N = 392	
≥ 1 Dose	115	(100.0)	277	(100.0)	392	(100.0)
≥ 1 Week	103	(89.6)	268	(96.8)	371	(94.6)
≥ 2 Weeks	98	(85.2)	265	(95.7)	363	(92.6)
≥ 4 Weeks	78	(67.8)	260	(93.9)	338	(86.2)
≥ 6 Weeks	45	(39.1)	245	(88.4)	290	(74.0)
≥ 8 Weeks	37	(32.2)	242	(87.4)	279	(71.2)
≥ 10 Weeks	18	(15.7)	232	(83.8)	250	(63.8)
≥ 12 Weeks	15	(13.0)	224	(80.9)	239	(61.0)
≥ 14 Weeks	5	(4.3)	216	(78.0)	221	(56.4)
≥ 16 Weeks	1	(0.9)	207	(74.7)	208	(53.1)
≥ 18 Weeks	1	(0.9)	201	(72.6)	202	(51.5)
≥ 20 Weeks	0	(0.0)	197	(71.1)	197	(50.3)
≥ 22 Weeks	0	(0.0)	184	(66.4)	184	(46.9)
≥ 24 Weeks	0	(0.0)	164	(59.2)	164	(41.8)
≥ 26 Weeks	0	(0.0)	127	(45.8)	127	(32.4)
≥ 28 Weeks	0	(0.0)	100	(36.1)	100	(25.5)
≥ 30 Weeks	0	(0.0)	91	(32.9)	91	(23.2)
≥ 32 Weeks	0	(0.0)	86	(31.0)	86	(21.9)
≥ 34 Weeks	0	(0.0)	81	(29.2)	81	(20.7)
≥ 36 Weeks	0	(0.0)	70	(25.3)	70	(17.9)
≥ 38 Weeks	0	(0.0)	39	(14.1)	39	(9.9)
≥ 40 Weeks	0	(0.0)	14	(5.1)	14	(3.6)
≥ 42 Weeks	0	(0.0)	5	(1.8)	5	(1.3)
≥ 44 Weeks	0	(0.0)	3	(1.1)	3	(0.8)
≥ 46 Weeks	0	(0.0)	3	(1.1)	3	(0.8)
≥ 48 Weeks	0	(0.0)	1	(0.4)	1	(0.3)
≥ 50 Weeks	0	(0.0)	1	(0.4)	1	(0.3)
Total Patient-Days	4830.0		47041.0		51871.0	
Total Patient-Weeks	690.0		6720.1		7410.1	
Total Patient-Years	13.2		128.8		142.0	

### 9.3 Adverse Events In Placebo-Controlled Trials

#### 9.3.1 Study 945-305/405

##### 9.3.1.1 Overview

As the following table provided by the sponsor indicates adverse events were more frequent in those treated with gabapentin than in those treated with placebo, more frequent in females than in males, and generally mild to moderate in severity. There were no deaths or adverse events leading to treatment

discontinuation, and only 1 serious adverse event (an upper respiratory infection) in patients treated with gabapentin

Overview of Adverse Events (AEs): Study 945-305/405				
	Placebo N=38		Gabapentin N=38	
<b>Number (%) of Patients With TESS AEs</b>				
All AEs	14/38	(36.8)	22/38	(57.9)
Associated AEs <sup>a</sup>	4/38	(10.5)	9/38	(23.7)
<b>Number (%) of Patients With TESS AEs by Gender</b>				
All AEs				
Males	10/22	(45.5)	13/24	(54.2)
Females	4/16	(25.0)	9/14	(64.3)
Associated AEs <sup>a</sup>				
Males	2/22	(9.1)	6/24	(25.0)
Females	2/16	(12.5)	3/14	(21.4)
<b>Number (%) of Patients With TESS AEs by Maximum Intensity</b>				
All AEs				
Mild	12/38	(31.6)	18/38	(47.4)
Moderate	2/38	(5.3)	3/38	(7.9)
Severe	0/38	(0.0)	1/38	(2.6)
Associated AEs <sup>a</sup>				
Mild	4/38	(10.5)	7/38	(18.4)
Moderate	0/38	(0.0)	2/38	(5.3)
Severe	0/38	(0.0)	0/38	(0.0)
Number (%) of Deaths	0/38	(0.0)	0/38	(0.0)
Number (%) of Patients With Serious AEs <sup>b</sup>	0/38	(0.0)	1/38	(2.6)
Number (%) of Patients Withdrawn Due to AEs	0	(0.0)	0	(0.0)
TESS = Treatment-emergent signs and symptoms.				
<sup>a</sup> AEs that the investigator considered definitely, probably, or possibly related to study medication, and those events for which there was insufficient information to make a determination of relationship.				
<sup>b</sup> No non-TESS serious adverse events were reported in this study.				

9.3.1.2 Adverse Events Occurring In ≥ 5% Of Patients In Either Treatment Group

These are summarized in the following (sponsor's) table. Adverse events more commonly seen in those treated with gabapentin than in those treated with placebo were nausea and/or vomiting, constipation, somnolence and otitis media

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Treatment Group	Placebo (n=38)		Gabapentin (n=38)	
None	24	(63.2)	16	(42.1)
Digestive System	1	(2.6)	9	(23.7)
Nausea and/or Vomiting	1	(2.6)	5	(13.2)
Constipation	0	(0.0)	2	(5.3)
Nervous System	1	(2.6)	8	(21.1)
Somnolence	1	(2.6)	6	(15.8)
Skin and Appendages	10	(26.3)	6	(15.8)
Rash	3	(7.9)	2	(5.3)
Skin Disorder	2	(5.3)	2	(5.3)
Pruritus	2	(5.3)	1	(2.6)
Dermatitis	2	(5.3)	0	(0.0)
Respiratory System	3	(7.9)	3	(7.9)
Rhinitis	2	(5.3)	0	(0.0)
Body Area Whole	2	(5.3)	2	(5.3)
Fever	2	(5.3)	1	(2.6)
Special Senses	0	(0.0)	2	(5.3)
Otitis Media	0	(0.0)	2	(5.3)
Any Adverse Event	14	(36.8)	22	(57.9)

9.3.1.3 Adverse Events Occurring In  $\geq 2\%$  of Patients In Either Treatment Group

These are summarized in the sponsor-provided table below. The commonest adverse events in the gabapentin-treated group relative to placebo were nausea and/or vomiting and somnolence.

Treatment Group	Placebo (n=38)		Gabapentin (n=38)	
Preferred Term				
Somnolence	1	(2.6)	6	(15.8)
Nausea and/or Vomiting	1	(2.6)	5	(13.2)
Rash	3	(7.9)	2	(5.3)
Skin Disorder	2	(5.3)	2	(5.3)
Constipation	0	(0.0)	2	(5.3)
Otitis Media	0	(0.0)	2	(5.3)
Fever	2	(5.3)	1	(2.6)
Pruritus	2	(5.3)	1	(2.6)
Abrasion	1	(2.6)	1	(2.6)
Pharyngitis	1	(2.6)	1	(2.6)
Anorexia	0	(0.0)	1	(2.6)
Antiepileptic Level Increased	0	(0.0)	1	(2.6)
Diarrhea	0	(0.0)	1	(2.6)
Elevated SGOT (AST)	0	(0.0)	1	(2.6)
Face Edema	0	(0.0)	1	(2.6)
Fecal Impaction	0	(0.0)	1	(2.6)
Hyperkalemia	0	(0.0)	1	(2.6)
Leukopenia	0	(0.0)	1	(2.6)
Myalgia	0	(0.0)	1	(2.6)
Nystagmus	0	(0.0)	1	(2.6)
Respiratory Infection	0	(0.0)	1	(2.6)
Stools Bloody	0	(0.0)	1	(2.6)
Upper Respiratory Infection	0	(0.0)	1	(2.6)
Sleep Disorder	0	(0.0)	1	(2.6)
Dermatitis	2	(5.3)	0	(0.0)
Rhinitis	2	(5.3)	0	(0.0)
Coughing	1	(2.6)	0	(0.0)
Localized Infection	1	(2.6)	0	(0.0)

### 9.3.2 Study 945-86/186

#### 9.3.2.1 Overview

As the following (sponsor's) table indicates adverse events were more frequent in those treated with gabapentin than in those treated with placebo, more frequent in males than in females, and generally mild to moderate in severity. There were no deaths; serious adverse events and adverse events leading to treatment discontinuation were infrequent overall, but more frequent in those treated with gabapentin than in those treated with placebo

Overview of Adverse Events (AEs): Study 945-86/186				
	Placebo N=128		Gabapentin -N=119	
<b>Number (%) of Patients With TESS AEs</b>				
All AEs	66	(51.6)	75	(63.0)
Associated AEs <sup>a</sup>	26	(20.3)	40	(33.6)
<b>Number (%) of Patients With TESS AEs by Gender</b>				
Males	43/75	(57.3)	41/59	(69.5)
Females	23/53	(43.4)	34/60	(56.7)
<b>Number (%) of Patients With TESS AEs by Maximum Intensity</b>				
No AEs	62	(48.4)	44	(37.0)
Mild	33	(25.8)	32	(26.9)
Moderate	30	(23.4)	29	(24.4)
Severe	3	(2.3)	14	(11.8)
<b>Number (%) of Patients With TESS Associated AEs by Maximum Intensity</b>				
No Associated AEs	102	(79.7)	79	(66.4)
Mild	14	(10.9)	15	(12.6)
Moderate	10	(7.8)	15	(12.6)
Severe	2	(1.6)	10	(8.4)
<b>Number (%) of Deaths</b>				
	0		0	
<b>Number (%) of Patients With Serious AEs</b>				
	4 <sup>b</sup>	(3.1)	9	(7.6)
<b>Number (%) of Patients Withdrawn Due to AEs</b>				
All AEs	3	(2.3)	6	(5.0)
Associated AEs <sup>a</sup>	1	(0.8)	6	(5.0)
TESS = Treatment-emergent signs and symptoms. <sup>a</sup> AEs that the investigator considered definitely, probably, or possibly related to study medication, and those events for which there was insufficient information to make a determination of relationship. <sup>b</sup> Includes 1 placebo-treated patient who had a serious adverse event that occurred during baseline.				

Serious adverse events using investigator terms are listed in the next table; the number of patients with each adverse event is in parentheses

Placebo	Gabapentin
Fracture of radius and ulna (during baseline period) (1)	Viral infection with dehydration (1)
Deterioration of pre-existing lung disease (1)	Acute asthmatic attack (1)
Acute laryngitis (1)	Upper respiratory infection with fever (1)
Near drowning with aspiration pneumonia (1)	Pneumonia and otitis media with fever (1)
	Study drug overdose (1)
	Central line infection with septicemia and right atrial thrombus (1)
	Shunt failure (1)
	Stupor (1)
	Headache (1)

Note that:

- All patients recovered except the individual with a headache
- The patient with stupor was receiving high doses of multiple anticonvulsant medications

Adverse event discontinuations using investigator terms are listed in the next table; the number of patients with each adverse event is in parentheses

Placebo	Gabapentin
Nausea and/or vomiting, Diarrhea (1)	Atypical absence and myoclonic seizures (1)
Somnolence and emotional lability (1)	Agitation, hostility, impaired coordination and thinking, reduced pain threshold (1)
Leukopenia (1)	Increased appetite, insomnia, hostility (1)
	Personality disorder (1)
	Somnolence (1)
	Insomnia and hyperkinesia (1)

*9.3.2.2 Adverse Events Occurring In  $\geq$  2% Of Patients In Either Treatment Group*

These adverse events are summarized in the next sponsor-provided table. Overall, adverse events were somewhat more frequent in those treated with gabapentin than in those treated with placebo.

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