

DEMOGRAPHICS/GROUP COMPARABILITY

A comparison of the baseline characteristics by treatment group shows that baseline characteristics were balanced across treatment groups in this study. An abbreviated version of Sponsor's table 8-15 below summarizes Baseline characteristics for the Intent-to-treat dataset. There was no statistically significant difference between the treatment groups with respect to sex, age, weight, race, age at onset of epilepsy, duration of epilepsy, and Baseline seizure frequency. Concurrent AED use was similar in both treatment groups, with a slightly higher percentage, but not statistically significant number of vigabatrin patients than placebo patients using valproic acid (30% versus 19%, $P=.071$).

Baseline Characteristic	Treatment		Total N=182	P value†
	Placebo N=90	3 g VGB N=92		
Sex				
Males %(N)	48% (43)	40% (37)	44% (80)	.304
Females %(N)	52% (47)	60% (55)	56% (102)	
Age (years)				
Median	33	34	33.5	.9944
Mean+Std Dev	34 ± 8	34 ± 9	34 ± 9	
Range	19 - 57	18 - 60	18 - 60	
Race				
Caucasian %(N)	91% (82)	90% (83)	91% (165)	.912
Negroid %(N)	7% (6)	7% (6)	7% (12)	
Other %(N)	2% (2)	3% (3)	3% (5)	
Concurrent use of AEDs				
One %(N)	43% (39)	33% (30)	38% (69)	.136
Two %(N)	57% (51)	67% (62)	62% (113)	
Concurrent use of Barbiturates %(N)	22% (20)	21% (19)	21% (39)	.796
Concurrent use of Benzodiazepines %(N)	7% (6)	5% (5)	6% (11)	.727
Concurrent use of Carbamazepine %(N)	70% (63)	66% (61)	68% (124)	.593
Concurrent use of Hydantoins %(N)	34% (31)	39% (36)	37% (67)	.512
Concurrent use of Valproic Acid %(N)	19% (17)	30% (28)	25% (45)	.071
† P values for Baseline comparability of categorical variables from chi-squared tests, for continuous variables from Kruskal-Wallis tests.				

SEIZURE CALENDARS. Daily seizure calendars were used to record patients' seizure counts.

SEIZURE COUNTS. Investigators classified the patients' seizure description on the calendar as either a IA, IB, or IC seizure (in accordance with the 1981 Revised International Classification of the Epilepsies).

SEIZURE FLURRIES. If seizure flurries occurred where there was no definite total number, the investigator gave the best estimate of seizure count. The investigator provided a comment in those instances to document the situation as clearly as possible.

CONCOMITANT ANTI-EPILEPSY DRUGS. While doses of antiepileptic drugs were to remain constant throughout the study, there were a number of deviations from this protocol requirement, specifically alterations in dose or addition of new or prn antiepileptic drugs including the benzodiazepines. Benzodiazepines were administered commonly during this study for seizures, anxiety, headache, insomnia and agitation.

Sponsor's Table 8-20 below gives the percentage of patients in Segments I, II and III who received benzodiazepines and other medications with anti-seizure properties during the study. The percentage of patients using these medications with anti-seizure properties during Segments I, II, and III was similar in the two treatment groups.

Medication Class and Indication	Segment I		Segments II and/or III		Total	
	Placebo (N=90)	3 g VGB (N=92)	Placebo (N=90)	3 g VGB (N=92)	Placebo (N=90)	3 g VGB (N=92)
Benzodiazepines for Epilepsy	5.6% (5)	5.4% (5)	5.6% (5)	5.4% (5)	7.8% (7)	7.6% (7)
Benzodiazepines for Other Indication	3.3% (3)	4.3% (4)	2.2% (2)	3.3% (3)	3.3% (3)	5.4% (5)
Non-Benzodiazepines with Anti-seizure Properties	2.2% (2)	2.2% (2)	1.1% (1)	1.1% (1)	2.2% (2)	2.2% (2)

In addition, and in general mean plasma levels of other concomitant AEDs either did not change or decreased during the study in the vigabatrin group compared to the placebo group. One important change in concomitant AED levels, however, occurred with phenytoin. Plasma phenytoin levels increased in the placebo group by an average 3.1% from Baseline to Endstudy while a 15.7% average decrease in plasma phenytoin ($P=.0003$) was seen in the vigabatrin treated group.

INTERIM ANALYSIS An interim analysis was planned according to the protocol, however no interim analysis was performed.

SPONSOR'S EFFICACY RESULTS

ANALYSIS DATASETS

Efficacy Analyses used the Intent-to-treat dataset composed of all 182 patients who were exposed to double-blind study medication. Supportive Efficacy Analyses included the following datasets:

- **Protocol Correct Completers:** All patients who completed the 12-week Maintenance Period and had no major protocol violations. (N=160: 84 PBO/76 VGB)
- **Protocol Correct:** All patients with no major protocol violations. (N=169: 86 PBO/ 83 VGB)
- **Study Completers:** All patients who completed the 12-week Maintenance Period.(N=170: 88 PBO/ 82 VGB)
- **8-Week Completers:** All patients with at least 8 weeks of postrandomization seizure data. (N=174 : 88 PBO/ 86 VGB)

These data sets were all subsets of the **Intent-to-Treat** dataset.

PRIMARY EFFICACY ANALYSIS. One hundred eighty-two (182) patients received study medication and were evaluated for efficacy (90 placebo and 92 vigabatrin). The primary endpoint for the evaluation of efficacy was the mean monthly frequency of complex partial seizures (IB) plus partial seizures secondarily generalized (IC) at Endstudy (last 8 weeks of study) compared to Baseline (last 8 weeks of Segment I).

For each class of seizures, the mean monthly (28 day) frequency of seizures was calculated for each visit window (interval between visits in which seizure data was collected) using the following formula:

$$\text{Mean Monthly Frequency} = \frac{(28 \times \text{number of seizures in window})}{(\text{number of days in visit window with seizure data})}$$

For each patient, seizure frequencies were computed for each class of partial seizures (simple partial seizures [IA], complex partial seizures [IB], and partial seizures secondarily generalized [IC]) and for complex partial seizures plus partial seizures secondarily generalized (IB + IC) using daily seizure calendar data.

Sponsor's Table 8-1 below presents the primary analysis of complex partial seizures plus partial seizures secondarily generalized (and the secondary analysis of

therapeutic success). There was a statistically significantly lower Endstudy frequency of seizures (complex partial seizures plus partial seizures secondarily generalized; IB + IC) for patients receiving vigabatrin than for patients receiving placebo. The median monthly frequency was reduced by 3 seizures per 28 days in the vigabatrin group (Baseline 8.3, Endstudy 5.3) versus 0.8 seizures per 28 days in the placebo group (Baseline 8.3, Endstudy 7.5) ($P=.0002$)

Sponsor's Table 8-1. Analysis of Complex Partial Seizures Plus Partial Seizures Secondarily Generalized and Therapeutic Success. Intent-to-treat Patients (N=182).					
<i>Treatment</i>	<i>N</i>	<i>Seizure Frequency Baseline Median (95% CI)</i>	<i>Seizure Frequency (Number/28 Days Endstudy Median (95% CI))</i>	<i>Therapeutic Success At Least 50% Reduction in the Mean Monthly Seizure Rate from Baseline to Endstudy</i>	
				<i>%</i>	<i>(N)</i>
Placebo	90	8.3 (6.5, 10.0)	7.5 (6.0, 9.0)	19%	(17)
3 g VGB	92	8.3 (6.5, 10.0)	5.3 (3.5, 6.0)	43%	(40)
<i>Treatment Comparison</i>		<i>P Value</i>		<i>P Value</i>	
3 g VGB versus Placebo		.0002		<.001	

The primary analysis was performed using the Intent-to-treat dataset, and supportive analyses were performed using the Protocol Correct Completer, Protocol Correct, Study Completer, and 8-Week Completer datasets. In all analyses, a two-tailed ($\alpha = .05$ significance level) was used to test the difference in response to VGB and placebo. These supportive analyses were consistent with the intent-to-treat analysis.

SECONDARY EFFICACY ANALYSES. Intent-to-treat analyses were performed for each of the secondary efficacy parameters.

1- Therapeutic Success: A patient who experienced at least a 50% decrease from Baseline to Endstudy in the frequency of complex partial seizures plus partial seizures

secondarily generalized was considered a Therapeutic Success. The frequency of Therapeutic Successes was compared for the two treatment groups using a Mantel-Haenszel procedure. Stratification by investigative site was included.

Therapeutic success was achieved in 43% of the vigabatrin patients versus 19% of the placebo patients ($P < .001$). This was shown in Table 8.1 on the previous page. Sponsor's analysis using the Protocol Correct Completer subset was consistent with the intent to treat results.

2-Frequency of Simple Partial Seizures (IA) The event rate in this group was so low as to preclude analysis.

3- Frequency of Complex Partial Seizures (IB) The analysis of complex partial seizures (IB) was performed using the 173 Intent-to-treat patients who had a non-zero Baseline frequency of complex partial seizures. The frequency of complex partial seizures at Endstudy was statistically significantly less for vigabatrin patients than for placebo patients ($P = .0006$). The median monthly rate of complex partial seizures was reduced by 3.5 seizures per 28 days in the vigabatrin group compared to 1.0 seizures per 28 days in the placebo group.

Sponsor's Table 8-30

.Analysis of Complex Partial Seizures (IB).			
Intent-to-treat Patients with Baseline Seizure Frequency > 0 (N=173)			
		Seizure Frequency (Number/28 Days)	
<i>Treatment</i>	<i>N</i>	<i>Baseline Median (95% CI)</i>	<i>Endstudy Median (95% CI)</i>
Placebo	89	8.0 (6.0, 9.5)	7.0 (5.5, 9.0)
3 g VGB	84	8.5 (6.0, 10.5)	5.0 (3.0, 6.0)
<i>Treatment Comparison</i>		<i>P Value</i>†	
3 g VGB versus Placebo		.0006	
<i>Model Factor</i>			
Baseline Seizure Frequency		.0001	
Investigative Site		.3581	
Treatment		.0006	
† P values from analysis of covariance of the ranked Endstudy seizure frequencies using model which adjusted for treatment, investigative site, and ranked Baseline seizure frequency.			

4-Frequency of All Secondarily Generalized Seizures (IC) The analysis of partial seizures secondarily generalized (IC) was performed using the 60 Intent-to-treat patients who had a nonzero Baseline frequency of partial seizures secondarily generalized. The median monthly rate of partial seizures secondarily generalized was reduced by 1.5 seizures per 28 days in the vigabatrin group versus 0 seizures per 28 days in the placebo group. *However, there was no statistically significant difference between the treatment groups (P=.3881).*

Table 8-31. Analysis of Partial Seizures Secondarily Generalized (IC). Intent-to-treat Patients with Baseline Seizure Frequency > 0. (N=60).			
		Seizure Frequency (Number/28 Days)	
Treatment	N	Baseline Median (95% CI)	Endstudy Median (95% CI)
Placebo	29	1.5 (1.0, 2.0)	1.5 (1.0, 2.5)
3 g VGB	31	4.0 (1.0, 5.0)	2.5 (1.0, 3.0)
<u>Treatment Comparison</u>		<u>P Value†</u>	
3 g VGB versus Placebo		.3881	
<u>Model Factor</u>			
Baseline Seizure Frequency		.0001	
Investigative Site		.8794	
Treatment		.3881	
† P values from analysis of covariance of the ranked Endstudy seizure frequencies using model which adjusted for treatment, investigative site, and ranked Baseline seizure frequency.			

5- Seizure Free Days: For seizure-free days, the mean monthly frequency of seizure-free days was calculated for each visit window using the following formula:

$$\text{Mean Monthly Frequency of Seizure-Free Days} = \frac{(28 \times \text{number of seizure-free days in window})}{(\text{number of days in visit window with seizure data})}$$

The mean monthly frequency of seizure-free days was compared for the two treatment groups. The results of the Intent-to-treat analysis of seizure-free days are shown in the table below. Vigabatrin significantly increased the number of seizure-free days compared to placebo (P=.0024). The adjusted mean change from Baseline was an increase of 2.2 seizure-free days per 28 days for the vigabatrin group versus 0.5 seizure-free days per 28 days for the placebo group.

<i>Mean Monthly Frequency of Seizure-Free Days</i>				
<i>Treatment</i>	<i>N</i>	<i>Baseline Mean ± Std Error</i>	<i>Endstudy Mean ± Std Error</i>	<i>Adjusted Change from Baseline † Mean + Std Error</i>
<i>Placebo</i>	<i>90</i>	<i>18.4 ± 0.7</i>	<i>19.1 ± 0.7</i>	<i>0.5 ± 0.4</i>
<i>3 g VGB</i>	<i>92</i>	<i>18.6 ± 0.7</i>	<i>20.8 ± 0.7</i>	<i>2.2 ± 0.4</i>
<i><u>Treatment Comparison</u></i>		<i><u>Mean + Std Error‡</u></i>	<i><u>(95% CI)‡</u></i>	<i><u>P Value‡</u></i>
<i>3 g VGB - Placebo</i>		<i>1.7 ± 0.5</i>	<i>(0.61, 2.77)</i>	<i>.0024</i>
<i><u>Model Factor</u></i>				
<i>Baseline Seizure-Free Days</i>				<i>.0011</i>
<i>Investigative Site</i>				<i>.1873</i>
<i>Treatment</i>				<i>.0024</i>
† <i>Adjusted means and associated standard errors from two-way analysis of covariance of change from Baseline to Endstudy in rate of seizure-free days. Model used adjusted for investigative site and the Baseline rate of seizure-free days.</i>				
‡ <i>Residual treatment effect (3 g VGB minus placebo) and P value were estimated using the above model.</i>				

6- Analyses of Physician's Global Assessments

Two assessments of therapeutic effect were performed by the investigator at the final study visit; the Physician's Evaluation of Therapeutic Effect and the Physician's Global Evaluation. The investigators also performed an Endstudy Physician's Overall Assessment of Tolerability of study drug. The basis for these assessments of tolerability, global improvement, therapeutic effect is not stated. Patients receiving vigabatrin were thought to have significantly greater improvement than placebo patients for both assessments.

7- Evaluation of Therapeutic Effect: The effect of vigabatrin on plasma levels of concomitant AEDs was assessed by comparing the percent change from Baseline to Endstudy for patients receiving placebo versus vigabatrin. The average percent reductions in plasma levels for phenytoin, phenobarbital, and valproic acid were statistically significantly greater for vigabatrin patients relative to placebo patients. The greatest reduction was seen in patients on phenytoin. Despite these, the efficacy was greater in vigabatrin-treated patients, Reduction in the plasma levels of antiepileptic drugs was not considered a factor contributing to the showing of efficacy in the vigabatrin-treated group.

FDA'S INDEPENDENT STATISTICAL ANALYSIS

The FDA statistical reviewer evaluated the Primary efficacy variable as mean monthly seizure frequency at Endstudy compared to baseline and the Secondary efficacy variable, the Therapeutic Success (Percent of patients achieving >50% reduction in seizures (IB+IC)).

Seizure frequencies were regenerated and means calculated. There was no statistically significant difference between the treatment groups at baseline ($p=0.6241$, Kruskal Wallis Test). The Endstudy (IB+IC) seizure frequency was analyzed using ANCOVA of rank transformed seizures adjusted for baseline and investigative sites. The test for difference in response to VGB versus placebo was statistically significant ($p=0.0002$).

Independent Analysis by FDA Statistical Reviewer of Complex Partial Seizures Plus Partial Seizures Secondarily Generalized and Therapeutic Success. Intent-to-treat Patients (N=183)					
Treatment	N	Seizure Frequency Baseline Mean	Seizure Frequency Endstudy Mean	Therapeutic Success At Least 50% Reduction in the Mean Monthly Seizure Rate from Baseline to Endstudy	
				%	(N)
Placebo	90	14.9±1.8	13.5±1.9	19%	(17)
3 g VGB	92	35.3±11.1	21.4±6.6	43%	(40)
<i>Treatment Comparison</i>		<i>P Value</i>		<i>P Value</i>	
3 g VGB versus Placebo		.0002		<..001	

FDA'S REQUEST FOR REANALYSIS EFFICACY

The FDA requested reanalysis of efficacy data in Study C024 in two ways. The first was a reanalysis as required by the protocol of patients who met criteria for withdrawal due to increased seizures, and the second was an analysis precipitated by specific language in the labeling. These are discussed below.

1-Analysis per protocol of patients who had status epilepticus or 2-fold increase in seizure frequency as withdrawals . By protocol, " those patients who experienced a twofold increase in complex partial seizure frequency (compare the monthly mean of the first 8 weeks of Segment III to the monthly mean of the last 8 weeks of Segment D) or who develops status epilepticus will be removed from the study and not replaced." (NDA vol 1.94, Protocol p.14 8-1509) A reanalysis of the data was

requested which incorporated not only the protocol guidelines but also, in keeping with what seemed to be the intent of the protocol stipulation, those patients who had a twofold increase in the frequency of secondarily generalized seizures (since those were also the seizures of interest) and those patients who required pharmacologic intervention for clusters or flurries of seizure during the study. A table showing the results of this reanalysis is shown below. It is apparent that these patients had little to no effect on the outcome of the study.

Reanalysis of Complex Partial Seizures Plus Partial Seizures Secondarily Generalized and Therapeutic Success. Removing data after patients experienced a 2-fold increase in seizures, status epilepticus or who required pharmacologic intervention for seizure flurries Intent-to-treat Patients (N=175).				
Treatment	N	Seizure Frequency	(Number/28 Segments II and III Median (95% C)	Therapeutic Success At Least 50% Reduction in the Mean Monthly Seizure Rate from Baseline to Endstudy
		Baseline Median (95% C)	Median (95% C)	% (N)
Placebo	87	8.0 (6.5, 9.5)	7.8 (6.5, 9.0)	15% (13)
3 g VGB	88	8.0 (6.5, 9.5)	4.0 (3.0, 5.5)	44% (39)
Treatment Comparison 3 g VGB versus Placebo		P Value .0001		P Value <..001

2-Complex partial secondarily generalized. The sponsor is seeking a claim for partial complex seizures with and without secondary generalization (from the proposed labeling). The analysis submitted does not address this claim. The firm, therefore was asked to a reanalysis of the primary efficacy variable (taken from the intent-to-treat dataset) for this group specifically. Both *complex partial onset generalized and simple partial onset generalized seizures* are coded as IC. The seizures of interest, *partial complex seizures with secondary generalization* are a subset of the group (IC) actually collected and evaluated in both the primary and secondary analyses. The sponsor informed the FDA that no subclass of IC was used and so the question of complex partial seizures that secondarily generalize cannot be addressed. Therefore the requested analysis was not performed.

OTHER CONSIDERATIONS REGARDING EFFICACY:

The use of benzodiazepines to treat seizures during the various segments of the study was evaluated as a factor which might potentially have affected the results of the study. The use of benzodiazepines in each of the treatment groups was comparable

between treatment groups and segments of the study.

The additional use of other concomitant antiepilepsy drugs (AEDs) did not affect the outcome of this study because the balance of patients between the vigabatrin and placebo groups receiving various AEDs was approximately equal and there was little manipulation of doses. Finally as noted above, the average percent reductions in plasma levels for phenytoin, phenobarbital, and valproic acid were statistically significantly greater for vigabatrin patients relative to placebo patients. The greatest reduction was seen in patients on phenytoin. Despite these, the efficacy was greater in vigabatrin-treated patients. Reduction in the plasma levels of antiepileptic drugs was not considered a factor contributing to the showing of efficacy in the vigabatrin-treated group.

CONCLUSIONS

The results of this study support vigabatrin 3 g/day as effective add-on treatment in those patients with complex partial seizures and partial seizures with secondary generalization.

8.2.2 US Study #71754-3-C-025

Protocol synopsis:

Title: Double blind randomized , Placebo controlled, parallel group Dose response Study of Vigabatrin in Patients with Uncontrolled Partial Seizures

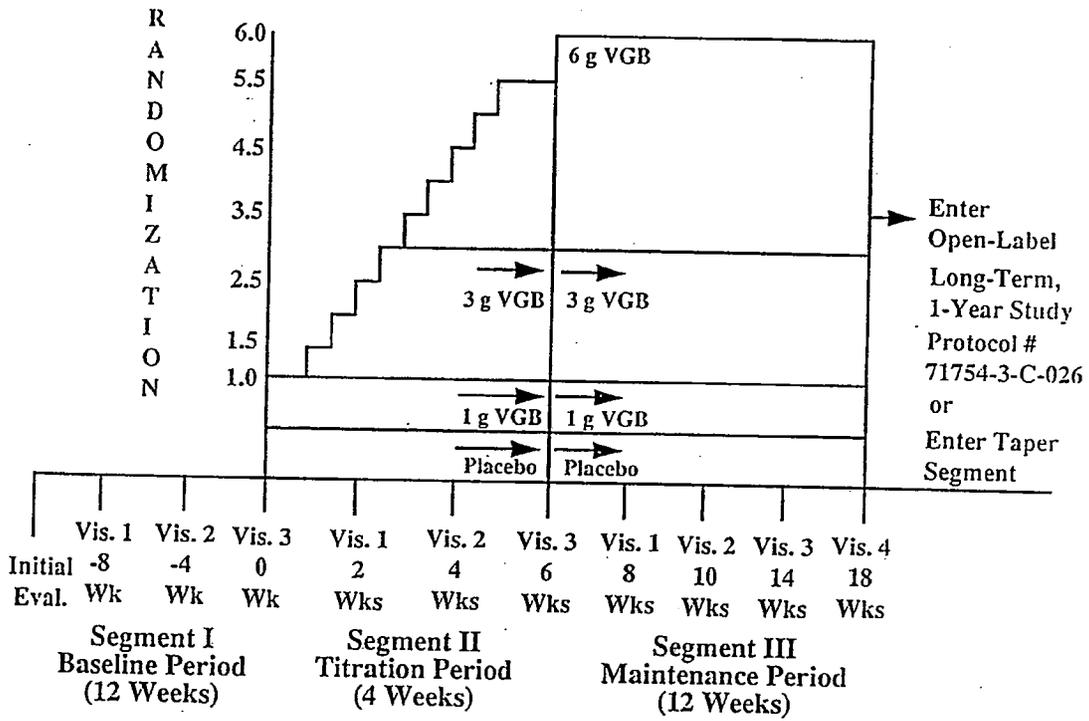
OBJECTIVE/RATIONALE:

To determine the efficacy of vigabatrin at doses of 1, 3, and 6 g/day when added to currently prescribed antiepilepsy drug therapy in patients refractory complex partial seizures.

STUDY DESIGN: The design and entry criteria are nearly identical to C-024, differing in only a few aspects. This study differs from C024 in that in Segment II, patients are randomized to vigabatrin 1g, 3 g, 6g or placebo. Vigabatrin was administered as add-on therapy to currently prescribed AED therapy.

The design is summarized by the schematic on the following page.

STUDY SCHEMATIC



Study Design Schematic (Protocol 025) - Segments I, II, III

ANALYSIS PLAN

As in study C024, the primary endpoint for efficacy was the mean monthly frequency of complex partial seizures plus partial seizures with secondary generalization (IB + IC) at Endstudy compared to Baseline. The seizures of primary interest were partial complex seizures (IB) plus all partial seizures with secondary generalization (IC). Secondary efficacy variables were the same.

INTERIM ANALYSIS: No interim analyses were planned or performed for this protocol.

CONDUCT OF STUDY**INVESTIGATORS/ LOCATION**

There were 15 centers which participated in this study. The distribution of patients and their randomization is shown below:

Sponsor's Table 8-11. Distribution of Randomized Patients By Treatment Group and Investigative Site (N = 174).

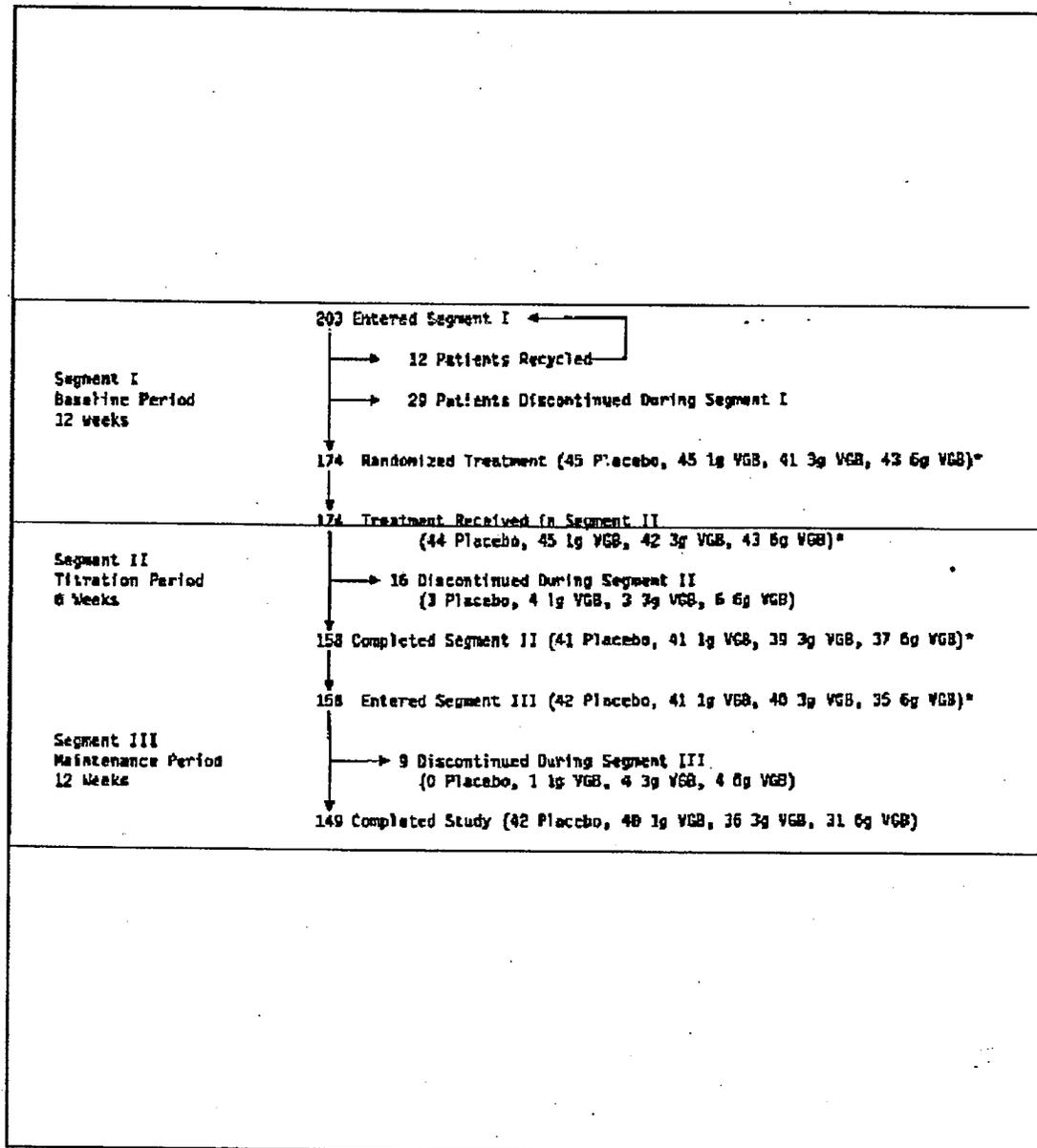
Investigative Site	Treatment				Total
	Placebo	1 g VGB	3g VGB	6g VGB	
006	3	3	3	3	12
010	5	5	5	5	20
011	5	5	5	5	20
012	4	4	4	4	16
013	3	3	4	2	12
069	2	2	1	1	6
070	3	3	3	2	11
071	3	3	3	3	12
072	4	4	4	4	16
073	3	3	2	3	11
074	1	1	0	0	2
075	2	3	3	3	11
089	4	3	4	3	14
093	3	3	2	3	11
Total	45	45	43	41	174

NUMBER OF PATIENTS

A total of 203 patients entered Segment I. Of these, 174 patients met entrance criteria at the end of Segment I and were randomized to either placebo or one of three doses of vigabatrin. Randomization was in a ratio of 1:1:1:1 (45 placebo, 45 1g vigabatrin, 43 3g vigabatrin, 41 6g vigabatrin). With 29 patients withdrawing from the study, 149 patients completed the study (42 placebo, 40 1g vigabatrin, 36 3g vigabatrin, 31 6g vigabatrin).

PATIENT DISPOSITION

There were 29 patients who discontinued study participation prior to randomization.



The number of patients who discontinued during each of the subsequent study segments is indicated on the flowchart above.

Due to a drug replacement error at Sites 013 and 070, eleven patients received incorrect study medication during Segment II. Segment II medication for Site 070 was sent to Site 013 and vice versa. Five of these patients completed the study. For these five patients, the correct medication was shipped and dispensed for Segment III. The other six patients discontinued prior to beginning Segment III.

Of the 174 patients who received study medication, 85.6% (149) completed the study.

Seventeen patients discontinued the study because of adverse events (1 placebo, 3 1g vigabatrin, 5 3g vigabatrin, and 8 6g vigabatrin). Three patients were lost to follow-up and five patients discontinued the study due to the drug replacement error. All Baseline characteristics were comparable between patients who discontinued and patients who completed. There was a dose dependent increase in the number of dropouts. Sponsor's Table 8-14 on the following page summarizes the number of dropouts by dose.

<i>Sponsor's Table 8-14. Summary of Postrandomization Dropouts</i>	
<i>Treatment</i>	<i>Total*</i>
<i>Placebo</i>	<i>6.7% (3/45)</i>
<i>1 g VGB</i>	<i>11.1% (5/45)</i>
<i>3 g VGB</i>	<i>16.3% (7/43)</i>
<i>6 g VGB</i>	<i>24.4% (10/41)</i>
<i>Total</i>	<i>14.4% (25/174)</i>

** Denominators used for total reflect the actual dose received in Segment II for patients discontinuing in Segment II and the actual dose received in Segment III for all other patients.*

DEMOGRAPHICS/GROUP COMPARABILITY

A comparison of the baseline characteristics by treatment group shows that baseline characteristics were balanced across treatment groups in this study. An abbreviated version of the Sponsor's Table of Baseline Characteristics shown on the next page gives a summary of the baseline characteristics in the intent-to-treat dataset. There was no statistically significant difference between treatment groups with regard to sex, age, weight, race, age at onset of epilepsy, duration of epilepsy or baseline seizure frequency. Concurrent AED use did not show any statistically significant differences between the various groups for any single AED.

Baseline Characteristics						
Baseline Characteristic	Treatment					P value†
	Placebo N=45	1 g VGB N=45	3 g VGB N=43	6 g VGB N=41	Total N=174	
Sex						
Males % (N)	38% (17)	42% (19)	56% (24)	56% (23)	48% (83)	.203
Females % (N)	62% (28)	58% (26)	44% (19)	44% (18)	52% (91)	
Age (years)						
Median	33	33	35	33	33	.9908
Mean ± Std Dev	35 ± 11	34 ± 9	34 ± 9	35 ± 11	35 ± 10	
Range	18 - 60	18 - 54	18 - 53	19 - 63	18 - 63	
Weight (kg)						
Median	68	71	70	72	70	.3477
Mean ± Std Dev	69 ± 15	76 ± 19	72 ± 17	75 ± 18	73 ± 17	
Range	49 - 118	50 - 132	44 - 116	46 - 125	44 - 132	
Race						
Caucasian % (N)	93% (42)	98% (44)	95% (41)	93% (38)	95% (165)	.838
Negroid % (N)	2% (1)	2% (1)	2% (1)	5% (2)	3% (5)	
Other % (N)	4% (2)	0% (0)	2% (1)	2% (1)	2% (4)	
Number of Concomitant AEDs						
One % (N)	42% (19)	53% (24)	53% (23)	37% (15)	47% (81)	.339
Two % (N)	58% (26)	44% (20)	47% (20)	63% (26)	53% (92)	
Three % (N)	0% (0)	2% (1)	0% (0)	0% (0)	1% (1)	
Concomitant use of Barbiturates % (N)	22% (10)	18% (8)	7% (3)	10% (4)	14% (25)	.151
Concomitant use of Benzodiazepines % (N)	7% (3)	4% (2)	12% (5)	15% (6)	9% (16)	.345
Concomitant use of Carbamazepine % (N)	69% (31)	62% (28)	74% (32)	71% (29)	69% (120)	.656
Concomitant use of Hydantoins % (N)	33% (15)	42% (19)	28% (12)	44% (18)	37% (64)	.369
Concomitant use of Valproic Acid % (N)	16% (7)	16% (7)	21% (9)	20% (8)	18% (31)	.878
Concomitant use of Other AED % (N)	11% (5)	7% (3)	5% (2)	5% (2)	7% (12)	.605
Frequency of Complex Partial Seizures plus Partial Seizures Secondarily Generalized (No./28 days)						
Median	9.0	8.5	8.0	9.0	8.8	.9625
Mean ± Std Dev	13 ± 13	44 ± 125	20 ± 42	12 ± 8	23 ± 68	
Range	3 - 71	3 - 786	1 - 228	2 - 45	1 - 786	

† P values for Baseline comparability of categorical variables from chi-squared tests, for continuous variables from Kruskal-Wallis tests.

PROTOCOL VIOLATIONS:

MEDICATION ERRORS: Due to a drug replacement error at Sites 013 and 070, eleven patients received incorrect study medication during Segment II. Segment II medication for Site 070 was sent to Site 013 and vice versa. Five of these patients completed the study. For these five patients, the correct medication was shipped and dispensed for Segment III, and the Segment III treatment assignment was used for all efficacy analyses. The other six patients discontinued prior to beginning Segment III. These six patients are counted once in the efficacy analysis using the treatment assignment they actually received.

SEIZURE COUNTS. Numerous irregularities occurred in the counting of seizures. In some cases changes were made to the seizure counts in the case report forms. Sometimes "W" or "Z" was assigned indicating no seizure count could be determined, but was later (up to 2 years) changed by the medical monitor of MMD to a specific number value.

SEIZURE FLURRIES. If seizure flurries occurred where there was no definite total number, the best estimate was given by the investigator. A comment was provided by the investigator to document the situation as clearly as possible. In some cases, the patient/investigator was unable to estimate the number of seizures in a flurry. In these cases, a neurologist at Marion Merrell Dow Inc estimated the number of seizures prior to unblinding. This was based on the patient's description of the seizure from the seizure history and review of any additional information from the study coordinator. Frequently the number assigned by the MMD monitor did not make sense in the context of the kinds of seizure counts that the patient was able to generate during the study.

In addition it was noted that when some patients were hospitalized for seizures they did not have a seizure count generated during the hospital stay, and therefore increase in seizures would not have been counted into the seizure frequency. These irregularities were not restricted to any given site.

CONCOMITANT ANTIPILEPSY DRUGS. Protocol violations also included the use of additional antiepileptic medications above and beyond those claimed in the baseline period for the purpose of treating additional seizures. The sponsor did report some of these, and others were learned from reading the case report forms. The total number of patients with protocol violations involving additional medications with antiepilepsy properties from both sources (sponsor plus reviewer) was 42. While the firm states that "these patients were not classified as minor or major protocol violators because none of these patients received adequate dosing of the benzodiazepine to affect seizure activity," this reviewer is of the opinion that they found that investigators were using these medications, not only benzodiazepines but occasionally other antiepileptic medications, with the intention of treating additional seizures, and in some cases even documented a response.

Nevertheless the use of additional medications with anti-seizure properties did appear to be balanced among the treatment groups. The percentage of patients using medications with anti-seizure properties during Segments I, II and III was similar across all treatment groups.

Sponsor's Table:

Table 8-25. Percent of Patients Using Medications with Anti-Seizure Properties in Addition to Concomitant AEDs				
Baseline				
Medication Class	Placebo (N=45)	1 g VGB (N=45)	3 g VGB (N=43)	6 g VGB (N=41)
Benzodiazepines	6.7% (3)	15.6% (7)	7.0% (3)	19.5% (8)
Non-Benzodiazepines	2.2% (1)	2.2% (1)	0.0% (0)	0.0% (0)
Titration and Maintenance				
Benzodiazepines	15.6% (7)	17.8% (8)	7.0% (3)	22.0% (9)
Non-Benzodiazepines	4.4% (2)	4.4% (2)	0.0% (0)	0.0% (0)
Total				
Benzodiazepines	15.6% (7)	20.0% (9)	11.6% (5)	26.8% (11)
Non-Benzodiazepines	4.4% (2)	6.7% (3)	0.0% (0)	0.0% (0)

SPONSOR'S EVALUATION OF EFFICACY

The primary assessment of efficacy was a linear trend test across the four treatment groups. The dose response relationship was further characterized using comparisons among the four treatment groups. The following three contrasts were tested.

- 1g VGB versus placebo
- 3 g VGB versus 6 g VGB
- Average of placebo and 1g VGB versus average of 3g VGB and 6g VGB

Each active treatment group was also compared to placebo.

Primary Efficacy Measure:

One hundred and seventy-four (174) patients received study medication and were evaluated for efficacy (45 placebo, 45 1g vigabatrin, 43 3g vigabatrin, 41 6g vigabatrin). The primary endpoint for the evaluation of efficacy was the mean monthly frequency of complex partial seizures (IB) plus partial seizures secondarily generalized (IC) at Endstudy (last 8 weeks of study) compared to Baseline (last 8 weeks of Segment I).

A highly significant dose response relationship was observed between increased vigabatrin dose and decreased seizure frequency ($P=.0001$). The effect of 1g vigabatrin dose was not statistically different from placebo, but the 3g and 6g vigabatrin doses were significantly superior to placebo. There was no statistically significant difference between the 3g and 6g vigabatrin dose groups.

The Baseline seizure frequency was a significant predictor of response ($P=.0001$). Specifically, patients who had higher seizure frequencies at Baseline also had higher seizure frequencies at Endstudy. The Baseline by treatment interaction was not statistically significant ($P=.5482$), indicating the vigabatrin effect relative to placebo was not significantly affected by Baseline seizure frequency.

Seizure Frequency (Number / 28 Days)				Therapeutic Success At least 50% Reduction in the Mean Monthly Seizure Rate from Baseline to Endstudy	
Treatment	N	Baseline Median (95% CI)	Endstudy Median (95% CI)	%	(N)
Placebo	45	9.0 (7.0, 10.5)	8.8 (6.0, 12.1)	7%	(3)
1 g VGB	45	8.5 (6.0, 12.3)	7.7 (4.1, 11.5)	24%	(11)
3 g VGB	43	8.0 (7.0, 10.5)	3.7 (2.5, 6.0)	51%	(22)
6 g VGB	41	9.0 (7.0, 14.5)	4.5 (3.3, 6.0)	54%	(22)
Treatment Comparison for Seizure Frequency				Pvalue †	Pvalue
Linear Trend				.0001	<.0001
Placebo vs 1 g VGB				.1263	.0248
Placebo vs 3 g VGB				.0001	<.0001
Placebo vs 6 g VGB				.0001	<.0001
3 g VGB vs 6 g VGB				.8140	.9655
(Placebo and 1 g VGB) vs (3 g VGB and 6 g VGB)				.0001	<.0001

† P values from analysis of covariance of the ranked endstudy seizure frequencies using model which adjusted for treatment, investigative site, ranked baseline seizure frequency, and investigative site by treatment interaction.

SECONDARY EFFICACY ANALYSIS:

1-Therapeutic success was defined as achieving at least a 50% reduction from Baseline to Endstudy in the mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized. All active treatment groups versus placebo showed a statistically significant difference in the percent of patients achieving therapeutic success; no significant difference was observed between the 3g vigabatrin and 6g vigabatrin dose groups. The results are seen in the previous table.

Separate analyses were performed for the three types of partial seizures; simple partial (IA), complex partial (IB), and partial seizures secondarily generalized (IC).

2- Complex Partial seizures

The analysis of complex partial seizures (IB) performed using the 171 Intent-to-treat patients who had a nonzero Baseline frequency of complex partial seizures is shown in the table on the next page.

ANALYSIS OF COMPLEX PARTIAL SEIZURES (IB).			
INTENT-TO-TREAT PATIENTS WITH BASELINE SEIZURE FREQUENCY > 0.			
(N = 171).			
<i>TREATMENT</i>	<i>N</i>	<i>SEIZURE FREQUENCY (NUMBER/28 DAYS)</i>	
		<i>BASELINE MEDIAN (95% CI)</i>	<i>ENDSTUDY MEDIAN (95% CI)</i>
PLACEBO	44	8.8 (7.0, 10.0)	8.3 (5.5, 11.5)
1 g VGB	45	7.5 (6.0, 12.3)	7.0 (4.0, 11.5)
3 g VGB	43	7.0 (5.5, 9.0)	3.5 (2.0, 4.6)
6 g VGB	39	8.5 (7.0, 14.5)	3.5 (2.0, 5.5)
<i>TREATMENT COMPARISON</i>			<i>P VALUE†</i>
LINEAR TREND			.0001
PLACEBO VERSUS 1 g VGB			.1662
PLACEBO VERSUS 3 g VGB			.0014
PLACEBO VERSUS 6 g VGB			.0001
3 g VGB VERSUS 6 g VGB			.0557
(PLACEBO AND 1 g VGB) VERSUS (3 g VGB AND 6 g VGB)			.0001
† P VALUES FROM ANALYSIS OF COVARIANCE OF THE RANKED ENDSTUDY SEIZURE FREQUENCIES USING MODEL WHICH ADJUSTED FOR TREATMENT, INVESTIGATIVE SITE, RANKED BASELINE SEIZURE FREQUENCY, AND INVESTIGATIVE SITE BY TREATMENT INTERACTION.			

3- Simple Partial Seizures (IA) The analysis of simple partial seizures (IA) was performed using 73 patients from the intent-to-treat dataset who had simple partial seizures during baseline (nonzero baseline). None of the treatment comparison contrasts were statistically significant and there was not a statistically significant difference between any group and placebo.

Table 8-98. Analysis of Simple Partial Seizures. Intent-to-treat Patients. (N = 174).			
<i>Treatment</i>	<i>N</i>	<i>Seizure Frequency (Number/28 Days)</i>	
		<i>Baseline Median (95% CI)</i>	<i>Endstudy Median (95% CI)</i>
Placebo	45	0.0 (0.0, 3.5)	0.5 (0.0, 4.5)
1 g VGB	45	0.0 (0.0, 4.0)	0.0 (0.0, 2.0)
3 g VGB	43	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)
6 g VGB	41	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
<i>Treatment Comparison</i>		<i>P Value†</i>	
Linear Trend		.0332	
Placebo versus 1 g VGB		.0913	
3 g VGB versus 6 g VGB		.2565	
Placebo and 1 g VGB versus (3 g VGB and 6 g VGB)		.1101	
Placebo versus 3 g VGB		.1758	
Placebo versus 6 g VGB		.0136	

Analysis of Simple Partial Seizures (IA). Intent-to-treat Patients with Baseline Seizure Frequency > 0. (N = 73).			
Treatment	N	Seizure Frequency (Number/28 Days)	
		Baseline Median (95% CI)	Endstudy Median (95% CI)
Placebo	21	6.5 (3.5, 41.0)	4.5 (2.0, 12.6)
1 g VGB	22	6.8 (4.0, 10.5)	3.6 (2.0, 7.5)
3 g VGB	16	11.0 (4.0, 20.5)	8.8 (3.5, 23.0)
6 g VGB	14	4.5 (2.0, 7.0)	1.3 (0.0, 7.3)
Treatment Comparison			P Value†
Linear Trend			.2051
Placebo versus 1 g VGB			.9088
Placebo versus 3 g VGB			.7511
Placebo versus 6 g VGB			.1773
3 g VGB versus 6 g VGB			.4035
(Placebo and 1 g VGB) versus (3 g VGB and 6 g VGB)			.2703

† P values from ANCOVA of the ranked endstudy seizure frequencies using model which adjusted for treatment, investigative site, ranked baseline seizure frequency, and investigative site by treatment interaction.

4- All Partial Seizures secondarily generalized (IC) Analysis of partial seizures secondarily generalized involved 53 Intent-to-treat patients who had a nonzero Baseline frequency of partial seizures secondarily generalized failed to show a statistically significant difference between the treatment groups in the Endstudy frequency of partial seizures secondarily generalized ($P = .4796$), and none of the treatment comparison contrasts were statistically significant ($P \geq .1828$). There was a trend toward reduction in median frequency of IC seizures as the dose of vigabatrin increased (0.7 for placebo, 1.0 for 1 g VGB, 1.0 for 3 g VGB, and 1.6 for 6 g VGB). Results are shown in the table below.

ANALYSIS OF PARTIAL SEIZURES SECONDARILY GENERALIZED (IC). INTENT-TO-TREAT PATIENTS WITH BASELINE SEIZURE FREQUENCY > 0. (N = 53).			
TREATMENT	N	SEIZURE FREQUENCY (NUMBER/28 DAYS)	
		BASELINE MEDIAN (95% CI)	ENDSTUDY MEDIAN (95% CI)
PLACEBO	10	2.0 (0.5, 6.0)	1.3 (0.0, 3.1)
1 g VGB	13	1.5 (0.5, 6.0)	0.5 (0.0, 6.5)
3 g VGB	17	1.5 (0.5, 4.5)	0.5 (0.0, 2.5)
6 g VGB	13	3.5 (0.5, 5.2)	1.9 (0.5, 6.0)
TREATMENT COMPARISON			P VALUE†
LINEAR TREND			.8064
PLACEBO VERSUS 1 g VGB			.7527
PLACEBO VERSUS 3 g VGB			.1828
PLACEBO VERSUS 6 g VGB			.8610
3 g VGB VERSUS 6 g VGB			.2184
(PLACEBO AND 1 g VGB) VERSUS (3 g VGB AND 6 g VGB)			.4140

ANALYSIS OF PARTIAL SEIZURES SECONDARILY GENERALIZED (IC). INTENT-TO-TREAT PATIENTS WITH BASELINE SEIZURE FREQUENCY > 0. (N = 53).
T P VALUES FROM ANALYSIS OF COVARIANCE OF THE RANKED ENDSTUDY SEIZURE FREQUENCIES USING MODEL WHICH ADJUSTED FOR TREATMENT, INVESTIGATIVE SITE, AND RANKED BASELINE SEIZURE FREQUENCY.

5- Analysis of Seizure-Free Days

The mean monthly frequency of seizure-free days was compared for the four treatment groups. There was a highly significant relationship between increased vigabatrin dose and increased number of seizure-free days (P=.0001).

6- Analysis of Physician's Global Assessment and Evaluation of Therapeutic Effect.

Two assessments of therapeutic effect were performed by the investigator at the final study visit at which time the investigator also performed an overall assessment of the tolerability of study medications. The basis for these assessments of tolerability, global improvement, therapeutic effect is not stated. Patients receiving vigabatrin were thought to have significantly greater improvement than placebo patients for both assessments. However, improvement in physician's global evaluation was not significantly increased with vigabatrin dose. Sponsor attributes this dichotomy to the fact that indeed 16 patients who received 6g vigabatrin experienced at least minimal deterioration.

7- Evaluation of Therapeutic Effect: Sponsor stated that the primary assessment of efficacy was an Intent-to-Treat analysis of the frequency of partial complex seizures and all partial seizures secondarily generalized. There was a highly statistically significant linear dose response across the four doses, indicating that seizure frequency is reduced with increasing dose. The 1g dose was not statistically significantly different from placebo nor was the 3g dose different from 6g.

FDA 'S INDEPENDENT ANALYSIS:

The FDA's statistical reviewer evaluated the following efficacy variables using the intent-to-treat dataset: Patient's mean monthly (28 day) frequency of complex partial seizures (IB) plus partial seizures secondarily generalized (IC) at endstudy compared to baseline and Therapeutic Success: comparison of responders between dosage groups, where a responder has demonstrated a 50% reduction in partial complex and secondarily generalized seizures of simple or complex partial origin.

The table on the following page is a summary of patients' mean monthly seizure frequency (IB + IC) for the intent-to-treat dataset at baseline and end study. (Note that Sponsor's analysis was median monthly seizure frequency (IB + IC).

FDA INDEPENDENT ANALYSIS OF PARTIAL COMPLEX + PARTIAL SEIZURES SECONDARILY GENERALIZED (IB + IC). INTENT-TO-TREAT PATIENTS (N=171).			
TREATMENT	N	SEIZURE FREQUENCY (NUMBER/28 DAYS)	
		BASELINE MEAN (95% CI)	ENDSTUDY MEAN (95% CI)
<i>PLACEBO</i>	45	13.2 ± 2.0	13.1 ± 1.9
<i>1 g VGB</i>	45	44.1 ± 18.6	28.7 ± 10.4
<i>3 g VGB</i>	43	20.2 ± 6.4	15.9 ± 6.0
<i>6 g VGB</i>	41	11.6 ± 1.3	6.6 ± 1.2
TREATMENT COMPARISON			P VALUE†
LINEAR TREND			.0001
PLACEBO VERSUS 1 g VGB			.1263
PLACEBO VERSUS 3 g VGB			.0001
PLACEBO VERSUS 6 g VGB			.0001
3 g VGB VERSUS 6 g VGB			.8140
† P VALUES FROM ANALYSIS OF COVARIANCE OF THE RANKED ENDSTUDY SEIZURE FREQUENCIES USING MODEL WHICH ADJUSTED OR TREATMENT, INVESTIGATIVE SITE, AND RANKED BASELINE SEIZURE FREQUENCY.			

The FDA's analysis of Therapeutic Success is virtually identical to that of the Sponsor's.

FDA'S REQUEST FOR REANALYSIS OF EFFICACY

The FDA again requested, as in Study C024, a reanalysis of study C-025 in keeping with the protocol which reads, "Any patient who experiences a twofold increase in complex partial plus partial seizures secondarily generalized seizure frequency (compare the monthly mean of the first 8 weeks of Segment III to the monthly mean of the last 8 weeks of Segment I) or who develops status epilepticus, will be removed from the study and not replaced." and "In patients who are randomized, but who do not complete Segment III, seizure rates available at the time of dropout will be utilized." In addition to the patients who developed status epilepticus post randomization, the sponsor was asked to include all patients who had seizure flurries that could not be accurately counted by patient or investigator, and for whom MMD monitor assigned a seizure count at a later date. In addition all patients who had a sufficient increase in seizure activity (flurries, clusters, for example) such that they either required hospitalization (we note that patients who were hospitalized sometimes did not have a seizure count generated during the hospital stay), or medication to control the seizures, such as ativan, valium, or loading dose of another antiepileptic drug would be included in the reanalysis and considered dropouts at the time of the episode in question. As in study C-024, the FDA requested that the sponsor perform additional analyses on the primary efficacy variable, adjusting for all seizure data for such patients. In order to address all protocol violations in the most rigorous analysis, the 11 patients who received the wrong medication were to be analyzed with the dosage group to which they were randomized rather than by the

paradigm used in the initial analysis by the firm.

The sponsor recomputed seizure frequencies for these patients, and all patients were then analyzed using the same statistical model used in the primary intent-to-treat analysis. For therapeutic success, the requested analysis was to assign all patients identified as non-responders. The table on the following page summarizes the reanalysis of the primary and secondary efficacy variable (therapeutic success) according to the paradigm suggested by the FDA.

Seizure Frequency (Number / 28 Days)				Therapeutic Success At least 50% Reduction in the Mean Monthly Seizure Rate from Baseline to Endstudy	
Treatment	N	Baseline Median (95% CI)	Endstudy Median (95% CI)	%	(N)
Placebo	45	9.0 (7.0, 11.0)	9.0 (6.0, 13.0)	8%	(4)
1 g VGB	39	7.5 (6.0, 11.0)	7.5 (4.0, 10.0)	26%	(10)
3 g VGB	39	8.0 (7.0, 12.5)	4.5 (3.0, 9.0)	44%	(17)
6 g VGB	38	8.3 (6.5, 14.0)	4.3 (2.5, 6.0)	53%	(20)
Treatment Comparison for Seizure Frequency				Pvalue †	Pvalue
Linear Trend				.0001	<.0001
Placebo vs 1 g VGB				.0786	.0379
Placebo vs 3 g VGB				.0012	.0007
Placebo vs 6 g VGB				.0001	<.0001
3 g VGB vs 6 g VGB				.5051	.3264
(Placebo and 1 g VGB) vs (3 g VGB and 6 g VGB)				.0001	<.0001

† P values from analysis of covariance of the ranked endstudy seizure frequencies using model which adjusted for treatment, investigative site, ranked baseline seizure frequency, and investigative site by treatment interaction.

These results were consistent with the intent-to-treat analysis formerly done.

CONCLUSIONS

Those patients with protocol violations involving medication errors, seizure counts that were considered inaccurate and additional medication for seizure control did not alter the outcome of the trial. That is, in the final analysis these violations did not alter the efficacy profile of the drug. This study was unable to distinguish a difference between 3g and 6g in terms of their efficacy.

It is clear that the response of partial complex seizures to vigabatrin was responsible for the effect in the primary efficacy analysis. The subgroup analyses added little to the results other than to show that partial onset generalized seizure response did not

contribute to overall efficacy. Given the fact that partial complex onset generalized seizures were not collected or analyzed separately, and the group (IC) overall did not show a response, there is no foundation for the claim that partial complex seizures secondarily generalized are affected by vigabatrin.

The results of this study support vigabatrin 3g and 6g/day as equally effective adjunctive treatment in those patients with difficult to control complex partial seizures.

8.2.3 NON-US CONTROLLED STUDIES

The summaries below reflect the analysis of the sponsor. An independent confirmatory review was not conducted by the FDA, since none of the studies appeared to contradict the findings of the two pivotal studies performed in the US.

Study 097-444 (UK) was a single-center, double-blind, placebo-controlled crossover study in patients with refractory epilepsy to assess the effects of two doses of vigabatrin on seizures and psychomotor and cognitive function. Patients were randomized to either 2g VGB or placebo for 6 weeks then titrated to 3g or placebo for a further 6 weeks. There was a 4-week washout period and then a 3 month comparative phase. Primary efficacy variables were seizure frequency, character and battery of psychometric tests. A total of 20 patients were randomized; 19 completed the study. Results: The estimated mean seizure rate for VGB demonstrated a statistically significant improvement over PBO. There was no apparent improvement in seizure rates when VGB was increased from 2g to 3g/day.

Study 230 (UK) was a single center, double-blind, placebo-controlled, crossover study of vigabatrin 1.5g/day as adjunctive therapy in patients with partial complex epilepsy. Treatment periods were 9 weeks followed by 1 week washout periods and followed finally by a 4 week single blind period. A total of 25 patients were randomized. Results: There was a statistically significant decrease in seizure frequency from baseline in the treatment group compared to the placebo. However, a common baseline seizure rate was used in this comparison rather than an independent baseline for each randomized treatment group. There was no correlation between efficacy and VGB plasma concentrations.

Study 242 (Belgium) was a double-blind placebo-controlled crossover study of oral vigabatrin 1.5g to 2.5g/day as adjunctive therapy in refractory epileptic patients. Nine patients were enrolled, none of whom adhered to the protocol. Results: The sponsor concedes that the results are uninterpretable.

Study 246 (Denmark) was a single-center, double-blind, placebo-controlled, randomized crossover study of vigabatrin as adjunctive therapy in patients with partial epilepsy. There were 21 patients enrolled in the study who were randomized to one

of two 12 week treatment schedules. Results: There were no raw data, case report forms or statistical analysis of this study supplied, however the accompanying publication suggests a numerical difference between mean seizure counts (total) during treatment with drug compared to placebo, favoring vigabatrin. Those patients who worsened on therapy outnumbered those who worsened on placebo, but no statistical analysis is supplied.

Study 247 (Finland) was a single-center, double blind, placebo controlled crossover study to evaluate efficacy and tolerance to oral vigabatrin as adjunctive therapy in the treatment of patients with uncontrolled epilepsy. There were 16 patients enrolled. The original design of the protocol called for a comparison of seizure frequency and severity rates on VGB and placebo. However, due to discrepancies between CRF records and the investigator's estimate of seizure frequency and occasional poor reliability of patient reporting, the number of seizure free days was used as the index of efficacy. Results: There was a trend in favor of the drug both for improvement and for worsening. There was no statistically significant difference in seizure free days while on VGB compared to placebo.

Study 253 (France) was a double blind placebo-controlled crossover study of vigabatrin 3g/day as adjunctive therapy in adults with severe uncontrolled epilepsy (requiring hospitalization). Treatment periods were 3 months each, followed by a one month single blind placebo period. There was no washout period between treatments. The primary variable of interest was seizure frequency. Twenty three patients were enrolled, and 17 were available for efficacy analysis. Results: Comparison of VGB and placebo rates did not show a significant treatment effect in the 17 evaluable patients either in worsening or in improvement, however there was a numerical trend in favor of the drug for improvement and for worsening.

Study 258 (France) was a double blind, single center, placebo-controlled crossover study to assess the efficacy of vigabatrin 3g/day as adjunctive therapy in the treatment of patients with partial complex seizures. Treatment periods were 10 weeks and there was no washout period. A total of 25 patients were recruited and 19 completed the study. Results: For the 19 patients who completed the study there was a significant decrease in seizure frequency in the treatment group compared to placebo. Withdrawal seizures were reported in 8 patients in the placebo group. The effects of rapid discontinuation to placebo from the open label VGB group were not acknowledged as a possible explanation for the difference.

Study 259 (Italy) was a single center, double blind, placebo-controlled crossover study of oral vigabatrin in the treatment of drug-resistant epilepsy. Treatment periods were 3 months, following an initial 2 month baseline run-in period. There was no washout phase. A total of 31 patients were enrolled in the study. Results: There was no significant difference between seizure frequencies when comparing treatment to placebo groups. A subgroup analysis demonstrated a significant response to

vigabatrin in the patients with complex partial seizures. The effects of rapid discontinuation to placebo from the open label vigabatrin group were not acknowledged as a possible explanation for the difference.

Study 262 (France) was a double blind placebo-controlled crossover study to determine the efficacy and safety of vigabatrin in patients with refractory epilepsy. Patients weighing <50 kg were treated with .5 g/day and those weighing >50 kg were treated with 1 g/day or placebo. Treatment periods were 10 weeks with a single blind placebo phase lasting 5 weeks at the end of the study. Primary efficacy variable was seizure frequency. A total of 11 patients were randomized. Compliance was poor, seizure counts were sometimes recorded as a work, such as daily, several, etc. and doses of AEDs were not kept constant in some cases. Results: No formal statistical analyses were conducted because of errors in study conduct and poor patient compliance.

Study 263 (Italy) was a single center, double-blind, placebo-controlled, crossover study of Gamma-vinyl-GABA 2-3 g/day as adjunctive therapy in patients with severe therapy resistant epilepsy. Treatment periods were 7 weeks each with no ostensible washout period. Twenty eight patients were recruited and only 20 were thought to be evaluable. The study included 5 pediatric patients. The primary efficacy variable was reduction in seizure frequency. Results: There was a statistically significant reduction in seizure frequency in the treatment group compared to placebo. The possible withdrawal effect of the drug was not addressed. The results with regard to children was inconsistent.

Study 309 (UK) was a single center, double-blind, placebo controlled study of vigabatrin 3g/day as adjunctive therapy in drug resistant epileptic patients who were responders in an open-phase titration. Patients who showed a response of 50% reduction in seizures after titration over 8 weeks to 3g/day were randomized into a double blind phase. Treatment period was 8 weeks. There were 33 patients enrolled in the study and 20 entered the double blind placebo controlled phase as responders. Results: In the double blind phase, there was a statistically significant reduction in seizure frequency in the treatment group as compared to placebo. The effects of rapid discontinuation to placebo from the open label VGB group were not acknowledged as a possible explanation for the difference.

Study W92-0034C No Protocol (Germany) was a double blind, placebo controlled, crossover study of the effect of one single 4.5g dose of vigabatrin in patients with therapy resistant focal epilepsy with and without secondary generalization. Ten patients were recruited for this study which was inconclusive by design. There were no data or case report forms for this study. It was noted that an increase in seizures appeared to follow cessation of VGB therapy from day 6 to 12. Maximum activity occurred on days 9 and 10 where the number of seizures increased up to 80%.

Study 097-W-AUS-01 (Australia) was a placebo controlled trial (details of design were not submitted) comparing vigabatrin 2-3g/day to placebo in the adjunctive treatment of patients with refractory epilepsy. Primary measures of efficacy were electrophysiologic parameters (EEG, evoked potentials) and seizure frequencies. Fifteen patients were enrolled. There was no data submitted. The sponsor suggests that this study may show significant differences between QEEGs of patients maintained on vigabatrin compared to placebo. One patient with myoclonic seizures showed a 50% increase in seizure frequency.

8.3 SPONSOR'S DEMOGRAPHIC ANALYSES OF EFFICACY

In the primary analysis of complex partial seizures plus partial onset generalized seizures, the consistency of effect was assessed in subgroups of patients. Analyses of efficacy as a function of gender, race and age were performed. None of these subgroups had a statistically significant interaction with treatment. This indicates that there was not a statistically significant difference in the relative response among treatment groups of patients defined by gender or age.

The sponsor did not submit any analyses with regard to race, due to the small numbers of non white subjects in the trials.

8.4 CONCLUSIONS REGARDING EFFICACY DATA

The sponsor has provided sufficient clinical and statistical evidence to establish that vigabatrin is efficacious as adjunctive therapy for the treatment of patients with difficult to control partial complex seizures. Evidence that 3 g is the optimum dose is supported by the fact that efficacy does not increase further with doubling that dose.

SECTION 9.0 SAFETY FINDINGS

This section will review the safety data submitted to NDA 20-427 in order to identify the risks associated with the use of vigabatrin administered in the manner proposed in the labeling and to determine if any additional analyses may be needed to establish the reasonable safety of the drug. This portion of the review will attempt to distinguish those adverse effects which may be attributed to the known pharmacokinetic actions of vigabatrin from any unexpected, local or idiosyncratic effects. This safety review focuses on data derived from clinical trials sponsored by Marion Merrell Dow in support of this NDA but in addition, information obtained in the postmarketing period were examined as well. This section contains the human safety findings, analyses, and interpretations coming from individual studies, and the entire population exposed in the sponsor's development program.

9.1 METHODS

In evaluating the safety of vigabatrin, the vigabatrin-exposed population was examined from the most clinically serious adverse events to the most commonly collected and reported safety data. All case report forms of serious adverse events and deaths, tabular and narrative summaries of serious adverse events were reviewed. A random check was made through other available case report forms to screen for serious adverse events that might have been missed through other methods. The case report forms from US Studies 097-005 and -006 were reviewed in detail since these studies were designed to collect data regarding the possible neurotoxicity and ocular toxicity of vigabatrin. The total exposed population was relied upon for the assessment of serious adverse events. Materials included the Integrated Safety Summary(vol 1.201-1.213, the Safety Update (vol 6.1-6.117) study reports of US Studies 097-005/6 and their case report forms.

The routine safety data was obtained from the group at large, but in particular, from the safety information gathered in US Controlled trials C-024 and C-025. The database in the CANDA was accessed regularly for both routine safety data as well as more serious adverse events, and to screen for unusual groups of findings and to follow them over time, to the extent to which that was possible.

This safety report routine safety data and information on deaths and dropouts and limited information about serious adverse events current to March 15, 1994.

Relevant background information (noted in section 1.0) in the preclinical development of vigabatrin necessitated a review of the safety data with neurotoxicity and ocular toxicity in mind. No other major preclinical issues emerged.

The data for review are derived from five data sources described earlier in section 6.0 of this review: Clinical studies (completed and ongoing), NonUS studies not included in the Integrated Safety Database, Compassionate use, Spontaneous postmarketing

surveillance, and publications not included in the Integrated Safety database.

The flowchart below shows the contribution of each separate source to the overall data regarding safety of vigabatrin. The MMD CRF Database is most complete in terms of information regarding dose, duration and details about circumstances of and cause of death.

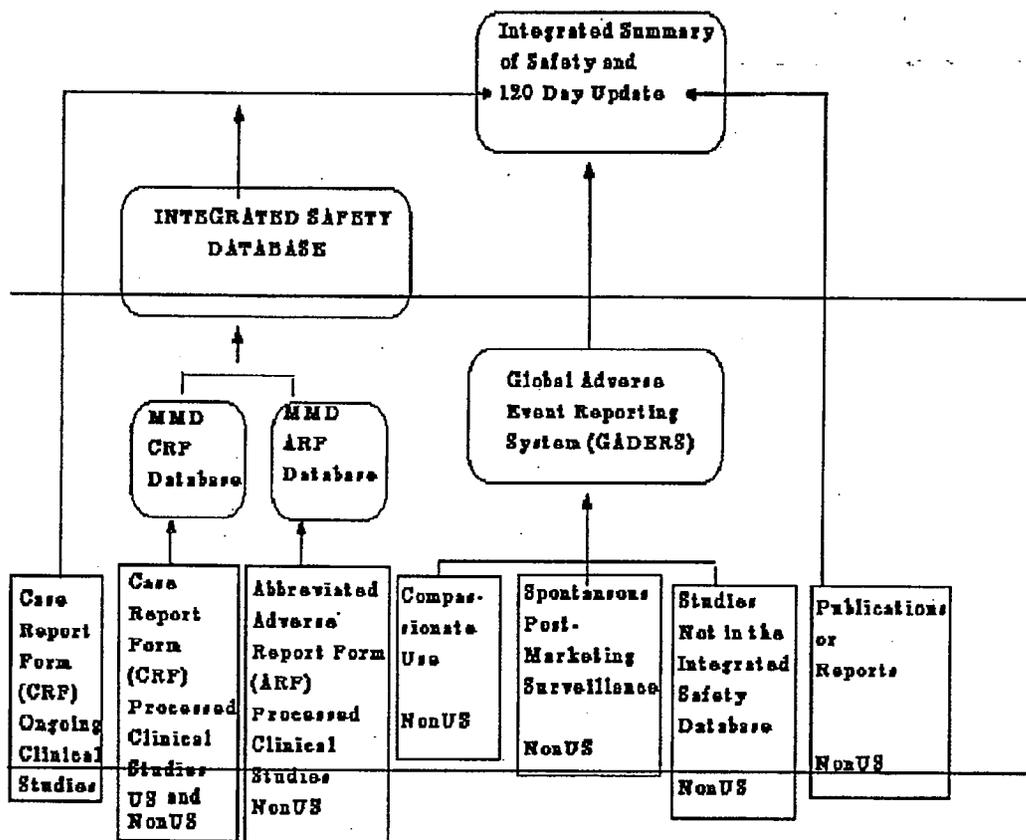


Diagram of Adverse Event Data Processing

Best Possible Copy

The actual number of total exposures in the Integrated Summary and 120 Day Update is estimated to be 200,000 patient years based on marketing estimates. The integrated safety database contains an estimated 3320 exposures and the MMD CRF database, 1770. (Please refer to Section 6.0 for clarification)

9.2 DEATHS

In the vigabatrin development program 97 deaths have been reported from all sources, including clinical studies (37/3320 exposures), compassionate use (21/unknown) and spontaneous postmarketing surveillance (39/unknown). The deaths in clinical studies and compassionate use are listed in the table below and on the following pages along with the deaths which have occurred in the setting of Postmarketing Surveillance.

Clinical Studies

Death was reported for 37 patients from clinical studies. The most common cause of death was unexplained (10) which included 5 patients found in bodies of water such as bathtub or lake but who were not observed to have drowned or for whom there is some question. Seven patients died from accidental death due to trauma. There were 6 deaths attributed to seizure activity or *status epilepticus*. Suicide was the fourth leading cause of death associated with vigabatrin. Cardiac, respiratory and neoplastic causes appeared to be related to an underlying disease process. One patient died from fulminant hepatitis for which there was no other explanation.

Compassionate Use (NonUS)

The second source of safety data in this NDA is that of the NonUS Compassionate use, which are not included in the 3220 patients comprising the NDA database, although these patients obtained their drug in the premarketing period. One important difference is, however in the quality of the data collected. For these patients there is little information about dose, duration of exposure and in some cases even the cause of death. Case report forms are not available. In this group (the total denominator is not estimated by the firm as it is said to be unknowable) there were 21 deaths. They were similar to those reported in the NDA + Safety Update group.

Postmarketing Surveillance

In the postmarketing surveillance database there were an additional 39 deaths. The spectrum of deaths is summarized in the table below under "postmarketing surveillance". There are more unknowns in this group, possibly a result of less rigorous record-keeping. In this group as in the nonUS compassionate use database there is much less information about exposure, dose or duration.

On the following 6 pages is a summary listing of all deaths reported to this NDA regardless of source. The deaths are grouped first by cause, and within each group by data source (designated in the far right hand column). The nonUS Compassionate Use and Postmarketing deaths are in smaller print. Estimated worldwide exposure is 200,000 patient-years.

SUMMARY OF DEATHS OCCURRING IN VIGABATRIN-TREATED PATIENTS					
STUDY/PATIENT NUMBER	AGE YRS	SEX	DOSE (G/D)	DURATION	CAUSE OF DEATH AND COMMENTS
UNEXPLAINED					<i>Clinical Trials</i>
97006 /012-007	49	M	2g	4 mos	Found dead :Cardiomyopathy/LVH/ASCVD/emphysema
97006/012-009	37	M	3g	5.7yr	Found dead WPW syndrome/ possible seizure
97WOLD/ 30330048	23	F	4g	2 yr	Found dead after 5-7 days: sponsor attributes death to possible sz but not witnessed
97WOLD/ 32330925	28	F	2g	12 mos	Drowning following a seizure: No further history--not observed
300/533300045	46	F	unk	unk	Unknown cause:On compassionate use protocol--no information
C026/070-010	20	F	3g	3.4 mos	Found nearly drowned in bathtub Comment: Never regained consciousness (episode not observed)
C026/071-009	40	M	3g	10.5 mos	Found dead in pond
JGVG-CL- 202/20218005	46	F	4g	7.4 mos	Found dead in bathtub :sponsor attributes death to possible sz but not witnessed
JGVGCL202/ 20215M02	59	F	3g	2.8 mos	Found dead in bathtub:Sponsor attributes death to possible sz but not witnessed

717543F2 /3141	40	M	2g	2.4 mos	Found dead Thought to have fallen on face and suffocated
					<i>Compassionate Use</i>
340300054	51	F	unk	unk	Unknown Comment: patient discontinued drug because of bad memory
					<i>Postmarketing Surveillance</i>
09108534	26	M	2g	2m	Undetermined
09108559	20	F	unk	6 m	Undetermined
09108594	27	M.	.5g	3wks	Undetermined; ? Relapse of pancreatitis
09108787	47	M	2g	5 m	Undetermined Comment: found dead in bathtub
09108794	21	M	3g	3m	Undetermined Comment: found dead in bed
09108950	49	M	1.5g	1m	Undetermined
09109008	27	F	2.25	5 m	Undetermined Comment: Autopsy revealed cerebral edema and medullary bleed
09109179	27	F	.5g	5 m	Undetermined
09109188	34	M	3g	3.5 yr	Undetermined Comment: "Natural causes"
09203952	unk	unk	unk	unk	Undetermined
09211323	12	M	2g	6 m	Undetermined—patient experienced sudden death
09216793	14	M	2g	6 wk	Found dead in bed: seizure at 5:30 am
09209910	4	M	.5g	8 m	Found dead in bed
09216968	2	M	.5g	unk	Found dead in bed: found in vomitus
09109281	13	M	2g	6 mos	Found dead
93013821	34	M	3g	2 yr	Cause: Undetermined
TRAUMA					<i>Clinical Trials</i>
97006/012-013	29	M	3g	2.3 y	Multiple blunt force trauma:Hit by bus
WDRISE/ 36731401	44	M	2g	4 mos	Killed in automobile accident:Passenger
C014/015-007	24	M	1g	SD	Motorcycle accident
VIGA4ST01/ 125701P22	43	M	.5g	10 mos	Head injuries related to fall:SDH

717543F2/2401	39	M	2g	.6 mos	Head injury related to fall:Sponsor attributes fall to a seizure
097WFR01/0004	22	M	2g	8.8m	Motorcycle accident
097FR01 /0008	26	M	2g	4.9m	Motorcycle accident
SEIZURES /COMA STATUS EPILEPTICUS					<i>Clinical trials</i>
97006/006-003	35	M	4g	8.8 yrs	Grand mal seizures Became cyanotic during seizure and could not be revived
	38	M	3g	3yrs	<i>Status epilepticus</i>
97WOLD/30330006	33	F	4.5g	2.25 yr	Generalized seizure Not necessarily witnessed
241/24173	15	M	1.5	5day	Familial myoclonic epilepsy, seizures worse
300/533300024	35	F	4g	6 mo	Seizure No details available
C020-C028/058-0001	34	M	4.5g	9.8 mo	<i>Status epilepticus</i>
					<i>Compassionate Use</i>
32433336 VGST-C333-117	10	F	unk	1.1mo	Increase in seizures Comment: no real information about actual cause of death
4063001\VGSTMUMF345	1	M	unk	3.5m	Severe epilepsy/No real information about the cause of death
43533301 VGST-C333-209	25	F	unk	6.0 mos	<i>Status epilepticus</i> 241/24173
53333301 VGST-C333-233	35	F	unk	6.6 mos	Epilepsy No information about cause of death
VGSTMUMF333	25	F	unk	11 m	<i>Status Epilepticus</i>
VGSTMUMF340	16	F	unk	6m	Coma
					<i>Postmarketing Surveillance</i>
90302311	66	M	3g	unk	Complications of status epilepticus: prolonged coma
93003732	11	F	1.5g	126 day	<i>Status Epilepticus</i>
93011558	31	F	2g	5 m	<i>Status epilepticus</i>
93015266	7wk	M	.1/kg	unk	<i>Status epilepticus</i>
09211364	28	F	.5	unk	Convulsions

09211335	32	M	1g	unk	<i>Status epilepticus</i>
09213509	34	F	unk	4 m	Epileptic crisis
09109193	28	F	unk	unk	Aspiration with seizure
09016577	19	M	4g	unk	Aspiration with seizure
93014849	25	M	1.25g	1.5yr	<i>Status epilepticus associated with hyperthermia and rhabdomyolysis</i>
09203891	5	M	2g	4.5wk	Complications of <i>status epilepticus</i>
SUICIDE					<i>Clinical Trials</i>
C024/067-010	35	F	3g	3 m	Suicide:CBZ OD--
97WDRISE/ 36631403	25	M	2g	12m	Suicide
202/20214	41	M	2g	unk	Jumped into Rhone R Huntington's Chorea
SAB0190/ 124701P5	39	M	2g	4 m	Cause:Suicide --hanging
					<i>(Compassionate use)</i>
30733301 VGST-C333-104	15	F	unk	5.8 mos	Suicide
31533301 VGST-C333-234	44	M	unk	.8	Suicide
93015216	unk	unk	unk	unk	Possible suicide (prev attempts) by overdose vs seizure
IPU VGST-AU170001	28	M	unk	1.5 mos	Possible suicide or accidental drowning
					<i>Postmarketing Surveillance</i>
09211150	28	M	3g	unk	Suspected suicide Drowned in swimming pool
93002970	41	M	3g	19 days	Suicide: hospitalized for psychotic reaction
93005020	52	M	2g	5 m	Suicide
CARDIAC					<i>Clinical Trials</i>
97WOLD/25816	60	F	3g	2.25yr	CHF
304/30430415	36	F	unk	5.75yr	Coronary heart disease: postmortem performed
314 /33131405					
					<i>Compassionate Use</i>
30330090	59	M	unk	9.8	Cardiac disease
RESPIRATORY/ INFECTIOUS					<i>Clinical Trials</i>
314/41931404	42	M	unk	6 yrs	Aspiration pneumonia Secondary to seizure

VIGA4ST01/ 125701	35	F	4g	10 mos	Pneumonia
224/22407	73	F	PBO	0	Respiratory insufficiency: Occult infection
					Compassionate Use
34033399 VGST-C333-229	6	F	unk	.6	Prolonged infection-deterioration of status
39999901	34	M	unk	1 mo	Pneumonia
32334551 VGSTMUMF188	33	F	unk	7.9m	Asphyxia
40133328	7	M	unk	6.4 m	Aspirated a toy
45433301	9	M	unk	sd	Pneumonia
					Postmarketing Surveillance
94000981	17	F	3g	unk	Pneumonia
09016701	59	M	2g	unk	Pulmonary embolus
<i>Neoplastic :</i>					<i>Clinical Trials</i>
717543-F- 2/4181	64	M	2g	2.4	Oligodendroglioma
97WOLD/ 30330028	45	M	4.5g	2.2yr	Colonic adenocarcinoma
97WOLD/2120 2	60	M	4.5g	4yr	Metastatic small cell carcinoma-Lung
					Compassionate Use
30330052 VGST_MUMF132	37	F	unk	8.1 mos	Astrocytoma
AV VGST-SWP300PY	58	F	unk	40mos	Metastatic breast Carcinoma
IPU VGST-AU16-001	46	M	unk	1.3 mos	Recurrent oligodendroglioma
36130001 VGST-C333-205	16	F	unk	6.5	Cause: Malignant brain tumor
Hepatic Necrosis :					Clinical Trials
JVGCL202/ 20206Y06	34	F	3 g	8.7 mos	Cause: Fulminant Hepatic Necrosis
					Compassionate Use
NAV VGSTMUMF350	40	M	unk	72 mos	Cause: Acute hepatic failure
					Postmarketing Surveillance
09203130	10	M	1g	14 m	Massive Hepatic Necrosis
94001440	35	F	2g	5 m	Necrotizing Hepatitis and hepatorenal syndrome: concomitant drugs CBZ/PHT

93003075	38	M	1g	6 days	Fulminant liver failure followed by ARF, CHF, GI bleed
Fetal/ Neonatal					Postmarketing Surveillance
09109007	1d	M	.5g	IU	Cause: Congenital diaphragmatic hernia
930000051	-	unk	3g	IU	Cause: Therapeutic Ab Comment: conjoin twins
93012948	-	unk	.5g	IU	Cause: Therapeutic Ab Comment: Myelodysplasia/ cardiac dysplasia

The deaths in this NDA are largely either epilepsy related or in general due to not unexpected events. However there are two categories which deserve a more careful look: deaths due to hepatic necrosis and deaths due to suicide.

Cause of Death (by Category)	NDA + Safety Update N=3220	Compassionate Use NonUS N= (est)	Postmarketing Surveillance GADERS N=200,000 pt years est*	Total
Unexplained	10	1	16	27
Seizure related, other CNS	6	6	11	23
Suicide	4	4	3	11
Trauma	7	0	0	7
Cardiac	6	1	0	7
Respiratory /Infection	3	3	3	9
Neoplasm	3	4	0	7
Hepatic Necrosis	1	1	3	5
Fetal/Neonatal	0	0	3	3
Total	37	21	39	97

*note that this is only a rough estimate since the firm has not collected dose and duration of exposure data for much of this population.

The average age of patients dying while exposed to vigabatrin therapy in the population at large is 30 years of age. This is probably a reflection of use among pediatric patients once the drug is marketed. However, the firm has done no analyses to evaluate selective vulnerability of the pediatric population. Since a claim is not being sought at this time, this analysis is likely being deferred. *Reviewer's note: Clearly, it is the intent of the firm to use this drug in the pediatric population based on European studies and ongoing US studies. An analysis could be submitted to this NDA later as a supplement which would address specific safety concerns in children not the least of which is death.*

Deaths due to pulmonary embolus (1), pancreatitis (1) and, hyperthermia associated with rhabdomyolysis (1) and hepatic necrosis (5) are unexpected. Except for hepatic necrosis no additional cases have emerged for analysis. These may be drug-related or may be isolated events. At this time there is no way of knowing this.

9.3 ASSESSMENT OF DROPOUTS

Overall Pattern of Dropouts:

US Epilepsy Studies (N=443)

In US controlled epilepsy studies, a total of 32 (14.4%) vigabatrin patients and 5 (3.7%) placebo patients discontinued treatment. The majority of patients who withdrew from studies did so as the result of adverse events. In US open-label epilepsy studies, 169 (40.8%) patients exposed to vigabatrin discontinued treatment. This significantly higher occurrence rate, as compared to the US controlled studies, may be attributed to the longer duration of the US uncontrolled studies. Lack of efficacy and adverse events account for the majority of dropouts in US studies in epilepsy.

NonUS CRF studies, US non Epilepsy studies (N= 1327) and ARF studies (N=1780)

For these databases only dropouts due to adverse events are available. The total number of dropouts is not found in the NDA.

Overall incidence of dropouts (N=3320)

The overall the rate of dropouts from vigabatrin studies is not known. The rate cannot be calculated because the withdrawals due to lack of efficacy, or other reasons is not available and also because there is significant overlap between the nonUS CRF group and the ARF group. The table below shows, instead, the rates of withdrawal due to adverse events and death for each group of studies, and the rates of withdrawal due to other reasons for US epilepsy studies.

<i>Rates of Dropout by Treatment Group and Reason for each of three main Databases</i>			
<i>Reason for Dropout</i>	<i>Percent Vigabatrin-exposed patients Dropping Out</i>		
	<i>US Epilepsy Studies (N =443)</i>	<i>*CRF studies (US nonEpilepsy an nonUS) N=1327</i>	<i>* nonUS ARF studies N=1780</i>
<i>Lack of Efficacy</i>	<i>101 (22.8%)</i>	<i>UNK‡</i>	<i>UNK‡</i>
<i>Adverse Experiences</i>	<i>76 (17.2%)</i>	<i>110 (8.3 %)</i>	<i>193 (11%)</i>
<i>Death†</i>	<i>7 (1.6%)</i>	<i>10 (.8%)</i>	<i>11 (.8%)</i>
<i>Other</i>	<i>31 (7.%)</i>	<i>UNK‡</i>	<i>UNK‡</i>
<i>Total Dropouts</i>	<i>198 (44.7%)</i>	<i>UNK‡</i>	<i>UNK‡</i>

†not all deaths are included in this chart. The sponsor was been made aware of this and is expected to rectify this discrepancy.

‡ sponsor was unable to provide this information

*There is sufficient overlap between these two databases such that the rows add up to a total N>3320. The sponsor is unable to reconcile this disparity (telecon 2/28/95 with G.Heilman, MMD)

Reviewer's comments: The previous table was extracted directly from sponsor's tables 7-77 and 7-78 (see appendix) and demonstrates rates of dropout from various databases within the NDA. The original tables underscore the recurring problems

that were seen in this NDA with data management. The total number of patients in US Epilepsy studies, CRF studies (US nonEpilepsy and Non US) and nonUS ARF studies are represented as three separate independent databases. However they are not discrete. There is considerable overlap between the CRF non US and ARF databases (at least 230 patients) and the actual size of the ARF group is not known for certain. It can be seen that the rows add to a total greater than 3320. As noted, the quality of data in this group is not typical for clinical studies, thus reporting of dropouts may be limited. Furthermore, the data on deaths from the sponsors tables is not complete as shown. The total number of dropouts due to death in this database is 39/3320 (1.2%) and not 28 as shown. Whether dropouts due to adverse events or lack of efficacy were similarly omitted cannot be determined by this reviewer.

Adverse Effects Associated with Dropout

The most common reason for discontinuation from treatment with vigabatrin from US epilepsy controlled trials was drowsiness followed by depression, paranoid reaction, and dizziness. Agitation, amnesia, confusion, fatigue and headache were also some of the more common reasons for withdrawal from treatment. The summary table below shows the adverse events most commonly associated with withdrawal from epilepsy trials and their incidence. They are listed in order of frequency from greatest to least. In some cases more than one adverse event was given as the reason for withdrawal.

**Table: Adverse Events Associated with Withdrawal
all US Clinical Trials in Epilepsy N=443**

<i>Adverse Events</i>	<i>N</i>	<i>%</i>
Psychiatric		
Depression	9	2
Paranoid reaction	9	2
Agitation	7	1.5
Thinking Abnormal	5	1
Hallucination	4	1
Emotional Lability	4	1
Anxiety	3	.6
CNS/PNS		
Drowsiness	12	3
Dizziness	8	2
Headache	7	1.5
Amnesia	7	1.5
Confusion	7	1.5
Aphasia	4	.9
Fatigue	7	1.5
Arthralgia	5	1

<i>Adverse Events</i>	<i>N</i>	<i>%</i>
Psychiatric		
Depression	9	2
Speech disorder	3	.6
Parasthesia	3	.6
Ataxia	3	.6
Diplopia	1	.5
Vision Abnormal	4	.9
Skin		
Rash	4	.9
General		
Asthenia	4	.9
Pain	3	.6

Reviewer's comments: This database was used to display data on adverse events leading to withdrawal primarily because there was no overall group provided by the sponsor. This data would seem to be the most reliable, since the firm has repeatedly raised questions about the accuracy of the European database. Nevertheless some of the European data will be shown below.

In addition to the above, a total of 169 patients discontinued from open label epilepsy studies due to adverse events.

Neurologic adverse events were the most frequent cause for withdrawal (34) and included convulsions, amnesia, confusion, aphasia, drowsiness, abnormal gait, ataxia, abnormal coordination, choreoathetosis, vertigo, and neuropathy. Psychiatric adverse events accounted for 19 withdrawals and included paranoid reaction, hallucinations, thinking abnormal, agitation, depression, and emotional lability. Among some of the more uncommon causes for withdrawal from therapy included rash, arthritis, photophobia, rash, and increased weight. For comparison the incidence of adverse events leading to withdrawal from non US Clinical studies is discussed below. This includes both controlled and uncontrolled data.

***Adverse Events Associated with Withdrawal
NonUS Clinical Trials (CFR based) N=1327***

A total of 110 patients discontinued from clinical studies due to adverse events (not including death)

A total of 51 psychiatric adverse events were the cause of withdrawal from nonUS studies (CRF Database) for reasons including frank psychosis, psychotic depression, schizophrenic reaction, apathy, hallucination, crying, abnormal, dreaming, abnormal, insomnia, nervousness, depression, paranoid reaction, thinking abnormal, emotional lability, agitation, anxiety, thinking abnormal, aggressive reaction, delusion, libido decreased, and personality change. These spectrum of adverse events was a recurring theme throughout the NDA, and were among the frequently reported adverse events.

Patients also commonly withdrew from the nonUS Clinical studies because of

neurological conditions (total 54) which ranged from exacerbation of seizures and *status epilepticus*, not unexpected events in epilepsy studies to the more unexpected such as stupor, amnesia, confusion, aphasia, delirium, , peripheral nerve signs such as parasthesias, abnormal gait, ataxia, extrapyramidal syndrome, dystonia, tone changes.

Among some of the more uncommon but potentially serious causes for withdrawal from therapy included rash, arthrosis, visual abnormalities and diplopia, rash, increased weight, urinary abnormalities including incontinence or urinary retention, palpitation and tachycardia, and laboratory abnormalities including increased bleeding time, leukopenia, anemia and purpura. One patient withdrew from therapy because of thyroid disease.

***Adverse Events Associated with Withdrawal
NonUS Clinical Trials (ARF based) N=1760***

A total of 193 patients were reported as dropouts (not including deaths) from this data set. Reviewer's note: this probably represents considerable underreporting since this data set was constructed from a variety of sources and did not represent primarily prospective data, but rather relied upon passive reporting to various sources.

A total of 62 psychiatric adverse events were the cause of withdrawal from nonUS studies (CRF Database) for reasons including frank psychosis, schizophrenic reaction, catatonic reaction, hallucination, manic reaction, apathy, insomnia, depression, paranoid reaction, thinking abnormal, emotional lability, agitation, euphoria, anxiety, thinking abnormal, aggressive reaction, and personality change. These spectrum of adverse events was a recurring theme throughout the NDA, and were among the frequency reported adverse events.

Patients also commonly withdrew from the nonUS Clinical studies because of neurological conditions (total 131) which ranged from convulsions, not unexpected events in epilepsy studies to the more unexpected such as stupor, amnesia, impaired concentration, confusion, aphasia, delirium, abnormal gait, ataxia, choreoathetosis, dystonia, dyskinesia, other tone changes, optic atrophy. With the exception of optic atrophy, these are similar to those conditions which led to dropout in the US database.

Among some of the more uncommon but potentially serious causes for withdrawal from therapy included dyspnea, allergic reaction, rash, rigors, arthrosis, congestive heart failure, rash, increased weight, leukopenia and purpura. Some of these were seen in the other databases. Although the numbers of these events remain small, leaving questions about causality unanswered.

In summary the adverse events which led to the most withdrawals from exposure to vigabatrin in clinical trials were psychiatric and neurologic. If convulsions are not included in the overall totals, psychiatric adverse events are clearly the leading cause of withdrawal from clinical studies.

9.4 OTHER SAFETY FINDINGS

ADR Incidence Tables

Adverse Events Observed Commonly in Controlled Clinical Epilepsy Trials

The table on the following page enumerates adverse events which occurred at a frequency of 5 % or more among vigabatrin-treated patients who participated in placebo-controlled studies of similar design. These figures provide some basis for estimating the relative contribution of drug vs. nondrug factors to the side effects incidence rate in the population studies. The US placebo controlled epilepsy studies (N= 357) were used for these comparisons. The remainder of the placebo controlled trials (9 nonUS studies) were very small, some had no requirements for prospective reporting of adverse events(9), and were of designs (crossover) which could potentially confound the overall clarity of the results.

The most commonly observed adverse events associated with the use of vigabatrin (incidence of 5% or greater) and not seen at an equivalent incidence among placebo treated patients (ie, incidence for vigabatrin is at least twice that of placebo) were depression, amnesia, thinking abnormal, concentration impaired, confusion, as well as hyporeflexia and paraesthisas, and weight increase. Categories such as visual abnormalities were more prominent in the vigabatrin treated group, but individual complaints were not twice as frequent, and are not reported here.

<i>Distribution of All Treatment-Emergent Adverse Events with an Incidence of \geq 5% in Vigabatrin treated patients (and $<$2.5 % in Placebo patients in US epilepsy Placebo-Controlled Clinical Trials</i>			
<i>Body System</i>	<i>Preferred Term</i>	<i>Vigabatrin (n=222)</i>	<i>Placebo (n=135)</i>
<i>Body as a whole</i>	<i>Weight increase</i>	<i>17 (7.7%)</i>	<i>5 (3.7%)</i>
<i>Nervous system</i>	<i>Amnesia</i>	<i>23 (10.4%)</i>	<i>4 (3%)</i>
	<i>Depression</i>	<i>27 (12.2%)</i>	<i>5 (3.7%)</i>
	<i>Paresthisias</i>	<i>22(9.9%)</i>	<i>4(3%)</i>
	<i>Confusion</i>	<i>16 (7.2%)</i>	<i>2 (1.5%)</i>
	<i>Coordination Abnormal</i>	<i>15 (6.8%)</i>	<i>4(3%)</i>
	<i>Concentration impaired</i>	<i>12 (5.4%)</i>	<i>2(1.5%)</i>
	<i>Hyporeflexia</i>	<i>12 (5.4%)</i>	<i>2 (1.5%)</i>
	<i>Thinking Abnormal</i>	<i>11 (5%)</i>	<i>1 (.7%)</i>

1Events reported by at least 5 % of patients treated with vigabatrin are included if their incidence is

Appears This Way
On Original

Other events seen during the premarketing evaluation of Vigabatrin (excluding compassionate use

During the premarketing assessment of vigabatrin multiple doses of vigabatrin were administered to 3320 patients many of whom were enrolled in clinical studies. The conditions and duration of exposure differed and included (in overlapping categories) open and double blind studies, fixed dose and titration studies, parallel and crossover studies, single patient and compassionate use, and others. The adverse events reported in the pool of all studies are listed in tabular form by the sponsor. It must be cautioned that for at least one cohort (ARF "studies") comprising more than half of this data base the adverse event data was not collected prospectively in case report forms, but gathered in part from formal and informal studies, literature reports, manuscripts and other unconventional sources. The sponsor's tabulations are attached to this review, but should not be considered for use in labeling until a more reliable compilation can be obtained from the sponsor.

Reviewer's comments: The firm initially analyzed the US controlled data separately from the remainder of the 3320 patient NDA database. Upon request the firm produced a table of all adverse events and their frequencies for the 3320 total patients exposed. In retrospect it would have been advisable to see the CRF databases (US and nonUS) separately, since presumably that information was reliably prospective and contemporaneous.

9.4.2 Laboratory Findings

Clinical laboratory data were obtained at pre and post dose visits in most vigabatrin treated patients in US studies, and in some European studies. This section will focus on a subgroup of exposed patients, those in US placebo-controlled epilepsy trials in order to explore contrasts with laboratory changes in the treated and the control groups. In this group, the relationship of the concomitant drugs to laboratory changes will be examined where appropriate. Because the US Controlled studies are known to have consistently collected prospective data, they will be used in the following comparisons.

Clinical Chemistry

The table below provides criteria for identifying patients with changes in clinical chemistry values from baseline which may be of possible clinical significance.

CRITERIA FOR IDENTIFYING PATIENTS WITH POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN CLINICAL CHEMISTRY VARIABLES		
	LOW	HIGH
Albumin	<2.5 g/dl	
Alkaline Phosphatase		>390 U/L

<i>BUN</i>		>30 mg/dl
<i>Calcium</i>	<8.2 mg/dl	>12 mg/dl
<i>Chloride</i>	<90 meq/L	>118 meq/L
<i>Cholesterol</i>		>600 mg/dl
<i>CPK</i>		>200 I.U./L
<i>Creatinine</i>		>2 mg/dl
<i>Globulin</i>	<1 g/dl	
<i>Glucose</i>		>175 mg/dl
<i>LDH</i>		>750 u/ml
<i>Phosphorous</i>	<1.7 mg/dl	
<i>Potassium</i>	<3 meq/L	>6 meq/L
<i>SGOT</i>		>150 U/L
<i>SGPT</i>		>165 U/L
<i>Sodium</i>	<126 meq/L	>156 meq/L
<i>Total Bilirubin</i>		>2 mg/dl
<i>Total Protein</i>	<4.5 g/dl	>10 g/dl
<i>Triglycerides</i>		>600 mg/dl
<i>Uric Acid; male</i>		>10.5 mg/dl
<i>Uric Acid; female</i>		>8.5 mg/dl

The table below provides the proportions of patients who were relatively normal at baseline and who then exceeded these criteria during treatment. There appeared to be no significant differences in the frequencies of specific laboratory abnormalities between the two groups. The reason for the 30% outliers in placebo and the 20% outliers in vigabatrin group with low calcium is not understood.

Proportions of Patients Having Potentially Clinically Significant Changes in Blood Chemistry Variables in Placebo-Controlled Studies				
Blood Chemistry Variables	Placebo N=135		Vigabatrin N=221	
	Abnormal #	%	Abnormal #	%
Albumin-Low	0	(0%)	0	(0%)
Alk. P'tase-High	0	(0%)	0	(0%)

Proportions of Patients Having Potentially Clinically Significant Changes in Blood Chemistry Variables in Placebo-Controlled Studies		
Blood Chemistry Variables	Placebo N=135	Vigabatrin N=221
<i>BUN-High</i>	0 (0%)	0 (0%)
<i>Calcium-Low</i>	40 (30%)	45 (20%)
<i>Calcium-High</i>	0 (0%)	0 (0%)
<i>Chloride-Low</i>	0 (0%)	2 (1%)
<i>Chloride-High</i>	2 (1%)	1 (0%)
<i>Cholesterol-High</i>	0 (0%)	0 (0%)
<i>CPK-High</i>	unk	unk
<i>Creatinine-High</i>	0 (0%)	0 (0%)
<i>Glucose-Low</i>	5 (4%)	8 (4%)
<i>Glucose-High</i>	5 (4%)	4 (2%)
<i>LDH-High</i>	1 (1%)	0 (0%)
<i>Phosphorus-Low</i>	4 (3%)	0 (0%)
<i>Potassium-Low</i>	0 (0%)	0 (0%)
<i>Potassium-High</i>	2 (1%)	2 (1%)
<i>SGOT-High</i>	1 (1%)	1 (0%)
<i>SGPT-High</i>	0 (0%)	0 (0%)
<i>Sodium-Low</i>	5 (4%)	8 (4%)
<i>Sodium-High</i>	0 (0%)	0 (0%)
<i>Total Bilirubin-High</i>	0 (0%)	0 (0%)
<i>Total Protein-Low</i>	0 (0%)	0 (0%)
<i>Total Protein-High</i>	0 (0%)	0 (0%)
<i>Triglycerides-High</i>	unk	unk
<i>Uric Acid -High</i>	0 (0%)	0 (0%)

Hematology

Criteria for identifying patients with changes from baseline in hematology variables of possible clinical significance are found in the table below.

CRITERIA FOR IDENTIFYING PATIENTS WITH POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN HEMATOLOGY VARIABLES		
	LOW	HIGH
Hemoglobin		
Female	<9.5 g/dl	
Male	<11.5 g/dl	
Hematocrit		
Female	<32%	
Male	<37%	
White Blood Cells	<2.8 ths/mm	>16 ths/mm
Neutrophils	<15%	
Lymphocytes		>75%
Monocytes		>15%
Eosinophils		>10%
Basophils		>10%
Platelets	<75 ths/mm	>700 ths/mm
Bands		>10%

The table below provides the proportions of patients in US placebo controlled trials who were relatively normal at baseline and who then exceeded these criteria during treatment. There is were twice the outliers in the vigabatrin treated group for low hematocrit and WBC count compared to the placebo group. The sponsor has made no comment on this. Randomization should have and did evenly balance exposure to concomitant drugs such as carbamazepine between the treatment groups. There was not an obvious problem with anemia and neutropenia in the database at large. It must be kept in mind that these numbers are rather small, so that firm conclusions about relative risk cannot be drawn.

Proportions of Patients Having Potentially Clinically Significant Changes in Hematology Variables in US Placebo-Controlled Studies				
Hematology Variables	Placebo N=135		Vigabatrin N=221	
	Abnormal #	%	Abnormal #	%

<i>Hemoglobin-Low</i>	0(0%)	2 (1%)
<i>Hematocrit-Low</i>	8 (6%)	28 (13%)
<i>WBC-Low</i>	7 (5%)	23 (10%)
<i>WBC-High</i>	0(0%)	0(0%)
<i>Neutrophils-Low</i>	6 (4%)	16 (7%)
<i>Lymphocytes-High</i>	0 (0%)	0 (0%)
<i>Monocytes-High</i>	unk	unk
<i>Eosinophils-High</i>	4 (3%)	4 (2%)
<i>Basophils-High</i>	unk	unk
<i>Platelet Ct-Low</i>	1 (1%)	0(0%)
<i>Platelet Ct-High</i>	0 (0%)	0 (0%)
<i>Bands-High</i>	unk	unk

There have been no reports of deaths or withdrawals from clinical trials due to abnormalities in hematology parameters.

Urinalysis

The table on the following page shows the criteria customarily used for identifying patients with changes from baseline in the urinalysis that is of potential clinical significance.

<i>Criteria for Identifying Patients with Clinically significant abnormalities in UA</i>		
	<i>LOW</i>	<i>HIGH</i>
<i>Specific Gravity</i>	< 1.001	
<i>pH</i>	< 4	> 9
<i>Protein</i>		> 10
<i>Ketone</i>		4+
<i>Glucose</i>		4+
<i>RBC- Female</i>		> 10/hpf
<i>RBC- Male</i>		> 8/hpf
<i>White Blood Cells</i>		> 10/hpf
<i>Casts</i>		> 9/hpf
<i>Epithelials</i>		> 50/hpf
<i>Crystals</i>		> 10/hpf

The firm did no analysis to determine those patients relatively normal at baseline who then exceeded these criteria while on treatment except for specific gravity and pH. There were no outliers for these data. *It appears that no urinary cellular data was collected.*

9.4.3 Vital Signs

The table below provides criteria for identifying patients with vital signs changes from baseline of potential clinical significance.

CRITERIA FOR IDENTIFYING PATIENTS WITH POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN VITAL SIGNS VARIABLES		
	LOW	HIGH
<i>Systolic Blood Pressure</i>	<i>< 90 mm Hg</i>	<i>> 180 mm Hg</i>
<i>Change in Systolic BP</i>	<i>Decrease > 30 mm Hg</i>	<i>Increase > 40 mm Hg</i>
<i>Diastolic Blood Pressure</i>	<i>< 50 mm Hg</i>	<i>> 105 mm Hg</i>
<i>Change in Diastolic BP</i>	<i>Decrease > 20 mm Hg</i>	<i>Increase > 30 mm Hg</i>
<i>Pulse</i>	<i>< 50 bpm</i>	<i>> 120 bpm</i>
<i>Change in Pulse</i>	<i>Decrease > 30 bpm</i>	<i>Increase > 30 bpm</i>

Those patients in controlled studies who were relatively normal at baseline and who then exceeded the criteria as noted above at some time during treatment are listed in the table below.

Proportions of Patients having Potentially Clinically Significant Changes in Vital Signs in US Placebo-Controlled Studies				
Vital Signs Variables	Placebo N=135		Vigabatrin N=221	
	Abnormal #	%	Abnormal #	%
<i>Systolic, mmHg-Low</i>	<i>1</i>	<i>(.8%)</i>	<i>3</i>	<i>(1.4%)</i>
<i>Systolic, mmHg-High</i>	<i>0</i>	<i>(0%)</i>	<i>0</i>	<i>(0%)</i>
<i>Diastolic, 1 mmHg-Low</i>	<i>0</i>	<i>(0%)</i>	<i>0</i>	<i>(0%)</i>
<i>Diastolic, mmHg-High</i>	<i>0</i>	<i>(0%)</i>	<i>0</i>	<i>(0%)</i>
<i>Pulse, 1 Bpm-Low</i>	<i>0</i>	<i>(0%)</i>	<i>1</i>	<i>(.5%)</i>
<i>Pulse, 1 Bpm-High</i>	<i>4</i>	<i>(3%)</i>	<i>6</i>	<i>(2.7%)</i>

Weight decrease > 15%	0 (0%)	0 (0%)
Weight decrease 7-15%	10 (7.5%)	11 (5%)
Weight increase > 15%	0 (0%)	1 (.5%)
Weight increase 7-15%	21 (15.8%)	62 (47.3%)

The only notable difference between the placebo and the vigabatrin treated group was the report of weight gain in the latter.

9.4.4 ECGs

Reviewer's note: sponsor has not provided analysis of this area. The statement in the NDA and safety update that "at doses of up to 6g/day, vigabatrin does not appear to be associated with any clinical relevant adverse effects on the cardiovascular system" should be accompanied by data presented in such a way as to support this statement. Tables of raw data or outliers could not be located.

The sponsor has indicated that specific electrocardiographic and cardiophysiologic studies have not been conducted. Routinely monitored EKGs were not collated. Sponsor indicates that no consistent abnormal changes in routinely monitored ECGs were observed.

9.5 SPECIAL SAFETY CONSIDERATIONS

9.5.1 Central Neurotoxicity

Based on the preclinical history of this drug there has been a sustained focus on human neurotoxicity. The human neurotoxicity might well be expected. However, considerable uncertainty remains as to how such toxicity could be recognized in humans. As this reviewer approaches the evaluation of human safety data and proposed labeling the following questions remain:

Does intramyelinic edema occur in humans?

If it does occur, how can it be recognized?

Does it result in a serious deficit?

Is it permanent?

Is it dose related?

Does its incidence or intensity increase with increased duration of exposure?

What are the clinical manifestations?

If the IME acute lesions or a chronic counterpart are shown to occur in humans it is not unreasonable to expect that the profile of this toxicity would be well worked out before the drug is marketed for human use. Patients were screened for central neurotoxicity in one to all of four ways (*reviewer's distinction*): neuropathologically, radiographically, electrographically and clinically. Each of these paradigms and the results, conclusions and shortcomings where appropriate will be discussed below.

Part 1 *Clinical Neuropathologic studies in Vigabatrin*

Material for the human pathologic studies derives from two sources autopsy and surgical pathology. Autopsy material from patients who died while taking vigabatrin was examined for evidence of IME. Age matched controls were examined. There were 11 patients autopsied and 10 controls. An additional 6 cases of vigabatrin-treated patients and 1 control were added since the original NDA.

The second source came from surgical specimens. Those patients who underwent seizure surgery, or resection of tumor were included in this group which numbered 51. There were 20 controls. An additional 2 surgical specimens and no further controls were examined since the original NDA was submitted. The sponsor admits that "In most cases the sections examined from autopsy cases were more valuable since they include all areas of the brain, and are not restricted to tissue rendered at surgery". In the animal studies, the microvacuolation was restricted to focal areas of the white matter. However in the surgical cases, only a limited area of the brain was available for examination, and the more relevant areas could not be examined. Hence, there is a discrepancy between the areas of human brain examined from surgical cases and the precise focal areas of vacuolation caused by vigabatrin treatment in rodents and dogs. The sponsor's reports confirm this, as the surgical cases in general provided little to no information about a very restricted area of sampling. Therefore this review will concentrate on autopsy material largely, although even this sample had its limitations.

Areas Sampled	Autopsy		Surgical Path		Total	
	Vigabatrin N=17	Control N=13	Vigabatrin N=54	Control N=20	Vigabatrin N=71	Control N=33
Optic Tracts/Chiasm	5 (29%)	7 (54%)	0	0	5 (7%)	7 (21%)
Cerebellum	13 (76%)	9 (69%)	0	0	13 (18%)	9 (27%)
Hypothalamus	2 (12%)	2 (15%)	0	0	2 (3%)	2 (6%)
Fornix	2 (12%)	5 (38%)	0	0	1 (1%)	5 (15%)
Uncus	2 (12%)	0	2 (4%)	1 (5%)	4 (6%)	1 (3%)
Hippocampus	8 (47%)	12 (92%)	22 (43%)	3 (1.5%)	26 (37%)	13 (39%)
Hindbrain (NS)	3 (18%)	0	0	0	3 (4%)	0
Pons	11 (65%)	7 (54%)	0	0	7 (10%)	5 (15%)
Medulla	8 (47%)	6 (46%)	0	0	4 (6%)	5 (15%)
Midbrain	5 (29%)	0	0	0	3 (4%)	0
Spinal Cord	3 (18%)	0	0	0	2 (3%)	0
Corpus Callosum	1 (6%)	2 (15%)	4 (8%)	0	4 (6%)	2 (6%)
Corpus Striatum	1 (6%)	2 (15%)	0	0	1 (1%)	2 (6%)
Internal Capsule	0	2 (15%)	0	0	0	2 (6%)
Thalamus	2 (12%)	0	0	0	1 (1%)	0
Basal Ganglia	3 (18%)	2 (15%)	0	0	2 (3%)	1 (3%)
Frontal Lobe	8 (47%)	6 (46%)	2 (4%)	0	5 (7%)	4 (13%)
Temporal Lobe	5 (29%)	1 (8%)	22 (43%)	9 (4.5%)	24 (39%)	10 (30%)
Parietal Lobe	4 (24%)	0	3 (6%)	2 (10%)	4 (6%)	2 (6%)
Occipital Lobe	3 (18%)	0	0	1 (5%)	1 (1%)	1 (3%)
Cortex (NS)	5 (29%)	4 (31%)	1 (2%)	0	4 (6%)	3 (10%)
Amygdala	0	0	21 (39%)	4 (20%)	21 (34%)	4 (13%)
Corpus striatum	1 (6%)	0	0	0	1 (1%)	0

The areas of brain sampled in the vigabatrin-treated patients and the controls is shown in the above table. This information was obtained from the individual pathology reports provided by the sponsor. As the table shows, only 5/71 (8%) patients in the treatment group had optic tract or chiasm examined, 13/71 (18%) were examined for lesions in the cerebellum, 2/71 (3%) in the hypothalamus, and 2/71 (2%) were examined for lesions in the fornix.

Several centers in Europe and the USA have been involved in the neuropathologic evaluation of vigabatrin. Standardization was attempted in order to obtain well-fixed

material and to minimize fixation artifacts. The tissue from biopsy or postmortem cases was fixed in 10% neutral buffered formalin by immersion of biopsy material or suspension of the whole brain in autopsy cases. Samples were routinely processed into paraffin wax and 5 μ m sections were stained with hematoxylin and eosin, luxol fast blue or a similar stain to demonstrate myelin. Where facilities were available, separate blocks of tissue were fixed in 4% glutaraldehyde and processed by EM. Since 2/28/93 (6 cases) additional immunocytochemical stains were added to attempt to distinguish artifactual from possible drug related changes. There is no documentation that these methods have been validated, even in the animal studies.

Slides were first evaluated by the pathologists at the center where the patient had been enrolled in study. The slides were then sent to an independent pathologist appointed by MMD, either [REDACTED] a neuropathologist or [REDACTED] a general pathologist for the [REDACTED]

b(4)

There have been a total of 97 deaths per an estimated 200,000 patient years of vigabatrin exposure, and of these autopsy material has been obtained on only 18. Only 17 of these are currently available for review. As noted, not all relevant areas were examined in these cases. Duration of exposure in autopsied cases ranges from 4.6 months to 107.7 months (nearly 9 years). In general clinical course was not described in most of these cases.

RESULTS:

The sponsor presented abbreviated summaries of the autopsy reports in an appendix to the report on neuropathologic findings with vigabatrin. In the report the sponsor provides summarized results "There was no myelin vacuolation in the white matter that was considered to be outside the control range. In one case from the UK coronal sections were cut at different levels throughout the brain. There was a loss of neurons in the hippocampus H1 area, a change attributed to epilepsy itself. In this particular case, small infarcts were identified in the cerebellum." There was no discussion of the perivascular macrophages and infarcts reported in the treated group compared to controls and no discussion of the four cases of torpedoes on Purkinje axons and axon ballooning. The sponsor concludes that "it was not possible to identify in patients who had received vigabatrin ...any pathologic changes which were in addition to those already present due to epilepsy."

Many of the autopsy reports are sketchy and do not all yield equally detailed descriptions of pathology. Only a few had case report forms which gave some clinical history, six did not even have a narrative summary. The table on the following page summarizes some of the relevant positive findings from the pathologic and clinical materials.

PAD	Rx	AGE	HISTOPATHOLOGY	CLINICAL
			VIGABATRIN TREATED PATIENTS	
30330052	7.87 mos	38	Diffuse infiltration with astrocytoma. Pons and cerebellum slight gliosis; reduced number of purkinje cells. †	Astrocytoma No relevant clinical hx
31133301	4 yrs	60	Forebrain, hindbrain, BS--extensive spongioform degeneration. Extensive hypoxic damage and postmortem artifact. EM shows autolysis and very marked degree of myelin splitting.(consultant attributes to clinical condition)†	Lack of coordination Died of liver failure
30330006 097- WOLD	29 m (3g)	32	Uncus: Loss of ganglion cells: Slight artefactual vacuolation fascia dentata. hippocampus: Imp: anoxia cerebri epilepsy† *Haemosiderin-bearing macrophages appear often around the vessels... There are no recent infiltrates, perivascular bleeding, thrombi or embolisms. A few subependymal vessels are hyalinated.	ICS and CRFs ¹ - no important clinical information
30430415	69 m	36	Frontal and temporal lobes examined: Postmortem artifact includes vacuolation of white matter.†	ICS-no CRF decr. memory slow thoughts
32333399	6m	19	Poor fixation. No myelin vacuolation†	no CRF
32330925	12.5 mos	29	Incidental findings of corpora amylacea around periventricular veins inferior to the caudate nucleus, and small glial nodules in the wall of the ventricle (more than expected for age, and not related to epilepsy); Temporal lobe: pigmented macrophages around blood vessels, small infarct, cerebellum, ; R/L hippocampus shows extensive loss of pyramidal cell neurons from the h1 area with gliosis. Patchy loss of Purkinje cells with Bergman glial cells throughout cerebellar cortex. Patchy infarction in depths of 2 sulci on superior surface of CB	
012-009 097-006	69 m	37	Patchy ischemic neuronal necrosis with diffuse cytoplasmic eosinophilia and pyknotic nuclei	CRF: slurred speech, retinal changes, ataxia

¹Most of the pages in the CRF were forms that had not been filled out.

919003*	107.7 mos	36	Periventricular gliosis, loss of some ependyma. Diffuse identification of microglial cells and perivascular cells in hypothalamus ² Hypothalamus, small area of increased staining of astrocytes by GFAP. PGM1 staining showed widespread identification of microglia and perivascular cells. Evidence of an ischemic lesion in the cerebellum. Inferior cerebellum: occasional torpedoes are seen on Purkinje cell axons. Multiple areas of ischemia.	no CRF
058-001* 097-006	21m	34	Loss of neurons and proliferation of glia in cortex (but no focal infarct). White matter shows vacuolation of oligodendrocyte cytoplasm and occasional vacuoles but no obvious myelin vacuolation. There are macrophages around some blood vessels indicating previous white matter damage. Increase number of cells in cortex, reflecting glial proliferation. White matter show occas. vacuoles but mostly around oligo nuclei Motor cortex: Accumulation of macrophages around blood vessels in white matter reflecting previous white matter damage. Increased glial nuclei reflecting neuronal loss and diffuse cortical damage. Accumulation of macrophages around blood vessels.	Difficulty with tandem walk. increasing tiredness found dead Autopsy rept incomplete No microscopic of other systems
901-009*	8.43 mos	59	Neuronal loss and moderate number of axon balloons and torpedoes were seen in the internal granule cell layer of the cerebellar cortex. Spinal cord at the decussation of the CST and gracile nuclei reveals eosinophilic axon balloons containing neurofilament protein	ataxia, confusion, increased ICP, coma
62992*	8.97 mos	41	A transverse band across the internal capsule shows loss of axons and myelin and activation of microglia and gliosis. Small infarcts (area through caudate), cerebellar and cortical white matter: torpedoes on Purkinje cell axons, extensive gliosis ³ ; Cortex, focal old infarction;; cystic infarct of the amygdala; General: widespread ischemic damage, focal ischemic damage; small infarcts. White matter vacuolation is seen but mainly around the oligo nuclei. Widespread focal ischemic damage.	Drowning
9100099*	4.63 mos	27	Recent infarct, pituitary; scattered cortex and white matter perivascular cells around vessels in white matter by PGM1 staining,	no CRF

²PGM1 Immunocytochemistry

³Sponsor's consultant attributes these to epilepsy.

3043001*	7.63 mos	41	PGM1 positive borders around blood vessels; Cerebellum: diffuse Bergmann glia GFAP staining and some empty basket cells and occasional torpedoes are seen; Optic nerve and hippocampus: occasional axon balloons are seen, perivascular macrophages and staining of microglia in perivascular positions. Perivascular cells stain with PGM1. Some macrophages in perivascular positions.	no CRF
31533301	3 wk	45	Autolysis throughout†	no CRF PB overdose
3613000	7 m	16	Infiltration of ependymoma and extensive edema underlying dilated ventricle. Pontine hemorrhage. Cerebellum—diffuse loss of Purkinje cells, white matter shows scattered vacuoles. Remainder of brain show diffuse vacuoles of white matter. †	Malignant ependymoma no CRF
012-013 097-006	28 m	29	Severe trauma to brain—autolysis and drying artifact†	
			CONTROLS†	
479	0	56	Artefactual vacuolation in frontal lobe. Patchy gliosis in cortex from previous boxing injuries. Contusions on surface of the brain with SAH. Generalized gliosis	Boxer Auto accident
442	0	69	Widespread autolysis, lymphocytic cuffing in hippocampus and optic tract, fornix and internal capsule with no vacuolation	Cardiac disease—died 2d after CABG
321	0	29	Encephalitis with hypoxic damage, eosinophilic neurons in hippocampus, No loss of purkinje cells	Encephalitis, cardiac arrest
107	0	4	Long standing gliosis and neuronal cell loss from hippocampus due to febrile seizures. Recent infarct in the hippocampus and old infarct in ICP.	Drowning
28	0	17	Small hippocampal scar, some vacuolation in pons but not associated with gliosis. No recent hypoxic changes.	Asphyxia
58	0	27	No purkinje cell loss, vacuolation without reactive astrocytosis noted in cerebellum optic tracts, fornix	Drowning
241	0	25	Hypoxic damage to the hippocampus.	Asphyxiation
459	0	71	Lacunar infarcts and status spongiosis is seen in GP with calcification of bv's, No vacuolation. No loss of neurons in hippocampus. Minimal gliosis in CB and hippocampus.	MI

189	0	18	Capillary telangiectasia (prob epileptic focus). Autolytic changes in cerebellum and vacuolation in white matter	Status epilepticus
461	0	27	AVM associated with gliosis. No loss of neurons. Some gliosis of hippocampus associated with epilepsy	Accidental death
481	0	49	No vacuolation. Bergman gliosis in CB and astrocyte proliferation in hippocampus	found dead
82	0	64	Patchy gliosis and loss of Purkinje cells with numerous corpora amylacia; amnon's horn sclerosis	systemic sclerosis
480	0	70	Patchy gliosis in cortex and loss of purkinje cells.	Multi infarct dementia

*Safety Update

†Abbreviated summary of neuropath-no specific breakdown of findings

A frequent finding in the vigabatrin treated cases, not seen to the same extent in controls was the finding of perivascular cellularity and staining and frequent small infarctions. In addition, 4 patients who had been treated for an extended period of time (from 7.63 to 107.7 months) had pathologic evidence of torpedoes, axonal balloons or spheroids in the cerebellum. There was no reasonable explanation or discussion as to whether they resembled the chronic lesions reported in the rodent.

Clinical correlates were hard to find, although in at least four cases there had been a preceding history of ataxia.

No definite IME was seen, however the incidence of infarcts in a young population , where controls did not have similar findings is suggestive of cerebromicrovascular disease. This parallels the eye findings (next section). The autopsy reports are sketchy and do not all yield the same detailed description of pathology. This limits the analysis.

Comments regarding the pathologic study:

While this study did not demonstrate that treatment with vigabatrin is associated with the appearance or risk of intramyelinic edema in humans, one could argue that this study was not really capable of doing so. There was no standardization with regard to areas that would be sampled, there appears to have not been blinding of the pathologists who read the slides. In the animal studies, the IME was limited to precise focal areas of involvement, specifically, the optic pathways, the hypothalamus and the columns of the fornix and cerebellar white matter. In the surgical cases these areas were not available for sectioning, and in the autopsy material, while the relevant areas could have been carefully studied, they were frequently not. As a result, this study leads to the perhaps faulty conclusion that this drug does cause the histopathologic lesions in the human that were seen in other species. The disparity between what was sampled in the human, and the precise focal areas of IME in the

animals cannot support the conclusions of safety rendered by the sponsor.

The number of patients who had complete autopsies was limited by not only the number of deaths compared to total exposure, but also by the number of autopsies actually obtained in those fatal cases. The absence of findings in these few autopsies does not rule out the possibility that the pathology is there.

There is further question as to whether these autopsies are really negative. The finding of torpedoes and axonal spheroids in 3 cases are not explained. The presence of myelin splitting is always dismissed by the sponsor. While active IME may not have been seen in most of these 18 autopsy cases, the finding of perivascular infiltration and patchy infarcts was noted in nearly half of the autopsies. The presence of vascular changes and local ischemia is not commented upon. The full reports of autopsies are not provided so that other organs (such as kidney) cannot be screened for evidence of vasculitis. This bears further investigation into its possible relationship to IME, if any, and also to its relationship to the microvascular findings in the eye, which were noted in over 25% of cases examined.

A final note is indicated about these cases for which autopsies were performed. In an effort to obtain more clinical insight, the case report forms corresponding to these 17 cases were sought. There were no case report forms corresponding to some of the patient ID numbers for which there were autopsies performed, nor did all of the numbers correspond to the cases of deaths reported. The firm is currently attempting to clarify this disparity.

Part 2 Clinical Electrophysiologic Studies: Evoked Potentials

The extensive testing of evoked potentials in dogs and rats given vigabatrin demonstrates that IME can be reliably detected by non-invasive techniques. The assumption on which the human evoked potential studies are based is that if IME occurs in humans, prolonged evoked potential latencies will be present. However, patients with epilepsy may have pre-existing abnormalities in evoked potential baseline tests. Additionally, human evoked potentials normally vary over time, tend to prolong with age and can be affected by different measurement techniques. For these reasons, pretreatment (baseline) evoked potential data were recorded for both treated and placebo groups in the two US adequate and well-controlled studies

In these studies, over 400 patients have been exposed to vigabatrin who had evoked potential studies at some time during treatment. Based on data from evoked potential studies in dogs, a guideline of $\geq 15\%$ prolongation from baseline to endstudy in SEP or VEP was used to detect a change that might suggest the presence of IME. Although the long term open label studies used different methods of comparison of data and often lacked adequate controls, the specific latencies measured were consistent across studies in most cases.

Results: Prolongation of any evoked potential latency $\geq 15\%$ from baseline occurred with about equal frequency in the placebo and treated groups. Some of the results of VERs obtained in clinical studies were so far out of the expected range in both placebo and vigabatrin-treated patients. These call into question the reliability and reproducibility of techniques used in these studies. Furthermore, many of the studies on which the sponsor relies are submitted in abstract form without actual data. The shortcomings of the evoked potential program of central neurotoxicological evaluation are discussed in a separate review (See attached review, J. Feeney, MD). One of the important shortcomings is the lack of long term evoked potential data. The US controlled studies are generally short-term (3-4 months) although longer term exposure is available. The longer term data, however, is uncontrolled.

There has been no concerted effort to validate abnormal findings. The patients with abnormal VERs do not appear to have not been followed up even in cases where abnormal evoked potentials led to a patient's withdrawal from treatment. Without clinical correlation or validation it is difficult to understand how any meaningful conclusions can be drawn.

In summary, electrophysiologic studies failed to produce conclusive evidence of IME, however, the design and conduct of the studies conducted may have made finding these lesions unlikely or difficult. Taken with all of their flaws, the studies of evoked potentials in humans provided no added insight into the safety profile of vigabatrin.

Part 3 Neuroradiologic Studies --MRI

Two separate studies have been done evaluating the ability of MRI to detect neuroanatomical changes produced by vigabatrin. In the first investigation involving only two dogs, the MRI procedure used was not capable of detecting pathological changes resulting from three months treatment with vigabatrin.

In a second study utilizing new technology, MRIs were obtained for each dog (8 treated, 4 control) at baseline and after 15 weeks of dosing with vigabatrin (300 mg/kg/day); MRIs were repeated in three treated and two control dogs at weeks 5 and 12 after discontinuation of dosing. MRI was performed at 1.5 Tesla on a GE Signa magnet, using the GE extremity coil. Sagittal and coronal images were obtained with T₁ and T₂ weighting. After dosing week 15, all treated dogs showed increased T₂ and decreased T₁ weighted signal, prominent in and surrounding the columns of the fornix, and less obvious in discrete areas extending throughout the thalamus, known to show microvacuolation in dogs dosed chronically with vigabatrin. Control dog MRIs and histopathology were unremarkable.

Thus, as a result of advances in MRI technology, a new technique was used in a second study. It appears that this technique will be capable of detecting intramyelinic

edema produced in dogs by vigabatrin, although its usefulness in humans has not been validated.

Scans in the two US placebo controlled studies were reviewed by independent radiologists who found no changes suggestive of IME on any scan in either group. An independent neuroradiologist from the ██████████ reviewed the scans from one of these studies (C025) for the FDA. He agreed with the absence of findings in these patients.

b(4)

The negative findings might be due to early sampling and the relatively small number of patients receiving high dose treatment just as much it would to lack of toxicity from this drug. As in the case of the evoked potential studies, this is not a validated screening method intramyelinic edema in humans, although there was hope that it would prove to be a valuable noninvasive technique.

Part 4 Clinical Studies

Psychosis:

The literature on vigabatrin is filled with reports of psychiatric and behavioral adverse events. No one syndrome emerges, but psychosis, hallucinations, aggression, and behavior changes are prominent. Suicides account for 10% of the total deaths associated with vigabatrin. In the NDA, routine reports, withdrawals, hospitalizations and deaths have included the gamut from frank psychosis to personality change and hyperactivity. In controlled clinical trials, adverse events in vigabatrin treated patients were reported with a frequency of up to two-fold that of the placebo group. See the table below.

<i>Overall Occurrence of Adverse Events Associated with the Psychiatric System Organ Class</i>		
Clinical Studies	All Adverse Events (%)	
	VGB	PLAC
US Controlled-Epilepsy (CRF)	90/222 (40.5)	41/135 (30.4)
Non-US Controlled-Epilepsy (CRF)	4/20 (20.0)	1/19 (5.3)
Non-US Controlled-Epilepsy (ARF)	39/199 (19.6)	20/172 (11.6)

Patients with serious adverse psychiatric ADRs were supposed to have been excluded from enrollment in US trials C024 and C025. Nevertheless, patients with psychiatric history were admitted. There was a somewhat higher incidence of psychiatric-related adverse events in patients receiving vigabatrin compared to placebo irrespective of

psychiatric history. The incidence of individual psychiatric adverse events for vigabatrin versus placebo was not influenced by psychiatric history.

Dropouts were evaluated to identify psychiatric adverse events severe enough to result in discontinuation of treatment. The overall dropout rate from psychiatric adverse events in studies C024 and C025 was 10.4% and for placebo it was 2.2%.

Effect of a History of Psychiatric Illness on the Dropouts in US Controlled Studies. (71754-3-C-024, 71754-3-C-025) Combined						
Protocol No. Report No.	Total Patients by Treatment	Total Dropouts From Adverse Events	Dropouts No Psychiatric History		Dropouts Psychiatric History	
			Any AE (%)	Psychiatric* AE (%)	Any AE (%)	Psychiatric* AE (%)
Totals	PLAC=135	3/135 (2.2)	3/110 (2.7)	1/110 (0.9)	0/25 (0)	0/25 (0)
	1 g VGB=46	3/45 (6.7)	3/35 (8.6)	1/35 (2.9)	0/11 (0)	0/11 (0)
	3 g VGB=136	13/135 (9.6)	9/108 (8.3)	6/108 (5.6)	4/28 (14.3)	3/28 (10.7)
	6 g VGB=44	8/41 (19.5)	7/34 (20.6)	1/34 (2.9)	1/10 (10.0)	0/10 (0)
All Vigabatrin	222	23/222 (10.4)	19/173 (11.0)	9/173 (5.2)	5/49 (10.2)	3/49 (6.1)

Dropouts were then evaluated for presence of a prior psychiatric history. Overall, the rate of discontinuation for behavioral adverse events in the patients with no previous psychiatric history (9/173; 5.2%) was nearly the same as the rate in patients with a psychiatric history (3/49; 6.1%). The firm interprets these data suggest that patients with a psychiatric history may take vigabatrin with the same risk as patients without a psychiatric history.

The sponsor did not perform similar analyses for hospitalizations, serious adverse events and death due to psychiatric events in patients treated with vigabatrin. Some of that information is available in the NDA, but in scattered form. For example, the incidence of hospitalizations overall for psychiatric ADRs is not known, but in the US controlled studies 4/222 patients on vigabatrin and 0/135 patients on placebo were hospitalized for psychiatric adverse events. In uncontrolled US studies, the incidence was 8/414. The reasons for hospitalization included paranoid reaction, personality change, hallucination, suicide attempt, agitation, emotional lability, depression and anxiety.

Information on hospitalization was generally not available in nodus CRF studies, except occasionally. Of the few reported hospitalizations 10 patients are known to have been hospitalized because of psychiatric adverse events.

In the postmarketing group, over 50% of hospitalized patients were hospitalized for psychiatric events, including psychosis, hallucination, hypomania, suicide attempt, acute brain syndrome, behavior disorder, depression, agitation, withdrawal, social degeneration, or paranoid psychosis.

The psychiatric adverse events associated with vigabatrin are not subtle. Their

apparent frequency and manifestations are somewhat unexpected in this population, particularly as compared to comparable recent NDA databases such as gabapentin (2096 patients). Psychiatric adverse events are associated with dropout from clinical studies, as well as hospitalization and death. Their actual frequency cannot begin to be generated based on the problems associated with reporting in this NDA.

The underlying neuropathological substrate (direct toxic or vasculitic for example) for these adverse events is unknown and remains unevaluated. One can only speculate whether this is the human clinical correlate of the neuropathologic lesions seen in animals.

Neurologic

Neurologic manifestations of vigabatrin toxicity are also found throughout the literature, ranging from encephalopathy and coma to confusion, ataxia and extrapyramidal disease. No one syndrome emerges, though several are prominent. The sponsor has not characterized the neurologic adverse events well.

The incidence of neurologic adverse events reported routinely in controlled clinical trials is as high as psychiatric events. Complaints such as amnesia, confusion, impaired concentration, and abnormal coordination occurred with a frequency of 2-3 higher in the vigabatrin treated group than the placebo group.

CNS adverse events accounted for 16% of dropouts from controlled US epilepsy studies, 20% from US open label studies, 4% from CRF nonUS studies, and 8% from nonUS ARF studies. The low incidences in the European data bases are likely a function of passive reporting practices.

In addition to encephalopathy, which is widely known from the epilepsy literature, ataxia (abnormal coordination) is reported often and has been a clinical finding preceding death in at least 3 of the autopsied cases described earlier.. There have also been rare reports (3) of patients with treatment emergent demyelinating disease associated with vigabatrin although details are limited.

Status Epilepticus

The firm was asked to do a specific analysis of *status epilepticus* as an adverse event. Since status was not considered an adverse event by many of the European investigators two strategies were utilized to identify patients who suffered from *status epilepticus* in clinical trials with vigabatrin. All adverse events reported were searched by terms including convulsions, seizures, status, absence, therapeutic effects unexpected, therapeutic response decreased, withdrawal convulsions and condition aggravated. The verbatim descriptions in the entire adverse event database were also reviewed. All available clinical study reports and case report forms for patients who died or discontinued because of an adverse event were reviewed.

A total of 36 patients identified to have status epilepticus by these searches is reported. Of these patients, 26 patients received vigabatrin, three received placebo, three received no treatment, and treatment is unknown for four patients. This incidence, if accurate, is not unexpected in this size database for an epileptic population.

9.5.2 Peripheral Neurotoxicity

There are frequent reports of parasthesias, loss of reflexes, stocking glove neuropathy, or peripheral neuropathy in patients treated with vigabatrin. In the placebo-controlled US epilepsy studies, treatment emergent parasthesias and hyporeflexia were seen at an incidence that was >3-fold higher in treatment than placebo groups (refer to section 9.4) but only occasionally were given as a reason for withdrawing from studies (3(6%) from US Controlled studies).

Peripheral neuropathy was occasionally noted as a reason for hospitalization in the CRFs but it was not displayed in the overall tabulations. Some of the many symptoms reported included numbness, "dead legs" peripheral neuropathy, stocking glove neuropathy, tightness and tingling in the extremities, decreased DTR's, parasthesias, and loss of vibratory sense.

The above symptoms have not been correlated with careful examinations, to validate the findings. In addition, these patients have been insufficiently evaluated electrically to know if a peripheral neuropathy exists, that it can be ascribed to vigabatrin alone, if it is axonal or demyelinating, if it is due to toxic effect or vasculitis, or if it is reversible.

The sponsor has done no formal analysis to evaluate the numerous adverse events which suggest the possibility of peripheral neuropathy. The sponsor should look at concomitant treatment in placebo-controlled trials to determine if other drugs (such as phenytoin) may be responsible for the findings. It is unlikely, however, since randomization should have allocated phenytoin equally to placebo and treatment groups. The firm should evaluate patients with hyporeflexia and sensory loss for NCV and EMG changes, determine if any studies such as peripheral nerve biopsy have been done in these patients. A number of patients were known to have been hospitalized for symptoms of peripheral neuropathy, but these results could not be located in the NDA.

9.5.3 Eye Findings in Vigabatrin

Clinical Studies

Evaluation of possible ocular toxicity from Vigabatrin has been initiated by the sponsor based on the theoretical possibilities that GABA disrupts the

normal inhibitory pathways present in the visual system, and also due to the normally high concentration of GABA in the retina. Further, retinal dose-dependent toxicity in albino Sprague Dawley rats exposed to vigabatrin has been reported. These lesions were characterized by focal, multifocal, and occasionally diffuse disorganization of the outer nuclear layer. In contrast to the neatly organized columns of rod and cone layers of control retinas, there were foci and areas of disorganization with nuclei extending into the zone normally occupied by the dendritic phototransduction elements of these cells. These findings have not been reproduced, however in pigmented rats, dog or monkey. The firm has suggested that the lesions found in the albino rats were due to exposure to light, however this is speculative, and presumably the control rats were also exposed to similar conditions of lighting.

Nevertheless, an effort was made by the sponsor to evaluate this problem in humans by means of 6 month eye examinations performed (although not necessarily by an ophthalmologist) in a nearly 60 patient US uncontrolled study of variable duration. A similar study was conducted in Europe in which regular eye examinations were performed. The firm asserts that these studies confirm the absence of ocular toxicity in humans by virtue of the absence of any defined pathology. The recorded findings in US Study 97-006 suggest to this reviewer that there may be toxicity which has not been recognized, and therefore not well characterized by the firm. The prominent recorded findings⁴ in this study include vessel narrowing, vitreous cells, retinal drusen, retinal pigment clumping, and RPE dropout. Cataracts were also noted. While some of these findings may have been a function of age, others are seen in relatively young patients. Of note is that the mean age of this study is 36 years. In a comparable data base of epileptic patients who participating in a drug development program of the same time frame (NDA 20-235 Gabapentin), and of only slightly smaller proportion, a similar spectrum of eye findings was not reported. This may in part be due to the fact that in other NDAs careful examinations by ophthalmologists are not done regularly. In this US study 57 patients participated, and 45 had eye examinations. Of those 45, the positive findings are recorded in FDA's Table 1. Along with reports from other studies. There were 12 reports of vessel narrowing, some in combination with RPE changes or retinal drusen (15 reports), and lenticular changes (7 reports). Fundus photographs were known to be taken in 5 cases. Only two were obtained, and demonstrate retinal pigment epithelial loss and narrowing of retinal vessels.

⁴The information was derived from the CRF's which were ostensibly an extract of the ophthalmologists' records. In those cases where original ophthalmology records were available there is greater detail. Therefore the original eye examinations and fundus photos when available were requested of the firm.

The European "study" did not contain the same descriptive comments, and exams were either characterized as normal or abnormal with little opportunity to qualify the assessment. The firm has indicated that this was not one study but rather a conglomerate of many very small studies in the "ICS" database. There are no original case reports and therefore the results cannot be confirmed. There were a few definite changes from normal, however, including macular edema in a 19 year old, small papillomacular hemorrhage (called "optitis vasculitis") in a 31 year old. In addition to the above reports, there have been scattered reports of retinal detachment, retinal atrophy, RPE changes, and ischemic optic neuropathy received from postmarketing surveillance reports filed as safety reports through the IND.

While there may not be one discrete mechanism which one could evoke to explain all of these findings, they do indeed merit further evaluation.

In view of the preclinical history of myelin pathology, another troublesome finding associated with exposure to vigabatrin was that of optic neuritis. A number of patients in the postmarketing surveillance dataset reported optic neuritis. These patients did not consistently receive VER testing. The mechanism of optic neuritis has not been fully evaluated, however at least one investigator is of the thinking that his patient developed an ischemic optic neuropathy from an allergic vasculitis associated with vigabatrin.

An in-house FDA ophthalmology consultant observed that there was an apparent increase in cataracts in a relatively young age group with the suggestion of progression in the study. With nothing in the case study data submitted to indicate metabolic and /or genetic conditions that could be responsible for these findings she concluded that "there appeared to be an onset and progression of cataracts and microvascular abnormalities of retinal vessels in a relatively young population (20 to 39 age group) exposed to vigabatrin." She goes on further to state that "given the evidence in the non-clinical as well as clinical data, baseline ocular exams should be required prior to administration of this medication and routine follow-up evaluations to include slit-lamp and dilated funduscopy every 6 months in a controlled clinical trial." and that while no common pathophysiologic pattern was found, " there is compelling suggestive evidence of possible oculotoxicity which requires additional study."

FDA Table: Eye findings in NDA 20-427

	<i>STUDY</i>	<i>AE</i>	<i>EXPOSURE (days)</i>	<i>DOSE (gm)</i>	<i>Age</i>
5-001	97-005/6	Retina:Arteriolar Narrowing	427	4	61
		Decreased Macular Reflex	1771		

		Retina: RPE changes	1771		
5-006	97-005/6	Retina:Arteriolar Narrowing	427	2	56
		Retina: Drusen	427		
5-005	97-005/6	Vessels:Early AV Crossing Chg	est. 190	1	26
5-010	97-005/6	Small Nuclear Flecks OU	est 340	4	33
		Vitreous-tr cells OU; PVD OD	est 1042	"	
		Mild arteriolar narrowing	est 1229	"	
5-011	97-005/6	Retinal Vessels Abn Narrowing	706	3.5	35
5-015	97-005/6	Early PCS cataract OS	est 590	4	35
		Several macular drusen OD	"	"	
		RPE atrophy OS	est 1195	"	
		Pigment clumping peripherally OD	est 1684	"	
6-003	97-005/6	Change in L optic Nerve	est 1307	4	27
6-012	97-005/6	Retina: Abn Macular Changes	526	3	61
6-017	97-005/6	Two Vitreoretinal traction tufts OD	267	3.5	22
		Mild attenuation of arterioles	2231	3.5	
9-002	97-005/6	Diffuse conjunctival injection	est 1492	5	24
9-003	97-005/6	Retinal tear	est 1703	5	44
9-004	97-005/6	Macular wrinkling	1522	4	41
		Macular Drusen	1797	"	
9-007	97-005/6	Early AV depression	est 1326	4	39
		posterior capsular opacity	est 2208	"	
9-012	97-005/6	Palbebral conjunctival follicles inc.	est 872	4	26
9-015	97-005/6	Cornea-punctate staining	est 383	4.5	21
		Folliculosis	est 794	"	
		Inc. tear film breakup	est 1536	"	
10-004	97-005/6	Nuclear sclerosis 1+	est 462	4	60
		small vacuoles posterior cortex OU	"	"	
		Retina:Arteriolar Narrowing	1423		
10-006	97-005/6	Narrowing of Retinal Arterioles	1151	4	35
10-007	97-005/6	Photophobia reported	est 981	3	35
		Retina:Drusen	1844	"	
		Retina:RPE changes	2372	"	
10-010	97-005/6	Conjunctival injection	est 1415	4	30
		Retina:Narrowed Arterioles	1483	"	
		Retinal Tear	2558	"	
11-002	97-005/6	Debris from blepharitis in tear films	est 491	3.5	20
		Vitreous cells tr OU--anterior	est 1385	"	
<i>PID</i>	<i>STUDY</i>	<i>AE</i>	<i>EXPOSURE (days)</i>	<i>DOSE (gm)</i>	<i>AGE</i>
11-003	97-005/6	Cornea with punctate staining	est 2790	4	23

11-004	97-005/6	Nuclear Sclerosis 1+ depigmentation anterior to equator trace pigment cells OU (vitreous)	est 462 " "	4 " "	60
11-005	97-005/6	Marked AV crossing OU Macula with fine Drusen Tear film with mucoid discharge Minimal nuclear sclerosis OU RPE changes OD	349 903 est 2264 " 2323	4.5 " " " "	35
11-006	97-005/6	Decr tear breakup OU Few small drusen OU Corneal Guttata centrally OU slight lenticular yellowing OU	est 383 " est 1298 est 2397	3 " " "	38
11-007	97-005/6	2+ Pigmented vitreous cells OU Retinal Schisis	258 258	4 "	32
11-008	97-005/6	Narrow Arterioles RPE dropout inferior macula OD White exudative material OS Decreased tear breakup OU	272 " " "	4 " " "	54
11-009	97-005/6	Macula with minor RPE changes Blepharitis with poor tear breakup	230 "	3.4 "	48
11-011	97-005/6	Retinal pigmentary disturbance Unusual hypersensitivity to light	272 "	3 "	27
11-013	97-005/6	Pigmented corneal guttata OU Vitreous syneresis OU Vitreous with anterior cells OS Blepharitis Posterior vitreous detachment lens changes OS Debris in tear film OU	est 280 est 479 est 926 " est 1605 est 2373 est 2524	4 " " " " " "	38
12-002	97-005/6	Posterior subcapsular vacuole Small drusen-like opacities Tear dysfunction OU	est 2210 " est 2384	3 " "	27
12-005	97-005/6	Punctate cortical opacities OU	est 454	4	30
12-009	97-005/6	Mild RPE clumps in maculas OU Perifoveal drusen-like opacities Corneal guttata OU Retina: small glial proliferation	209 est 389 " 1659	3 " " "	31
12-006	97-005/6	Corneal Guttata OU	est 441	4	39
12-010	97-005/6	Optic nerve atrophy OU	est 344	4	34
12-011	97-005/6	Retinal Tear	1980	4	27
PID	STUDY	AE	EXPOSURE (days)	DOSE (gm)	AGE
12-011	97-005/6	Retinal Tear	1980	4	27

		Retina: Drusen	2824		
12-012	97-005/6	Retina: Evulsed vessels	225	4	31
		Retina: RLF	225		
W-030-039	97-WUK14	Posterior vitreous detachment	est 388	2	44
30430406*	097-306	Optic papillomacular hemorrhage, sm	est.486	3	27
		"Optitis vasculitis"	"	"	
31730716*	307	Phosphenes in visual field--abn ERG	30	2	47
407332505*	97WFR04	Cataract	est 378	1	3
		Posterior Vitreous detachment	unk	"	
25229*	252	Increased optic atrophy--dec visual acuity	unk	unk	34
30430442*	097-306	Scotoma	est 200	3	32
25935*	259	Retinal detachment	unk	unk	24
93012550	VGSTMUMF111	Retinal detachment	unk	3	24
9204204	VGSTA00765098	Optic discs--temporal pallor OU Opacity --vitreous body OU Concentric bilat impairment fields Decreased visual acuity OD	5yr	3	30
94000904	VGZ9400-0305	Pallor of Optic disc Restriction of visual fields	est 330	3	9
93000643	VGZ930102238	Atrophy of Retina	unk	unk	37
93012587	VGSTMUMF-136	Optic Vasculitis Vision Abnormal	1.2 yrs	3	26

In the US safety study 97-006 there is a high incidence (26%) of vascular narrowing in patients who have received vigabatrin. While this is not placebo controlled data it is unexpected in a population with an average age in the mid 30s. It is particularly troublesome when one considers the neuropathologic data in which >40% of patients had some evidence to suggest perivascular activity or ischemic lesions suggesting microinfarcts.

It was initially difficult to reconcile the findings in the US safety study with the almost normal European data. Certainly numerous postmarketing reports have been received which include atrophy of the retina, changes in the macula, allergic papillitis and vascular changes at fovea. With regard to the European eye study which actually consists of many studies, some up to 15 years old, the original CRFs are not available for review. These data have been transcribed to ICS forms in conjunction with the investigators, sometimes contemporaneously, sometimes not. This data does not meet the standard for affirmative evidence. If there had been data, which could be reviewed and verified, a normal eye study would have been quite convincing and would provide some weight against the very disturbing findings in US Study 097-

005/6. However this was not the case, so that the US Study must stand on its own as preliminary and unopposed evidence for ocular toxicity.

The presence of vascular findings in the retina raises questions as to whether similar vascular constriction is occurring in brain or other organs (peripheral nerve, kidney, skin, other). The sponsor has not addressed this.

9.5.4 Hepatic Necrosis

Because of the reports received through the IND safety reporting requirements, a number of cases of fatal hepatic necrosis as well as nonfatal cases came to the attention of the FDA. The sponsor was asked to include these in the safety update and to do analysis of these for the record. They were included in tabular form but no analysis was done. There appeared to be a considerable range in exposures associated with hepatitis, from 4 days to 6 years with the median at 8.5 months. Routine liver function studies appear not to have been done, and there fore no clear indication of a warning was observed in these cases. Of the reported cases 7/12 were fatalities. Approximately 50% of all cases reported were 10 years of age and under.

HEPATIC FAILURE ASSOCIATED WITH VIGABATRIN

PID	Age	Dose	Rx	Clinical Hx	Death
09223130	10	1g	17m	Bili 47; Extensive hepatocellular necrosis with diffuse reticulin collapse, Surviving hepatocytes showed ballooning degeneration and fatty change. Proliferating cholangioles were seen in the periportal areas and there was inflammatory infiltrate of lymphocytes and neutrophil polymorphs	yes
94001440	34	2g	61/2 m	Increased LFTS preceded the patient's death by approximately 1 month. Pt experienced icterus, cholestasis and hepatic cytolysis. Biopsy done--not available	yes
94003033	10	1.5g	1 yr	jaundice; hepatic failure; survived 2 weeks in hospital; Subacute leukodystrophy with extensive parenchymal necrosis and considerable intrahepatic cholestasis	yes
93003075	38	g	4 days	Fulminant liver failure: Elevated bilirubin; hepatocellular necrosis with little inflammatory response.	yes
93004965	34	2-3g	7 m	Icterus, fulminant hepatitis. Hx of hyperpyrexia Autopsy results unavailable	yes
93013552	40	3.5g	6 yr	Hepatic coma, yellow atrophy of liver; Autopsy report unavailable	yes
09213654	7	g	8.5 m	Hepatocellular failure. Prior month history of ataxia and nystagmus. Icteric. Clinical improvement with d/c of medication	no
09108795	2	250 mg	unk	Hepatic coma Outcome unknown	unk

93014657	27	2g	4m	Icterus, cytolytic hepatitis. No liver biopsy. Recovered	no
93013516	8	g	8.5 m	Hepatorenal insufficiency, No biopsy; recovered on discontinuing medication	no
94000407	63	g	1 m	no description	no
unk	10	g	3 mos	Hepatocyte ballooning degeneration and fatty change proliferating cholangioles	yes

These cases were not analyzed with regard to prior warning signs, natural history of preceding LFTs, duration of treatment, dose or age..

Liver Function Studies in clinical trials

Clinical laboratory liver function values were generally unremarkable with the exception of reduction in SGPT. Significant decreases in SGPT were observed in US controlled in all vigabatrin dose groups (1 g, 3 g, and 6 g) when compared to placebo. It was seen at endstudy in uncontrolled extension studies also. A reduction in SGPT levels is believed by the sponsor to be a manifestation of transaminase inhibition by vigabatrin, as has been demonstrated in animal studies. The sponsor asserts that this is a clinically unimportant phenomenon and not an indication of a hepatotoxic effect.

One might speculate conversely that this transaminase inhibition renders the liver vulnerable to toxins which cannot be broken down. This could explain the incidence of hepatic necrosis associated with vigabatrin use. More must be known about this before intelligent labeling can be written.

9.6 WITHDRAWAL PHENOMENA/ABUSE POTENTIAL

Withdrawal Phenomena

Seizures

Withdrawal seizures have been documented in animal models using acute single dosing with vigabatrin in the amygdala-kindled rat. Withdrawal seizures have also been seen in humans in the context of clinical trials with vigabatrin during discontinuation of vigabatrin therapy. In these instances, withdrawal seizures including *status epilepticus* have occasionally occurred.

Sponsor proposed that there were 10 studies which by design were capable of demonstrating withdrawal phenomena. These included double-blind, placebo-controlled studies, double blind crossover periods and double-blind, placebo-controlled studies that had a structured follow-up period following cessation of vigabatrin. Seven of the studies were non-US studies in which patients were withdrawn from vigabatrin and crossed over to placebo. Two studies were conducted in the US; patients who did not continue into another protocol were tapered from vigabatrin. The 10th study was specifically designed to evaluate withdrawal effects of a single dose of vigabatrin.

For the purposes of evaluation, withdrawal seizures were defined by a twofold or greater increase in weekly seizures compared to the maximum seizure rate noted during baseline (or active therapy) within 4 weeks after vigabatrin was discontinued or after tapering was begun, or documented status epilepticus not present during baseline and occurring within 4 weeks after vigabatrin was discontinued or after tapering was begun. By this definition the incidence of withdrawal seizures in clinical trials ranged from 0-15.7%. The incidence of *status epilepticus* during withdrawal in controlled trials was 1.3%.

Behavioral Phenomena

There is a low incidence of acute behavioral events reported in clinical trials following withdrawal of vigabatrin, however the numbers of patients who are available for prospective reporting after the cessation of treatment is potentially very low also. In US controlled and uncontrolled studies there was an incidence of 2.7% (1/37), with the only reported event not related to vigabatrin. In Europe, the incidence of behavioral adverse events in the four studies in which these adverse events were reported was also low, 2.9% (6/207). The possible mechanism for behavioral changes following withdrawal from vigabatrin is unknown, although some investigators believe the incidence can be reduced through tapering, and treatment may include restarting vigabatrin. The spectrum of behavioral symptoms described with vigabatrin withdrawal included anxiety, confusion, hostility to hallucinations and paranoid reaction.

Abuse Potential

In animal studies, vigabatrin has produced CNS effects similar to drugs commonly associated with abuse. Vigabatrin potentiated the effect of thiopental on sleep and the analgesic activity of morphine. Vigabatrin attenuated morphine consumption in morphine-dependent rats; however, the effects of vigabatrin on morphine withdrawal symptoms were inconsistent. Other CNS effects at clinical doses of vigabatrin during animal studies included analgesia, muscle relaxation, sedation, reduction in food and water intake, and decreased motor activity and aggressive behavior. Higher doses of vigabatrin produced CNS excitation.

An ongoing study in Japan evaluated the dependence potential of vigabatrin in sub-human primates. The results are not yet available.

The abuse potential was not evaluated during human studies.

9.7 HUMAN REPRODUCTIVE DATA

In animal studies a number of safety findings have been reported. The most troublesome of these is the finding of intramyelinic edema in the brains of mice, rats, dogs and monkeys. The finding of intramyelinic edema has not been evaluated in the immature nervous system with the goal of determining if there is any deleterious effect on the ability to lay down myelin. The drug has been given to infants outside

of the US and there is some in utero exposure as will be discussed further. The sponsor at present is only seeking labeling in adults.

Also reported was the finding of disorganization of the outer nuclear layer of the retina in albino Sprague Dawley rats.

In animal models of reproductive safety, cleft palate was reported in New Zealand White rabbits. There have been reports of adverse pregnancy outcomes in humans in association with the use of vigabatrin during pregnancy ranging from spontaneous abortion to multiple congenital anomalies. Many of the pregnancies reported to date have had normal outcomes (approximately 50%), however the incidence of congenital abnormalities does appear to exceed the malformation rates reported among drug treated mothers with epilepsy as seen below in the table adapted from Sponsor's Table A "Malformation Rates in Live Births of Mothers with Epilepsy Related to whether or not Antiepileptic Drug Treatment was Given".

<i>Authors</i>	<i>Drug Treated Mothers with Epilepsy</i>		<i>Untreated mothers with Epilepsy</i>	
	<i>Pregnancies</i>	<i>Malformation Rate</i>	<i>Pregnancies</i>	<i>Malformation Rate</i>
<i>Monson 1973</i>	205	5.3%	101	2.3%
<i>Annegers 1974</i>	141	7.1%	56	1.8%
<i>Nakane 1980</i>	3703	7.1%	825	4.5%
<i>Dansky 1982</i>	114	15.9%	50	6.5%
<i>Lindhout 1992</i>	170	9.9%	14	7.0%
<i>Koch 1982</i>	89	10.0%	20	7.0%

There have been 72 pregnancies reported to this NDA. Of these, there were 7 spontaneous abortions, 16 infants with either obvious congenital malformations abnormal development on followup. For many of the pregnancies there is insufficient information to determine outcome. Of the remainder approximately 50% appeared normal. There have been reports of markedly abnormal pregnancy outcomes including, a child with multiple congenital abnormalities (intraventricular agenesis of the cardiac septum, pulmonary artery atresia, microcephaly and spina bifida), a child with microcephaly dorsolumbar menigomyelocele (aborted), cerebral dysgenesis and seizures, neonatal seizures of unspecified etiology, conjoint twins (aborted), diaphragmatic hernia with death in 24 hours. In addition more common and less severe abnormalities such as hypospadias and dysmorphism, cleft palate, club feet, delayed speech, congenital hip dysplasia, and strabismus.

The outcomes of the pregnancies associated with vigabatrin are summarized in the table on the next page which time of exposure and presence of concomitant AED use.

**Table: Pregnancy Outcomes in Vigabatrin-exposed Mothers
(NDA + Safety Update)**

<i>Pt ID</i>	<i>Dose VGB</i>	<i>Trimesters Exposed</i>	<i>Other AEDs</i>	<i>Comments</i>
21204	3g	1,2,3	CBZ	38/40 week ND male
—	unk	unk	unk	Bilateral cleft palate
93012948	unk	unk	CBZ, PB	Cardiac anomaly, Spina bifida, Microcephaly
101268	3g	3	VPA	Cerebral dysgenesis-seizures
█	2g	1,2,3	CBZ	Club feet-mild
21208	3g	1,2,3	CBZ	Congenital hip dysplasia
93-92-003	2g	1,2,3	CBZ	Died at 24 hrs/diaphragmatic hernia
93-92-008	unk	1,2,3	VPA, PRM, Propranolol	Died: intracerebral hemorrhage
21208	3g	1,2,3	CBZ	Difficulty feeding;SGA; microcephaly;undescended testicles;strabismus, congenital hip dysplasia
█	3g	1,2,3	CBZ, CLZ, PB	Elective CS (no information about infant)
0753160	4g	1,2,3	CBZ	FT
—	unk	unk	unk	FT (little information)
█	unk	1,2,3	CBZ	FTN
1355038	unk	unk	unk	FTND
308055	unk	1	unk	FTND
█ 24-05-71	1g	1,2,3	CBZ	FTND
█ -02-61	1g	2,3	CBZ	FTND
-25 yrs	3g	1,2,3	VPA	FTND female
3-4-57	4.5g	1st only	PHT, LTG	FTND female
615964	1g	1,2,3	CBZ, CLB, PB	FTND female
64-87-00106	1g	1st only	CBZ, PB	FTND female
77/7738	unk	1st only	unk	FTND female
909785	3g	1,2,3	PB	FTND female
91-033	1g	1,2,3	CBZ	FTND female
94-103	3g	1,2,3	VPA	FTND female
█	1g	1,2,3	unk	FTND female
█	unk	1st only	CBZ	FTND female
UK07	1g	1st only	CBZ, PHT	FTND female
UK09	2g	1st only	CBZ	FTND female
UK11	3g	1,2,3	VPA	FTND female
UK12	1g	1st only	PHT	FTND female
UK13	1.5g	1st only	CBZ	FTND female
—Age 20	1g	1	CBZ, PB	FTND male
30430410	3g	1st only	CBZ, PHT	FTND male
56-92-001	2.5g	1st only	none	FTND male
781002	unk	1,2,3	unk	FTND male
9-12-64	1-2g	1,2,3	CBZ, VPA, CLZ	FTND male
91-062	1.5g	1,2,3	CBZ	FTND male
959378	3g	1,2,3	PHT	FTND male
96-92-00214	2g	1,2,3	CBZ	FTND male
█	3g	1,2,3	none	FTND male
█ C-S	2.5g	1,2,3	CBZ, CLB	FTND male

b(6)

b(6)

b(6)

██████	unk	Ist only	PRM, PB	FTND male
1-05-69	4g	1,2,3	CLB	FTND male
██████	1g	Ist only	CBZ, PHT	FTND male
UK06	4g	1,2,3	CBZ, CLB	FTND male
0909785	3g	1,2,3	PB	FTND-strabismus
25807	3g	1,2,3	PB, CBZ, VPA	Hyperkinetic/ delayed speech
██████	2.5g	1,2,3	CBZ	Hypospadias , clinodactyly, dysmorphism syndrome,
93-89-001	2g	1,2,3	unk	Neonatal seizures (no further information)
93-92-002	5g	1,2,3	OCBZ	No information
93-92-005	unk	1,2,3	unk	No information
██████	3g	>1,2,3	PHT	No information
██████	1.5g	1,2,3	unk	No information
9400-1377	unk	unk	VPA	Normal
██████	3g	1,2,3	PB, CLP	Normal male (C-section)
93-92-004	unk	unk	unk	Premature (no further information)
93-92-001	unk	1,2,3	CBZ	Premature; maternal diabetes
93-92-002	5g	1,2,3	OCBZ	Second pregnancy, No information
303301	3g	Ist only	PB	Spontaneous abortion
93-92-007	unk	Ist only	CBZ, VPA	Spontaneous abortion
██████	1g	Ist only	CBZ, LTG	Spontaneous abortion
██████	1.5g	Ist only	CBZ, VPA	Spontaneous abortion
UK08	4g	Ist only	CBZ, PHT	Spontaneous abortion
UK16	3-2g	Ist only	CBZ	Spontaneous abortion
8-7-50	2g	Ist only	CBZ	Spontaneous abortion
—	unk	unk	unk	Therapeutic abortion
92-037	unk	unk	unk	Therapeutic abortion
██████	3g	1	CBZ, PHT, PR	Therapeutic abortion
			M	
93-92-006	2g	1,2,3	unk	Twin pregnancy
64-92-00243	.5g	Ist only	CBZ, PB	Twins—conjoint at head
8650915	1g	1,2,3	CBZ	Twins-premature

While the known malformation rate calculated from the information gleaned from various sources was 12.5% (this does not include spontaneous abortions). The likelihood of spontaneous abortions occurring as the result of congenital malformations is high. It must also be pointed out that for many of the pregnancies there is little or no information with regard to fetal outcome provided. Therefore this rate of congenital malformations may be falsely low. Nevertheless as it stands it is still within the range reported for malformations in the sources quoted above.

Additional reports received through the IND 17,213 (Vigabatrin) have included the following reports:

Pt ID	Dose	VGB	Trimesters Exposed	Other AEDs	Comments
94007330	unk	unk	unk		Delayed speech at 3 years old
95000301	unk	unk	unk		Shuddering when handled
95000320	3g	1,2,3	none	VD	
94007123	unk	unk	VPA/cbz		Premature, Musculoskeletal prob

Discussion:

There are two questions that arise with this drug regarding intrauterine exposure. The first is that of teratogenicity in a general sense. The second question is whether prenatal exposure to vigabatrin affects myelination.

Consultation with FDA Division of Epidemiology was completed 2/21/95 with regard to the teratogenic potential of vigabatrin compared to currently available antiepileptic medications. It was concluded that while the data are somewhat limited, the spectrum of malformations is not substantially different from existing antiepileptic drugs with known teratogenicity (specifically carbamazepine). The limited pregnancy experience does not suggest risk beyond that seen with other antiepileptic agents, however additional data are needed. The incidence of twins is in excess of that expected.

A more careful review and analysis of the raw data by the sponsor is indicated as well as follow-up on all pregnancies. This is particularly important in view of the effect of this drug on myelin and its unknown effect on myelin deposition. In order to adequately inform the public of what is known about this drug, the information that is available must be made known to the FDA. There is no objective evidence that any attempt was made to determine the effect of this drug on myelination.

As in the long-term safety 97-005/6 study there is a disparity between the tabular information and the raw data (as well as the IND data). This undermines the conclusions drawn by the sponsor minimizing the malformation rate of this drug.

9.8 OVERDOSE EXPERIENCE***Animal Experience:***

The LD₅₀ for vigabatrin in mice and Sprague Dawley rats was estimated to be 2.8-3.3g/kg and 3-4g/kg respectively. The most consistent features of vigabatrin overdose in animals were sedation, decreased motor activity and catatonic appearance. Toxicity in most animals occurred within 13-117 minutes of exposure and regressed within 3-4 days.

Subacute toxicity studies were performed in mice, rats, dogs and monkeys. Symptoms varied by species but included emesis, anorexia, inhibition of body weight gain, diarrhea, convulsions (rodents), emaciation and death. Microvacuolation was noted histologically in mice, dogs and rats in various regions according to species.

Human Experience: There are seven known cases of human overdose with vigabatrin. No fatalities and one child with permanent sequelae were reported.

NDA Safety Database

Two cases of vigabatrin overdose were reported to the NDA through clinical trials.

- The first was a 26 year old man who had been taking vigabatrin for approximately 4 years, whose customary dose was 8.5g/day. He accidentally took 14 g/day for 3 days. Aside from vertigo and tremor he had no serious complaints and recovered without sequelae.
- The second case was an 18 year old woman maintained on vigabatrin 3-4g/day for 8 months who ingested 30 g of vigabatrin and 250 mg dipotassium chlorazepate in a suicide attempt. She was hospitalized in coma vigil, and lapsed into further unconsciousness, requiring assisted ventilation. She completely recovered with supportive therapy after 6 days.

Postmarketing Surveillance

There were 5 cases of overdose spontaneously reported through postmarketing surveillance. These contain little information. It is known that none of the patients died.

- A 6 year old little girl (weight not given) accidentally ingested 7.5 g of vigabatrin. The child's behavior and ability to communicate deteriorated. The child has had some permanent behavioral and cognitive sequelae. The child had some underlying developmental delay prior to the overdose. There is no information regarding MRIs or evoked potentials done.
- A female patient ingested 9g of vigabatrin and 4g of carbamazepine in a suicide attempt. She was hospitalized with loss of consciousness. No details about prior use of vigabatrin, treatment for overdose.
- A patient took 10g vigabatrin as a suicide attempt. No other information.
- A 44 year old female maintained on vigabatrin (dose and duration unknown) ingested 11g in a suicide attempt. There was no information provided regarding symptomatology. Patient recovered and continued on vigabatrin.
- A 27 year old woman ingested approximately 65g of vigabatrin in a suicide attempt. Symptoms reported included vertigo, agitation, headache, coma. Patient was treated with gastric lavage. The patient had recovered and did not require assisted ventilation by day 3.

There is scant information regarding these overdoses and no follow-up information available. It would be advisable to learn, particularly in the case of the child with

permanent sequelae whether the sequelae correlate with any structural lesions that could be demonstrated radiographically (MRI) or electrically (evoked potentials).

While the sponsor has collected the information passively, there is little attempt shown by the sponsor to pursue the cases for further insights that might benefit patients of further overdose, particularly with regard to the issue of central neurotoxicity.

These cases illustrate only that toxicity can occur at even low doses. Coma was reported at 9g, 30g and 65g of vigabatrin. In the first two cases, however overdose was associated with other medications. Permanent sequelae was only reported in the child, however, with the paucity of information available as well as the lack of follow-up, certainly other sequelae might have simply been missed in other cases.

9.8 SUMMARY OF DRUG INTERACTIONS

Reviewer's note: Much of the information upon which the sponsor relies for analysis of drug interactions is based on literature reports or gleaned from clinical studies not primarily designed to look at drug interactions, not primarily from formal interaction studies.

● DRUG DRUG INTERACTIONS

Effect of vigabatrin on PK of antiepileptic drugs

There have been no formal studies investigating the potential interaction between vigabatrin and carbamazepine, phenobarbital, or valproic acid. NonUS studies have indicated that vigabatrin has not effect on barbiturate levels. However, in two controlled US studies barbiturate levels were significantly reduced by vigabatrin vs. placebo. In Study C024, barbiturate levels were reduced by 8.5% compared to an increase of 2.1% in placebo patients. In Study C025, barbiturate levels were reduced 16.2% in vigabatrin patients and increased 19% in placebo patients. Carbamazepine levels appear to be unaffected by vigabatrin. Valproic acid levels may sometimes be decreased. There have been isolated reports of interaction between vigabatrin and these agents. There are no reports of interaction between vigabatrin and oxazolidones and succinamides. There appears to be no interaction between clonazepam and vigabatrin based one interaction study.

An interaction exists between vigabatrin and phenytoin, demonstrated in formal interaction studies and confirmed by data from the two US controlled clinical trials. Vigabatrin causes a 16-33% mean reduction in plasma phenytoin concentrations.

Effect of antiepileptic drugs on the PK of vigabatrin

The effect of adding drugs to vigabatrin at steady state has not been evaluated.

● DRUG-DISEASE INTERACTIONS

Renal Disease: Because vigabatrin is 82% excreted the influence of impaired renal disease was studied formally by the sponsor. (Refer to section 7.0 Human Pharmacology). Clinical trial data added no new insights.

Psychiatric Disease: (Refer to section on special safety issues, psychiatry) It appears that the incidence of psychiatric adverse events occurring in association with vigabatrin increases with a prior history of psychiatric disease. The firm has not evaluated these sufficiently to determine if new psychopathology occurs in these patients or if underlying conditions are exacerbated. This is a safety issue needing further evaluation.

Hepatic disease was not evaluated.

● DRUG DEMOGRAPHIC INTERACTIONS

Since the population studied in this program was so homogeneous, the interactions between this drug and demographic variables was not studied. There was sufficient balance, however, between the sexes that male female differences could be studied. There appeared to be no such interaction. Issues such a catamenial epilepsy were not addressed. While no safety data are available in the extremes of age, a single study in normal elderly males has evaluated the PK of vigabatrin. Renal clearance was 33% less in elderly subjects compared to normal male controls. The pediatric population was not studied in a manner sufficiently systematically to yield reasonable safety information regarding selective safety issues in children versus adults..

9.9 SERIOUS ADVERSE EVENTS

Reviewer's note: The NDA and safety update lacks an overall sponsor's analysis of serious adverse events.

An adverse events is considered serious for purposes of reporting to the IND (21 CFR 312.32(a)) if it is "fatal or life threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose." Such serious adverse events would be reported, in turn, to the NDA. Some serious adverse events have been described in various sections of this NDA and are among the reasons for attrition from studies and hospitalization. Congenital anomalies were included in the section on human reproduction. Overdoses were discussed in the section of overdose. Special groups of adverse events, some requested by the FDA are found in one section which includes status epilepticus, psychosis, and neurotoxicity. However serious adverse events which did not require hospitalization, lead to congenital anomaly or overdose are not discussed anywhere as a unit, for example, pancreatitis, blindness, demyelinating disease, peripheral neuropathy, glomerulonephritis, and so on. There is no way to know if sponsor has reported all

serious adverse events, such as cancers or those adverse events which led to permanent disability in various parts of the NDA.

The sponsor felt that most serious adverse events led to hospitalization and these were presented as a unit . A summary of hospitalizations will be presented below. There are no case report forms or narrative summaries for these unless the patients withdrew from studies.

Hospitalizations due to Adverse events

US Epilepsy trials (N=443)

In all US epilepsy studies a total of 85 (19%) patients were hospitalized due to adverse events. This is unexpectedly high.

In the US controlled clinical trials for epilepsy a total of 15 patients required hospitalization because of adverse events. Of these, six vigabatrin and no placebo patient hospitalizations were thought by the sponsor to be related to treatment and were exclusively psychiatric and neurologic. These included *status epilepticus*, convulsions (grand mal or nonspecified), depression, personality change and psychosis. However if all adverse events in this group are considered, the organ systems with the greatest number of vigabatrin patients reporting adverse events associated with hospitalization were: neurologic, respiratory, psychiatric and general. It is somewhat unexpected that the patients hospitalized with convulsions and status is not equally represented in the placebo group.

In the US uncontrolled clinical trials for epilepsy seventy vigabatrin patients required hospitalization because of adverse events. The sponsor attributes 15 of these hospitalization to treatment with vigabatrin and they were also exclusively psychiatric and neurologic (including autonomic). These included *status epilepticus*, convulsions, confusion, emotional lability, and depression. However if all adverse events are considered, the organ system yielding the greatest number of patients with adverse events leading to hospitalization were neurologic, psychiatric, gastrointestinal, respiratory, and neoplasms.

In summary, the most common reasons for hospitalization in US epilepsy studies included seizures, psychiatric events and other neurologic conditions.

Us NonEpilepsy Studies and NonUS CRF studies (N=1327)

Reviewer's note: It is important to recall here that 51% of the nonUS CRF database did not capture information on hospitalizations.

Thirty-one patients exposed to vigabatrin required hospitalization as a result of adverse events. The most common adverse events associated with

hospitalization were psychiatric and neurologic, specifically psychosis and convulsions.

NonUS ARF studies (N=1760 est)

Information on hospitalization was not collected in this group.

nonUS Compassionate Use (N=unknown)

Reviewer's note: It is important to recall that this group is of undetermined size and relied on passive reporting of adverse events, much in the same manner as the postmarketing surveillance group, but with perhaps even less rigor.

In this group 43 hospitalizations were reported as the result of ADRs while on vigabatrin. The most common causes of hospitalization were psychiatric and included: psychosis, "psychiatric disturbance", suicide attempt, hallucinations, behavior changes and confusion. Other reasons for hospitalization included worsening of seizures including *status epilepticus*.

Postmarketing Surveillance

150 patients experienced ADRs which met one or more criteria for serious ADRs. An additional 93 from the safety update (2/28/93-3/15/94) have experienced serious ADRs. The criteria used by the firm include

- Fatal or life threatening
- Permanently disabling
- Resulting in prolonged inpatient hospitalization
- Congenital anomaly
- Overdose
- Cancer

The majority of the serious ADRs were from England and France. Most were considered serious because they resulted in inpatient hospitalization. The most common reasons for hospitalizations were: psychosis, convulsions, confusion, aggressive reaction, depression, hallucinations, and behavior changes. Patients also withdrew because of malignant hyperthermia, new onset "hemophilia", visual problems (including macular changes), urinary retention, hypotension, hepatic necrosis, angioedema, allergic reaction, abnormalities of glucose metabolism, leukopenia, and hemolytic uremic syndrome.

In summary, for about half of the NDA safety database there exists some core information regarding hospitalizations. Psychiatric disturbances are frequent and will be discussed in a later section. Other serious adverse events leading to hospitalization included neurologic conditions, predominantly related to seizures.

Discussion of the Overall Safety of Vigabatrin:

A host of unanswered questions remain with vigabatrin. While a great deal of information has been provided in the NDA, much of it has not been carefully

screened, organized and analyzed. The eye findings and CNS pathology, for example, raise the spectre of a vasculitis, the incidence of which can only be achieved by speculation, but certainly exceeds 25-30%. More must be known.

Peripheral neuropathy, other neurological symptoms such as ataxia, encephalopathy, and psychosis should be more carefully worked out.

SECTION 10.0 OVERALL QUALITY OF THE DATA

There is some evidence in this NDA of inadequate disclosure of information in study reports. Certain issues relating to inaccuracy in reporting the data in two trials which were reviewed in great detail has led this reviewer to question the overall integrity of the data in this NDA. The two examples are discussed below:

Example #1

Study #097-006:

Evaluation of possible ocular toxicity from vigabatrin was initiated by the sponsor based on preclinical findings of retinal dose dependent toxicity in rodents. The lesions were characterized by focal, multifocal and occasionally diffuse disorganization of the outer nuclear layer. The firm suggested that perhaps the lesions could be explained by light exposure, but human studies were conducted, nevertheless. In an open label study of variable duration, **Study #097-006** ophthalmological examinations were conducted every 6 months in 45 patients. A similar study was performed in Europe. The firm asserts that **Study #097-006** confirms the absence of ocular toxicity.

Tabulations of ocular findings reported to the NDA which included those found in **Study #097-006** were incomplete and did not include 24/36 of the abnormal eye examinations documented in the case reports in this study. If the reviewer had relied only on the tabulations, 2/3 of the pathology would have been missed. Case reports for the European study are not available so that confirmation of these findings could not be achieved. In the appendix to this review, Attachment 1 contains FDA's table summarizing Eye reports in NDA 20-427 based largely on the results of **Study #097-006**, where starred entries represent those not found in the Sponsor's summary. There were 12 reports of vessel narrowing, some in combination of retinal pigment epithelial (RPE) changes or retinal drusen (15 reports), and lenticular changes (7 reports). The table (attachment 2) which follows, containing fewer reports, is the Sponsor's summary of findings in this NDA. The sponsor writes:

"Routine ophthalmologic examinations (external, ocular media, and retinal evaluation) were conducted in the long-term study, protocol 097006; in response to reported retinal changes seen in albino rats. All patients receiving vigabatrin at the time of their first examination served as their own controls. Seventeen (17) patients had treatment related ophthalmologic adverse events;

only 4 of these were retinal but not degenerative in nature (macular druse,retinal drusen, macula with fine drusen, and retinal vascular disorder). No evidence of ophthalmologic changes suggestive of retinal degeneration in humans has been found."

In summary, not all abnormal eye findings were tabulated. The problem did not seem to rest with any given site. If the case record forms had not been requested this information would not have been found. A similar European study has also been reported as normal, however there are no case record forms from which to reevaluate the conclusions. Had the data in the case record forms not been requested and reviewed, the overall impression of the safety of this drug with regard to the visual system might have been very different. The raw data prompted review by ophthalmologic consultants and will likely lead to increased surveillance of this drug with regard to the visual system until more is learned.

Example #2
Study #CO25

This was a double-blind, randomized, placebo-controlled, parallel group, dose-response study of vigabatrin in patients with uncontrolled complex partial seizures. The primary objective of this study was to determine the efficacy of vigabatrin at doses of 1, 3, and 6 g/day when added to currently prescribed antiepilepsy drug Endstudy compared to Baseline. In the protocol for this trial, additional antiepileptic drugs were allowed, but only in constant doses through all phases of the study.

Protocol violations included the use of additional antiepileptic medications above and beyond those claimed in the baseline period for the purpose of treating additional seizures. The sponsor did report these, however, the numbers of such protocol violations reported by the sponsor, and the handling of these in the report was not accurately represented. First, not all protocol violations involving medications were reported. The numbers of patients with protocol violations involving additional medications reported by the firm was 34 (Attachment 3, sponsors tabulation of protocol violations involving medications with antiepileptic properties). The number of patients with protocol violations involving medications with anticonvulsant properties found by this reviewer in examining the case record forms was 42. The firm claimed that "these patients were not classified as minor or major protocol violators because none of these patients received adequate dosing of the benzodiazepine to affect seizure activity." This reviewer found that investigators were using these medications, not only benzodiazepines but occasionally other antiepileptic medications, with the intention of treating additional seizures, and in some cases even documented a response. These patients with protocol violations involving medication were excluded in a reanalysis of the data by the firm as requested by the FDA. They did not alter the outcome of the trial.

Additional discrepancies between case record forms and sponsor's reports occurred in the actual counting of seizures. In some cases changes were made to the seizure counts in the case report forms. Sometimes "W" or "Z,, was assigned to a seizure count and changed by the medical monitor of MMD up to 2 years later. The magnitude of protocol violations that involved the primary outcome variable were minimized in the study report was not fully revealed by the sponsor, however the following language was used in the study report:

"Seizure Flurries. If seizure flurries occurred where there was no definite total number, the best estimate was given by the investigator. A comment was provided by the investigator to document the situation as clearly as possible. In some cases, the patient/investigator was unable to estimate the number of seizures in a flurry. In these cases, a neurologist at Marion Merrell Dow Inc estimated the number of seizures prior to unblinding. This was based on the patient's description of the seizure from the seizure history and review of any additional information from the study coordinator.

Frequently the number assigned by the MMD monitor did not make sense in the context of the kinds of seizure counts that the patient was able to generate during the study. Regardless, this was not divulged openly when the data was tabulated. There were numerous examples of this found in reading the case record forms as shown in attachment 5.

In addition it was noted that when some patients were hospitalized for seizures they did not have a seizure count generated during the hospital stay, and therefore increase in seizures would not have been counted into the seizure frequency.

These two studies may be isolated, however, they undermine this reviewer's confidence in the overall reliability of the data. The matter is currently under review with the Division of Scientific Investigations.

SECTION 11.0 LABELING REVIEW

While there are some elements of clinical efficacy and safety labeling which are at issue, more importantly there is insufficient data with which to effectively evaluate the safety portion of labeling. Therefore, final labeling review is deferred at this time.

SECTION 12.0 DISCUSSION AND CONCLUSIONS

Vigabatrin has been demonstrated to be effective as an adjunctive medication in the treatment of partial complex seizures at doses of 3g/day. No additional efficacy is found at doses of 6g/day or higher.

The sponsor has failed to provide adequate affirmative evidence of the drug's safety.

According to 21 CFR §314.125 (b)(4) The FDA may refuse to approve an application if there is insufficient information about the drug to determine whether the product is safe to use under the conditions prescribed, recommended or suggested in its proposed labeling. In the following five ways the sponsor has failed to provide sufficient reliable affirmative evidence about this drug's safety.

1. In spite of a large cohort of exposed patients the sponsor has failed to obtain "normal" data. The firm has exposed a large number of patients to this drug in an investigational context and has failed to obtain potential safety information from these exposures. There have been 3350 to possibly greater than 5000 patients exposed to vigabatrin in a premarketing setting. The NDA database contains prospectively collected routine safety data (such as routine EKG, urinalysis, and so on) as well as safety data with regard to possible neurotoxicity on only a fragment of these patients. By not evaluating these subjects, the sponsor has failed to show that they are normal.

What is ostensibly a large exposure base and a seemingly benign outcome (as the sponsor asserts) should and cannot be misconstrued as a sign of safety when there has been a failure to adequately look for abnormalities.

2. There is uncertainty about the integrity and completeness of the data upon which this application relies. While many adverse events are known, much of the data is retrospectively collected or gathered by passive reporting. There is no means by which one could ascertain how complete this is.

3. Inaccuracies in reporting the data upon which the sponsor relies for safety analysis. There are discrepancies between the raw data and the tabular summaries for even the core studies. Not merely in European database but also, as noted in section 10.0, in two major US studies, one safety and one efficacy study.

4. The sponsor has failed to explore important leads and follow up on important abnormal findings.

The firm has failed to follow up on important safety information such as the vascular narrowing seen in the eye findings, perivascular cellular response and infarcts noted in the neuropathologic data set, the overdose with sequelae, the abnormal evoked

potentials and the peripheral nerve findings to name a few. There has been a plethora of clinical CNS findings. The firm made no attempt to correlate findings with available screening techniques, such as MRI, evoked potentials.

5. The sponsor has failed to analyze important elements of safety data.

The most striking example of this is the fact that the serious adverse events are not analyzed by the sponsor.

SECTION 12.0 RECOMMENDATIONS

It is recommended by this reviewer that vigabatrin be deemed Not Approvable by virtue of the fact that the sponsor has not met its burden to establish this drug's safety.


Cynthia G. McCormick, MD
Cynthia G. McCormick, MD
Clinical Reviewer

Review completed March 2, 1995

Revised with editorial changes only on March 14, 1995

ATTACHMENT 1

FDA Summary of Eye Reports in NDA # 20-472

PID	STUDY	ADVERSE EVENTS	EXPOSURE (days)	DOSE (gm)	Age
5-001	97-005/6	Retina:Arteriolar Narrowing	272	4	61
		Decreased Macular Reflex	1771		
5-006	97-005/6	Retina: RPE changes	1771	2	56
		Retina:Arteriolar Narrowing	427		
5-005*	97-005/6	Retina: Drusen	427		
5-005*	97-005/6	Vessels:Early AV Crossing Chg	est.190	1	26
5-010*	97-005/6	Small Nuclear Flecks OU	est 340	4	33
		Vitreous-tr cells OU; PVD OD	est 1042 "		
5-011	97-005/6	Mild arteriolar narrowing	est 1229 "		
5-015*	97-005/6	Retinal Vessels Abn Narrowing	706	3.5	35
		Early PCS cataract OS	est 590		
6-003*	97-005/6	Several macular drusen OD	" "	4	35
		RPE atrophy OS	est 1195 "		
6-003*	97-005/6	Pigment clumping peripherally OD	est 1684 "		
6-012*	97-005/6	Change in L optic Nerve	est 1307	4	27
6-012*	97-005/6	Retina: Abn Macular Changes	526	3	61
6-017*	97-005/6	Two Vitreoretinal traction tufts OD	267	3.5	22
		Mild attenuation of arterioles	2231		
9-002*	97-005/6	Diffuse conjunctival injection	est 1492	5	24
9-003*	97-005/6	Retinal tear	est 1703	5	44
9-004	97-005/6	Macular wrinkling	1522	4	41
		Macular Drusen	1797 "		
9-007*	97-005/6	Early AV depression	est 1326	4	39
		posterior capsular opacity	est 2208 "		
9-012*	97-005/6	Palbebral conjunctival follicles inc.	est 872	4	26
9-015*	97-005/6	Cornea-punctate staining	est 383	4.5	21
		Folliculosis	est 794 "		
10-004	97-005/6	Inc. tear film breakup	est 1536 "	4	60
		Nuclear sclerosis 1+	est 462		
10-006	97-005/6	small vacuoles posterior cortex OU	" "	4	35
		Retina:Arteriolar Narrowing	1423		
10-007	97-005/6	Narrowing of Retinal Arterioles	1151	3	35
		Photophobia reported	est 981		
10-010	97-005/6	Retina:Drusen	1844 "	4	30
		Retina:RPE changes	2372 "		
11-002*	97-005/6	Conjunctival injection	est 1415	3.5	20
		Retina:Narrowed Arterioles	1483 "		
11-002*	97-005/6	Retinal Tear	2558 "		
11-003*	97-005/6	Debris from blepharitis in tear films	est 491	4	23
		Vitreous cells tr OU--anterior	est 1385 "		
11-003*	97-005/6	Cornea with punctate staining	est 2790		
11-004*	97-005/6	Nuclear Sclerosis 1+	est 462	4	60
		depigmentation anterior to equator	" "		
11-005*	97-005/6	trace pigment cells OU (vitreous)	" "	4.5	35
		Marked AV crossing OU	349		
11-006*	97-005/6	Macula with fine Drusen	903 "	3	38
		Tear film with mucoid discharge	est 2264 "		
11-007	97-005/6	Minimal nuclear sclerosis OU	" "	4	32
		RPE changes OD	2323		
11-007	97-005/6	Decr tear breakup OU	est 383	4	32
		Few small drusen OU	" "		
11-007	97-005/6	Corneal Gutta centrally OU	est 1298 "	4	32
		slight lenticular yellowing OU	est 2397 "		
11-007	97-005/6	2+ Pigmented vitreous cells OU	258	4	32
		Retinal Schisis	258 "		

FDA Summary of Eye Reports in NDA # 20-472

PID	STUDY	AE	EXPOSURE (days)	DOSE (gm)	AGE
11-008	97-005/6	Narrow Arterioles	272	4	54
		RPE dropout inferior macula OD	"	"	
		White exudative material OS	"	"	
		Decreased tear breakup OU	"	"	
11-009*	97-005/6	Macula with minor RPE changes	230	3.4	48
		Blepharitis with poor tear breakup	"	"	
11-011*	97-005/6	Retinal pigmentary disturbance	272	3	27
		Unusual hypersensitivity to light	"	"	
11-013*	97-005/6	Pigmented corneal guttata OU	est 280	4	38
		Vitreous syneresis OU	est 479	"	
		Vitreous with anterior cells OS	est 926	"	
		Blepharitis	"	"	
		Posterior vitreous detachment	est 1605	"	
		lens changes OS	est 2373	"	
		Debris in tear film OU	est 2524	"	
12-002*	97-005/6	Posterior subcapsular vacuole	est 2210	3	27
		Small drusen-like opacities	"	"	
		Tear dysfunction OU	est 2384	"	
12-005*	97-005/6	Punctate cortical opacities OU	est 454	4	30
12-009*	97-005/6	Mild RPE clumps in maculas OU	209	3	31
		Perifoveal drusen-like opacities	est 389	"	
		Corneal guttata OU	"	"	
		Retina: small glial proliferation	1659	"	
12-006*	97-005/6	Corneal Guttata OU	est 441	4	39
12-010*	97-005/6	Optic nerve atrophy OU	est 344	4	34
12-011	97-005/6	Retinal Tear	1980	4	27
		Retina: Drusen	2824	"	
12-012	97-005/6	Retina: Evulsed vessels	225	4	31
		Retina: RLF	225	"	
W-030-039*	97-WUK14	Posterior vitreous detachment	est 388	2	44
30430406*	097-306	Optic papillomacular hemorrhage, sm	est.486	3	27
		"Optitis vasculitis"	"	"	
31730716*	# 307	Phosphenes in visual field--abn ERG	30	2	47
407332505*	97WFR04	Cataract	est 378	1	3
		Posterior Vitreous detachment	unk	"	
25229	#252	Increased optic atrophy--dec visual acuity	unk	unk	34
30430442*	097-306	Scotoma	est 200	3	32
25935*	#259	Retinal detachment	unk	unk	24
93012550	VGSTMUMF111	Retinal detachment	unk	3	24
9204204	VGSTA00765098	Optic discs--temporal pallor OU	5yr	3	30
		Opacity --vitreous body OU			
		Concentric bilat impairment fields			
		Decreased visual acuity OD			
94000904	VGZ9400-0305	Pallor of Optic disc	est 330	3	9
		Restriction of visual fields			
93000643	VGZ930102238	Atrophy of Retina	unk	unk	37
93012587	VGSTMUMF-136	Optic Vasculitis	1.2 yrs	3	26
		Vision Abnormal			

ATTACHMENT 2

Table 3: Summary of Adverse Events Related to Retinal Disorders or Optic Atrophy or Optic Neuritis Contained in the Clinical Research Database

Patient Number/Protocol	Age/Sex	Preferred Term	Included Term	Verbatim Description	VGB Dose at Time of Event (g/day)	VGB Therapy Duration Prior to Event (years)	Outcome	VGB Related	Comments
25229	34/M	Optic atrophy	Optic atrophy	increased optic nerve atrophy	Not reported	Not reported	Not reported	Possibly	No additional data available
123701-P12	18/F	Optic neuritis	Optic neuritis	overdosage: optic neuritis	2.0-4.0	Not reported	Not reported	Possibly	No additional data available
005-001/097-006	61/M	Retinal disorder	Retinal disorder	decreased macular reflexes; decreased foveal reflex	4.0	2.22	Recovered	No	Concurrent illness VGB continued
005-006/097-006	56/M	Retinal disorder	Retinal disorder	retinal vessels narrowed	4.0	4.85	Uncertain	No	Concurrent illness VGB continued
005-011/097-006	34/M	Retinal disorder	Retinal vasc. disorder	retina-drusen	2.0	1.17	Uncertain	No	Concurrent illness VGB continued
009-004/097-006	41/M	Retinal disorder	Retinal vasc. disorder	retina-arteriolar narrowing	2.0	1.17	Uncertain	No	Concurrent illness VGB continued
010-004/097-006	60/M	Retinal disorder	Retinal vasc. disorder	retinal vessel - abnormal (arteriolar narrowing)	3.5	1.93	Recovered	No	Concurrent illness VGB continued
010-006/097-006	34/M	Retinal disorder	Retinal disorder	macular drusen	3.0	4.92	Uncertain	Possibly	VGB continued
010-007/097-006	35/F	Optic atrophy	Optic atrophy	retina-arteriolar narrowing	4.0	3.90	Alive w/ sequelae	No	Other, VGB continued
010-010/097-006	29/M	Retinal disorder	Retinal vasc. disorder	narrowing of retinal arterioles	4.0	3.15	Recovered	No	Concurrent illness VGB continued
011-005/097-006	35/M	Retinal disorder	Retinal vasc. disorder	pale optic disks	3.0	3.81	Recovered	Possibly	Not present at next clinic visit
011-007/097-006	31/M	Retinal disorder	Retinal disorder	retina: drusen	3.0	5.05	Recovered	Possibly	VGB continued
011-008/097-006	54/M	Retinal disorder	Retinal disorder	retinal tear	4.0	7.01	Recovered	No	Other, VGB continued
012-011/097-006	26/M	Retinal disorder	Retinal vasc. disorder	retina: narrowed arterioles	4.0	4.06	Alive w/ sequelae	No	Concurrent illness VGB continued
012-012/097-006	30/M	Retinal disorder	Retinal vasc. disorder	macula with fine drusen	4.5	2.47	Recovered	Possibly	VGB continued
				hypertensive retinopathy	4.5	0.96	Recovered	No	Concurrent illness VGB continued
				retinal schisis	4.0	0.71	Recovered	No	Old trauma/pathology VGB continued
				narrow arterioles	3.4	0.75	Uncertain	Possibly	VGB continued
				retinal drusen	4.0	7.7	Recovered	No	Other, VGB continued
				retinal tear	4.0	5.4	Recovered	No	Other, VGB continued
				retina: retrolental fibroplasia	4.0	0.62	Recovered	No	Concurrent illness VGB continued
				retina: evulsed vessels	4.0	0.62	Recovered	No	Concurrent illness VGB continued

Table 4: Summary of Serious Vision-Related Adverse Events Contained in the Global Product Safety Database

Global Product Safety Database ID (Patient ID)	Age/ Sex	Preferred Term	Included Term	Verbatim Description	VGB Dose at Time of Event (g/day)	VGB Therapy Duration Prior to Event	VGB Related	Outcome	Comments
93012550 (VGST-MUMF-111)	24/M	Retinal detachment	Retinal detachment	Retinal detachment	3.0	Not reported	Related	Resolved
09204204 (VGST-A007-65098)	30/M	Retinal disorder Eye abnormality Vis field defect Vision abnormal	Retinal disorder Eye abnormality Vis field defect Vision abnormal	Mild temporal pallor of the optic disk in both eyes Opacity of vitreous body in left eye Concentric bilateral impairment of visual field Decreased acuity in right eye	3.0	5 yrs	No	Not resolved, follow-up continuing	Visual damage pre-existed VGB treatment, therapy unchanged.
94000907 (VGZ-9400-0907)	9/F	Retinal disorder Vis field defect	Retinal disorder Vis field defect	Pallor of the optic disk Restriction of the visual field	3.0	11 months	Unlikely	Not resolved, follow-up continuing	Event pre-existed VGB treatment, therapy unchanged
94000305 (VGZ-9400-0305)	43/F	Retinal disorder Retinal Disorder Vis field defect	Retinal disorder Retinal Disorder Vis field defect	Pallor of the optic disk Pannetinal defect of the inner layer Bilateral concentric partial defect of the visual field	2.0	2 yrs	Possible	Not resolved, follow-up continuing	Therapy discontinued because of event
93000643 (VGZ-9301-2238)	37/F	Retinal disorder	Retinal disorder	Atrophy of retina	Not reported	Not reported	No	Unknown	demyelinating disease? pre-existed VGB treatment
93012238 (VGZ-9301-2238)	21/F	Retinal disorder Vis field defect Optic neuritis	Retinal disorder Vis field defect Optic neuritis	Peripheral retinal atrophy Tunnel vision	2.0	3 yrs	Possible	Not resolved, follow-up continuing	Therapy discontinued because of event
09205962 (VGST-A011-65127)	30/M	Optic neuritis Vasculitis allergic Vis field defect Optic atrophy Papilledema Vasculitis	Optic neuritis Vasculitis allergic Vis Field Defect Optic atrophy Papilledema Vasculitis opticus Vision abnormal	Anterior ischemic optic neuropathia Immune vasculitis Concentric visual field narrowing of left eye Partial atrophy of left optic nerve Papilledema Optic vasculitis	2.0	6 months	Probable	Resolved w/ sequelae	Therapy discontinued because of event.
93012587 (VGST-MUMF-136)	26/M	Vasculitis Vision abnormal	Vasculitis opticus Vision abnormal	Optic vasculitis Visual disturbances	3.0	1.2 yrs	Possible	Resolved	Therapy discontinued because of event

ATTACHMENT 3

Attachment 3
Sponsor's Table

Table 8-26. Summary of Patients Using Medications With Antiseizure Properties in Addition to Concomitant AEDs

Patient ID	Segment	Medication and Dose	No. Days	Indication
Placebo				
010-104	Segment III	Ativan 2 mg	4	Seizure Exacerbation
010-105	Segment I	Tranxene 7.5 mg	8	Anxiety
	Segment II	Tranxene 7.5 mg	2	Anxiety
	Segment III	Tranxene 7.5 mg	6	Anxiety
011-108	Segment III	Tranxene 15 mg	2	Seizure Clusters
069-001	Segment I	Valium 5 mg	4	Patient Feeling Strange
	Segment II	Valium 5 mg	1	Patient Feeling Strange
072-001	Segment I	Diamox 250 mg	PRN	Pre-Menses X 5 days
	Segment II	Tranxene 3.75-7.5 mg	PRN	Anxiety
	Segment III	Diamox 250 mg	PRN	Pre-Menses X 5 days
		Tranxene 3.75 mg	PRN	Anxiety
		Diamox 250 mg	PRN	Pre-Menses X 5 days
072-007	Segment II	Tranxene 7.5 mg	1	Anxiety
	Segment III	Tegretol 100 mg	1	Post Seizure; extra dose
		Tranxene 7.5 mg	4	Anxiety
089-005	Segment I	Tranxene 3.75 mg	85	Anxiety
	Segment II	Tranxene 3.75 mg	43	Anxiety
	Segment III	Tranxene 3.75 mg	86	Anxiety
1 g Vigabatrin				
006-104	Segment I	Mysoline	PRN	Seizure Clusters
010-102	Segment I	Valium 5 mg IV	≤ 1	Severe Secondary Seizure
010-107	Segment I	Xanax 0.5 mg	PRN	Anxiety
	Segment II	Xanax 2 mg	PRN	Anxiety
	Segment III	Xanax 0.5 mg	PRN	Anxiety
010-113	Segment I	Xanax 0.25 mg	2	Anxiety
	Segment II	Tranxene 3.75 mg	2	Anxiety
011-105	Segment I	Tranxene 3.75-11.25 mg	17	Seizures
	Segment II	Tranxene 3.75-7.5 mg	5	Seizures
	Segment III	Tranxene 3.75-7.5 mg	50	Seizures
011-114	Segment I	Ativan 2-4 mg	3	Seizure Prevention
	Segment II	Ativan Unknown	1	Seizure Prevention
	Segment III	Ativan 2 mg	7	Seizure Prevention
011-118	Segment I	Tranxene 3.75 mg	PRN	Seizure/Anxiety
	Segment II	Tranxene 3.75 mg	PRN	Seizure/Anxiety
	Segment III	Tranxene 3.75 mg	PRN	Seizure/Anxiety
013-008	Segment III	Phenobarbital 130 mg	1	Prolonged Seizure
	Segment III	Valium 15 mg	1	Prolonged Seizure
069-002	Segment III	Valium 10 mg IV	≤ 1	Molar Extraction
072-010	Segment III	Diamox 250 mg	1	Water Retention
089-002	Segment I	Ativan 1 mg	85	Chest Pain W/Anxiety
	Segment II	Ativan 1 mg	45	Chest Pain W/Anxiety
	Segment III	Ativan 1 mg	84	Chest Pain W/Anxiety
3 g Vigabatrin				
010-103	Segment I	Tranxene 7.5 mg	9	Seizures and Anxiety
071-004	Segment II	Ativan 1-2 mg	9	Sedation
	Segment III	Ativan 1-2 mg	38	Sedation/Status

Table 8-26. Summary of Patients Using Medications With Antiseizure Properties in Addition to Concomitant AEDs

Patient ID	Segment	Medication and Dose	No. Days	Indication
071-012	Segment I	Ativan Unknown IV	≤ 1	Seizure Control
075-001	Segment I	Ativan 2 mg	PRN	Prolonged Seizure
	Segment III	Ativan 2 mg	PRN	Prolonged Seizure
093-007	Segment III	Ativan 3 mg	≤ 1	Heavy Seizure Activity
6 g Vigabatrin				
006-111	Segment I	Ativan 1/2 tab	PRN	Anxiety
	Segment III	Ativan 1/4-1/2 tab	PRN	Anxiety
010-111	Segment III	Valium 2 mg	≤ 1	GTC Seizure
010-114	Segment I	Ativan 1 mg	≤ 1	Severe GTC Seizure
011-107	Segment I	Tranxene 3.75 mg	5	Increased Seizures
	Segment II	Tranxene 7.5 mg	1	Seizure Cluster
011-109	Segment I	Tranxene 30 mg	1	Seizures
	Segment II	Tranxene 15-30 mg	34	Seizures
011-119	Segment I	Tranxene 3.75 mg	2	Seizures
	Segment III	Tranxene 3.75 mg	1	Emotionally Upset
069-003	Segment II	Ativan 1 mg	1	Seizure Status
	Segment III	Ativan unknown	1	Seizure
075-008	Segment I	Valium 5 mg	PRN	Nervousness (minimum of 8 doses)
	Segment III	Valium 5-10 mg	PRN	Nervousness/Hiccoughs
075-009	Segment I	Ativan 4 mg	PRN	Seizure Clusters
	Segment II	Ativan 4 mg	PRN	Seizure Clusters
	Segment III	Ativan 2 mg	PRN	Seizure Clusters
089-003	Segment II	Ativan 8 mg	≤ 1	Stajus
089-006	Segment I	Valium 10 mg	≤ 1	Dental Work
Supporting Data:				Page, Vol
Appendix G3, Listing 7: Concomitant Medication with Anti-seizure Properties				8-13348, v1.128

ATTACHMENT 4

Attachment 4
FDA's Table

Patients Using Medications With Antiseizure Properties in Addition to Concomitant AEDs				
Patient ID	Segment	Medication and Dose	No. Days	Indication
Placebo				
010-104	Segment III	Ativan 2 mg	4	Seizure Exacerbation
010-105	Segment I	Tranxene 7.5 mg	8	Anxiety
	Segment II	Tranxene 7.5 mg	2	Anxiety
	Segment III	Tranxene 7.5 mg	6	Anxiety
011-108	Segment III	Tranxene 15 mg	2	Seizure Clusters
069-001	Segment I	Valium 5 mg	4	Patient Feeling Strange
	Segment II	Valium 5 mg	1	Patient Feeling Strange
072-001	Segment I	Diamox 250 mg	PRN	Pre-Menses X 5 days
	Segment II	Tranxene 3.75-7.5 mg	PRN	Anxiety
	Segment III	Diamox 250 mg	PRN	Pre-Menses X 5 days
		Tranxene 3.75 mg	PRN	Anxiety
072-007	Segment II	Diamox 250 mg	PRN	Pre-Menses X 5 days
		Tranxene 7.5 mg	1	Anxiety
	Segment III	Tegretol 100 mg	1	Post Seizure; extra dose
		Tranxene 7.5 mg	4	Anxiety
089-005	Segment I	Tranxene 3.75 mg	85	Anxiety
	Segment II	Tranxene 3.75 mg	43	Anxiety
	Segment III	Tranxene 3.75 mg	86	Anxiety
1 g Vigabatrin				
012-102*	Segment I	Valproic Acid 1000 mg	1	Flurry for 3 hrs; SPS. Given VPA 1000 mg in ER
073-009*	Segment I	Carbamazepine	6 days	Took an additional 1/2 tab qHS (Recycled)
	Segment II	Carbamazepine	2 days	Stopped CBZ when started study meds
011-104*		Carbamazepine	2 days	Tegretol dose changed X 2 days while patient was in hospital
072-005 *	Segment III	Carbamazepine		CBZ increased on 10/9/91 due to increased number of seizures. He continued to take the increased dosage. We only became aware of it at the time of the visit.
006-104	Segment I	Mysoline	PRN	Seizure Clusters
010-102	Segment I	Valium 5 mg IV	≤ 1	Severe Secondary Seizure
010-107	Segment I	Xanax 0.5 mg	PRN	Anxiety
	Segment II	Xanax 2 mg	PRN	Anxiety
	Segment III	Xanax 0.5 mg	PRN	Anxiety
010-113	Segment I	Xanax 0.25 mg	2	Anxiety
	Segment II	Tranxene 3.75 mg	2	Anxiety
011-105	Segment I	Tranxene 3.75-11.25 mg	17	Seizures
	Segment II	Tranxene 3.75-7.5 mg	5	Seizures
	Segment III	Tranxene 3.75-7.5 mg	50	Seizures
011-114	Segment I	Ativan 2-4 mg	3	Seizure Prevention
	Segment II	Ativan Unknown	1	Seizure Prevention
	Segment III	Ativan 2 mg	7	Seizure Prevention

Patients Using Medications With Antiseizure Properties in Addition to Concomitant AEDs				
Patient ID	Segment	Medication and Dose	No. Days	Indication
011-118*	Segment I	Tranxene 3.75 mg	PRN	Takes some Sundays-- prevent ezs
	Segment II	Tranxene 3.75 mg	PRN	Seizure/Anxiety
	Segment III	Tranxene 3.75 mg	PRN	Seizure/Anxiety
013-008	Segment III	Phenobarbital 130 mg	1	Prolonged Seizure
	Segment III	Valium 15 mg	1	Prolonged Seizure
069-002	Segment III	Valium 10 mg IV	≤ 1	Molar Extraction
072-010	Segment III	Diamox 250 mg	1	Water Retention
089-002	Segment I	Ativan 1 mg	85	Chest Pain W/Anxiety
	Segment II	Ativan 1 mg	45	Chest Pain W/Anxiety
	Segment III	Ativan 1 mg	84	Chest Pain W/Anxiety
3 g Vigabatrin				
073-008*	Segment I	Ativan 1 mg	2 days	Pt took 1 mg extra Ativan due to increased seizures
069-004*	Segment II	Carbamazepine	3 wk	Pt decreased CBZ dose due to decrease in sz and increase in lethargy
072-011 *	Segment III	Phenobarbital	1	Extra dose of Phenobarbital taken Monday ...due to seizures
073-008*		Ativan	1	Ativan for increased seizures
010-103	Segment I	Tranxene 7.5 mg	9	Seizures and Anxiety
071-004*	Segment II	Ativan 1-2 mg	9	Sedation
	Segment III	Ativan 1-2 mg	38	Status Epilepticus
071-012	Segment I	Ativan Unknown IV	≤ 1	Seizure Control
075-001*	Segment I	Ativan 2 mg	>11	Prolonged Seizure
	Segment III	Ativan 2 mg	2	Prolonged Seizure
093-007*	Segment III	Ativan 3 mg	≤ 1	"Heavy seizure activity" per patient report. Took a total of 3 mg Ativan for seizure flurry with good response.
6 g Vigabatrin				
071-001 *	Segment III	Tegretol	1 day	Tegretol intoxicated took too much CBZ. Confused about dosage. Hospitalized.
006-111	Segment I	Ativan 1/2 tab	PRN	Anxiety
	Segment III	Ativan 1/4-1/2 tab	PRN	Anxiety
010-111	Segment III	Valium 2 mg	≤ 1	GTC Seizure
010-114	Segment I	Ativan 1 mg	≤ 1	Severe GTC Seizure
011-107	Segment I	Tranxene 3.75 mg	5	Increased Seizures
	Segment II	Tranxene 7.5 mg	1	Seizure Cluster
011-109	Segment I	Tranxene 30 mg	1	Seizures
	Segment II	Tranxene 15-30 mg	34	Seizures
011-119	Segment I	Tranxene 3.75 mg	2	Seizures
	Segment III	Tranxene 3.75 mg	1	Emotionally Upset
069-003	Segment II	Ativan 1 mg	1	Seizure Status
	Segment III	Ativan unknown	1	Seizure
075-008	Segment I	Valium 5 mg	PRN	Nervousness (minimum of 8 doses)
	Segment III	Valium 5-10 mg	PRN	Nervousness/Hiccoughs
075-009	Segment I	Ativan 4 mg	PRN	Seizure Clusters
	Segment II	Ativan 4 mg	PRN	Seizure Clusters
	Segment III	Ativan 2 mg	PRN	Seizure Clusters
089-003	Segment II	Ativan 8 mg	≤ 1	Status

Patients Using Medications With Antiseizure Properties in Addition to Concomitant AEDs				
Patient ID	Segment	Medication and Dose	No. Days	Indication
089-006	Segment I	Valium 10 mg	≤ 1	Dental Work
Supporting Data:				Page, Vol
Appendix G3, Listing 7: Concomitant Medication with Anti-seizure Properties				8-13348, v1.128