

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20-427**

**STATISTICAL REVIEW(S)**

RECEIVED NOV 03 1997

## Statistical Review and Evaluation

OCT 31 1997

**NDA#:** 20-427

**Applicant:** Hoechst Marion Roussel

**Drug:** Sabril (vigabatrin)

**Indication:** Epilepsy

**Documents reviewed:** (1) Vol. 75 of sponsor's May 29 response to FDA Not Approvable letter; (2) 2 volumes, dated July 23 and July 28, responding to FDA's June 30 request

**Medical Reviewer:** James Sherry, M.D. (HFD-120)

### Background

The FDA sent a Not Approvable (NA) letter to the sponsor on April 28, 1995. In the NA letter, the Medical Division (HFD-120) cited major deficiencies in the application with respect to (1) inadequate collection and availability of safety information for non-US patients and (2) inadequate analysis and reporting of information collected relative to both efficacy and safety. The FDA review team partly addressed concern (2) through a thorough audit/reanalysis of data from Trial 025, one of two adequate well-controlled efficacy trials. The FDA requested that the sponsor perform a similar audit/reanalysis of data for Trial 024.

The sponsor submitted a response to the NA letter in the form of an amendment dated May 29, 1997. The Medical Division teleconferenced with the sponsor on June 30, 1997, to discuss the submission. During the telecon, the Division asked the sponsor to perform additional analyses of Trial 024, beyond those submitted in the amendment, more consistent with an intent-to-treat (ITT) statistical approach.

### The Amendment

#### Methods

Trial 024 was a parallel group comparison of vigabatrin 3g and placebo. Seizure rates per 28 days were compared based on the combined frequency of complex partial seizures (type 1B) and partial seizures secondarily generalized (type 1C) occurring during Segments I, II or III:

**Segment I (12 weeks):** The last 8 weeks was considered the baseline period.

**Segment II (4 weeks):** Patients were randomized to test drug and titrated upward.

**Segment III (12 weeks):** Maintenance period, the last 8 weeks of which was used to calculate endstudy seizure rates. Endstudy rates for noncompleters were calculated based on (up to) the last 8 weeks in the trial.

TEG: A VOM

The sponsor interpreted the content of the NA letter as a directive to undertake a re-analysis of efficacy data from Trial 024 excluding all seizures occurring after protocol violations<sup>1</sup>. This interpretation has its roots in an analysis of 024 which the FDA asked the sponsor to perform during the 12-month NDA review cycle. The FDA asked the sponsor to reanalyze seizure data making sure to exclude seizures occurring subsequent to:

- a 2-fold increase in seizure frequency compared to baseline
- pharmacologic intervention for clusters or flurries of seizures

Results of the analyses were incorporated in the Medical Officer's Review (p.38). These patients had little or no effect on the outcome of the trial.

In the current amendment, the sponsor audited case report forms and 'databases' to identify an even broader set of patients with protocol violations, namely those satisfying at least one of the following:

- medical intervention for seizures
- changes in concomitant AED dose
- twofold increase in 1B or 1C seizures, or status epilepticus

The sponsor excluded seizures occurring in the aftermath of the audit drop date, i.e., the date of the first occurrence of the three events. For example, the sponsor identified patient 5-102 randomized to placebo as receiving 1mg lorazepam for 'seizure activity'. The endstudy seizure rate was recalculated as if the patient dropped from the trial on that day.

Some patients were dropped during baseline or titration, prior to the last 8 weeks of their endstudy period. The sponsor removed these patients entirely from the statistical analyses.

Seizure rates for four patients (59-001, 58-006, 63-008, 62-008) were recomputed on an individualized basis.

The audit included a 4th category, inaccurate seizure counts. Inaccurate counts were revised regardless of whether a patient did or did not have a protocol violation. Generally, inaccuracies involved undercounts of existing data or recovery of count data from CRFs or patient diaries where none had previously been reported. Seizure rates for these patients were recomputed using a worst case approach. Questionable seizure counts (e.g., an uncountable number of cluster seizures) for a placebo patient during the baseline period were inflated to make the endstudy rate

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<sup>1</sup> By protocol, "Any patient who experiences 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 I) or who develop status epilepticus will be removed from the study and not replaced".

a 2-fold *decrease*. Questionable seizure counts for a vigabatrin patient during endstudy were inflated to make the endstudy rate a 2-fold *increase*. Questionable seizure counts for a placebo patient during endstudy or vigabatrin patient during baseline were left unchanged.

Statistical analyses of vigabatrin's efficacy were performed twice, once making all changes identified in the audit ('all changes' analysis) and a second time making only changes identified as unfavorable to vigabatrin ('unfavorable changes' analysis). Both types of changes used the worst-case approach described above for recomputing seizure rates.

### Sponsor's results

One hundred eighty three (183) patients (90 placebo, 93 vigabatrin) were randomized to treatment. One vigabatrin patient was discontinued prior to receiving the drug. Fifty-four (54) of the 182 ITT patients were identified as falling into one or more of the four audit categories. The sponsor's table below shows the number of patients in each category. Each patient is counted just once. The category for patients falling into 2 or more categories was determined by the first finding requiring a data change or the first finding if no change was required. Individual patient changes are shown in the Appendix.

audit category	identified	requiring data change	changes favoring vigabatrin	changes unfavorable to vigabatrin
medical intervention for seizures *	19	19	7	12
inaccurate seizure count	13	7	0	7
change in AED dose *	11	8	3	2
twofold increase in seizures or status epilepticus *	11	11**	6	4
total	54	42	16	25

\* protocol violation

\*\* favorable plus unfavorable changes do not sum to total due to one change having no effect

Tables 1 and 2 at the end of this review show the results of the statistical analyses using the ANCOVA of ranked endstudy seizure frequency adjusting for treatment, center and ranked baseline seizure frequency. This statistical model was also used in the original NDA submission. Both 'all changes' and 'unfavorable changes' analyses retained statistical significance ( $p < .02$ ). Note that 17 patients were completely excluded from the all-changes analyses as were 9 patients from the unfavorable changes analyses.

## **ITT Reanalyses**

### **Methods**

At FDA's request, seizure rates were calculated only for patients with inaccurate seizure counts. The analysis reinstated those patients who had protocol violations only (and no inaccurate seizure counts) using the seizure rates in the original application. Rates for patients with inaccurate counts were recalculated on a worst case basis using the method described above.

### **Sponsor's results**

Twenty two (22) patients had inaccurate seizure counts. Twelve (12) of the 22 had revised rates because the changes discovered during the audit were unfavorable to vigabatrin. Table 3 shows the results of the primary statistical analysis using the same ANCOVA model as before. Results remained statistically significant ( $p=.014$ ). Statistical significance was also achieved by the Wilcoxon rank sum ( $p=.015$ ) and CMH (stratified by site,  $p=.014$ ) analyses.

### **Reviewer's analysis**

The sponsor's May 29 analysis suffers from the very flaw I believe the sponsor was attempting to guard against, namely bias. For the analyses of efficacy, the sponsor deleted all seizure data subsequent to a protocol violation (medical intervention, change in AED dose, etc). This action resulted in the exclusion of some patients entirely from the analyses, up to 9% of randomized patients depending on the particular analysis chosen. This deviation from the ITT principle, and the exclusion of data for patients entering into the analyses, have the potential to introduce bias.

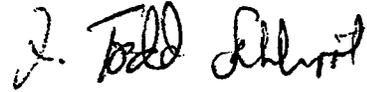
The sponsor's action is particularly illustrative in the case of hospitalizations. As the NA letter noted, the FDA found individual records for which seizure counts for subjects were not recorded during hospitalizations, an omission that "has the potential to introduce significant bias" (NA letter). As a 'remedy', the sponsor chose to delete not only seizures occurring during hospitalizations but also to delete all seizures occurring after hospitalizations until the end of the trial.

The correct analytic strategy, found in the June 24 and 30 submissions, is an ITT analysis of all patients that incorporates revised (worst case) seizure rates only for patients with inaccurate counts. Empirical distribution functions of revised rates are shown in Figures 1 (baseline) and 2 (endstudy). The horizontal axes are constructed on the natural log scale, so that, for example, 2 corresponds to a 28-day seizure rate of just under 7. The endstudy curves separate early but come together at about the 80th percentile. Several of the large vigabatrin endstudy rates are inflated rates.

Statistical results were robust ( $p \leq .015$  all analyses).

**Conclusions**

The ITT re-analyses do not alter the statistical results contained in the original submission.



**J. Todd Sahlroot, Ph.D.  
Mathematical Statistician**

concur: Dr. Chi



10/31/97

cc: NDA 20-427  
HFD-120  
HFD-120/Drs. Leber, Katz, Shiery  
HFD-344/Dr. Barton  
HFD-120/Mr. Purvis, Ms. Ware  
HFD-710/Drs. Chi, Sahlroot

<b>Table 1 Analysis of Complex Partial Seizures Plus Partial Seizures Secondarily Generalized, Making All Data Changes Identified in Table D3, Sd-V75-P16, Intent-to-treat Patients (N=165)</b>			
<b>Treatment</b>	<b>N</b>	<b>Seizure Frequency Baseline Median (95% CI)</b>	<b>(Number/28 Days) Endstudy Median (95% CI)</b>
Placebo	82	8.0 (6.5, 9.5)	7.3 (5.5, 9.0)
3 g VGB	83	8.0 (6.5, 9.5)	5.0 (3.0, 6.0)
<b>Treatment Comparison</b>		<b>P Value*</b>	
3 g VGB versus Placebo		.0104	
<b>Model Factor</b>			
Baseline Seizure Frequency		.0001	
Investigative Site		.4187	
Treatment		.0104	
* P Values from analysis of covariance of ranked seizure frequencies using model which is adjusted for treatment, investigative site, and ranked baseline seizure frequency.			

<b>Table 2 Analysis of Complex Partial Seizures Plus Partial Seizures Secondarily Generalized, Making Only Unfavorable to Vigabatrin Changes Identified in Table D3, Sd-V75-P18. Intent-to-Treat Patients (N=173)</b>			
<b>Treatment</b>	<b>N</b>	<b>Seizure Frequency Baseline Median (95% CI)</b>	<b>(Number/28 Days) Endstudy Median (95% CI)</b>
Placebo	88	9.0 (6.5, 11.0)	7.3 (6.0, 9.0)
3 g VGB	85	8.0 (6.5, 10.0)	5.5 (3.5, 6.8)
<b>Treatment Comparison</b>		<b>P Value*</b>	
3 g VGB versus Placebo		.0198	
<b>Model Factor</b>			
Baseline Seizure Frequency		.0001	
Investigative Site		.3966	
Treatment		.0198	
* P Values from analysis of covariance of ranked seizure frequencies using model which adjusted for treatment, investigative site, and ranked baseline seizure frequency.			

<b>Table 3. Analysis of Complex Partial Seizures Plus Partial Seizures Secondarily Generalized, Making All Data Changes Identified in Table 2. Intent-to-treat Patients (N=182)</b>			
<u>Treatment</u>	<u>N</u>	<u>Seizure Frequency Baseline Median</u> <u>(95% CI)</u>	<u>(Number/28 Days) Endstudy Median</u> <u>(95% CI)</u>
Placebo	90	9.0 (6.5, 11.0)	7.5 (6.0, 9.0)
3 g VGB	92	8.3 (6.5, 10.0)	5.5 (3.5, 7.0)
<u>Treatment Comparison</u>		<u>P Value*</u>	
3 g VGB versus Placebo		.0143	
<u>Model Factor</u>			
Baseline Seizure Frequency		.0001	
Investigative Site		.6190	
Treatment		.0143	
* P Values from analysis of covariance of ranked seizure frequencies using model which is adjusted for treatment, investigative site, and ranked baseline seizure frequency.			

Figure 1

# Vigabatrin Trial 024

Empirical distribution functions using  
sponsors revised seizure rates

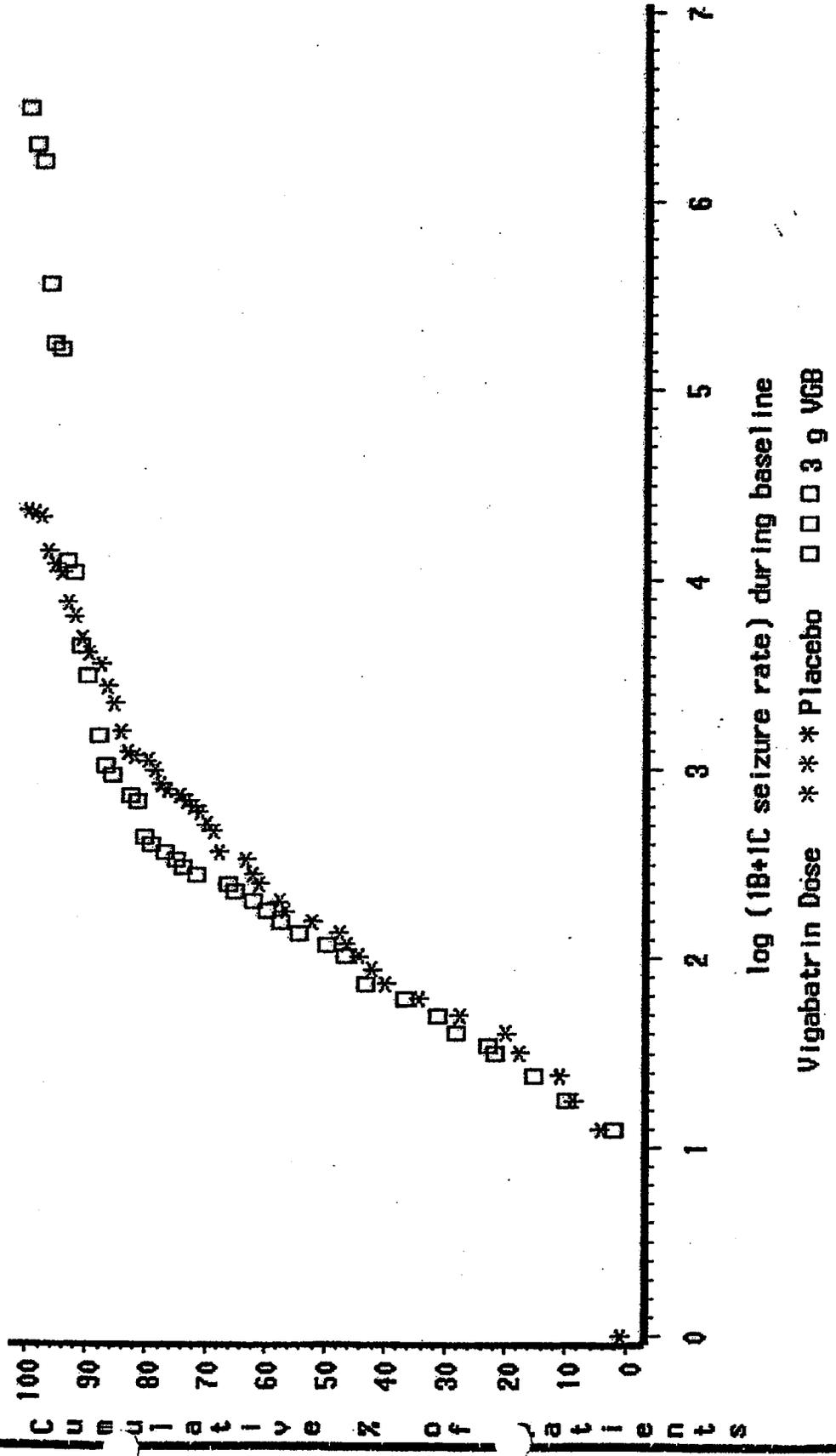
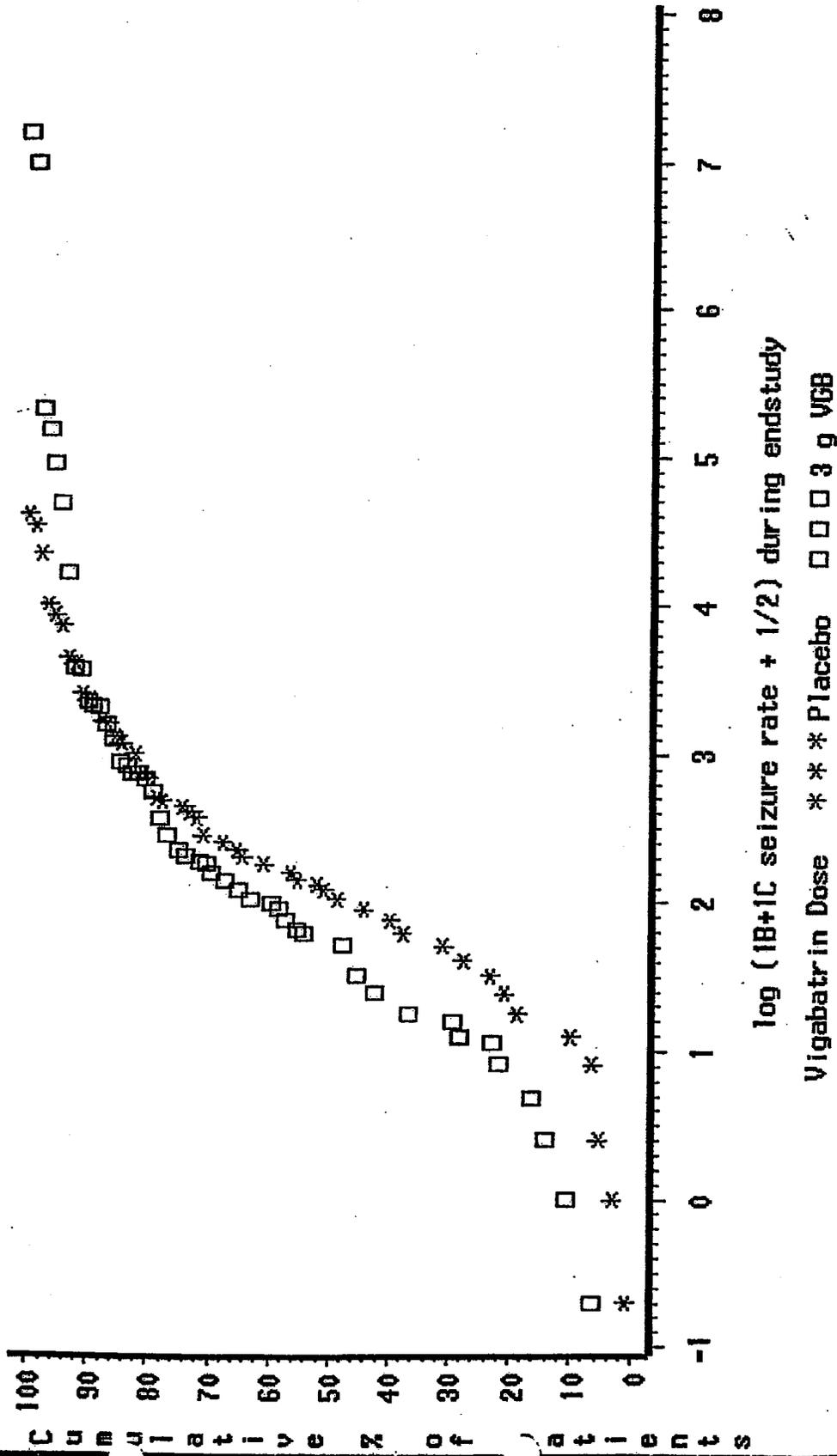


Figure 2

# vigabatrin Trial 024

Empirical distribution functions using  
sponsors revised seizure rates



# Appendix

Patients Identified in Audit of Protocol 71754-3-C-024				
Patient #/ Treatment	Date/ Segment Visit	Seizures Recorded in Daily Seizure Record	Reason Patient was Flagged	Action
005-102 Placebo	8-May-91 S3V4	4 IB2A	Concomitant medication record indicates lorazepam 1 mg for seizure activity.	Drop on 8-May-91
005-106 Placebo	12-Apr-91 S1V3	10 IC 1 IB2C 1 IB1B	Adverse event comment indicates status epilepticus was confirmed by EEG and was secondary to anxiety when having MRI. Treated with phenytoin and lorazepam 4 mg	Drop on 12-Apr-91, eliminates patient from analysis
	22-Apr-91 S2V1	0	Seizure record comment indicates patient had at least one IB1B seizure in MRI, then one IB2C witnessed by EEG technician during EP electrode application and at least 10 witnessed IC type in EEG lab and ICU.	Previously dropped
054-002 Placebo	S1V2	4 Total	Seizure record comment indicates 5-6 seizures in S1V2 window	Change IB seizure count on 1-Jan-91 (last day of S1V2) to 32, resulting in a baseline IB+IC seizure rate of 22. This creates a twofold decrease at endstudy.
054-003 3 g VGB	██████ S1V2	1 IC	Hospitalized due to seizure	Drop on ██████, eliminates patient from analysis
054-004 Placebo	10-May-91 S3V3	1 IB1A	Seizure record comment indicates intermittent dizzy spells (possible seizures)	Vigabatrin worst case—No Change
054-006 Placebo	19-Jul-91 S3V3	2 IB1B	Seizure record comment indicates seizures coming in clusters	Vigabatrin worst case—No Change
	15-Aug-91 S3V3		Twofold increase in IB seizures	Drop on 15-Aug-91
054-007 Placebo	14-May-91 S1V2	3 IB2C	Seizure record comment indicates patient had clusters of seizures on 5/14 and 5/29 all of which were described as staring, posturing with arm, difficulty speaking, and postictal confusion.	Change IB seizure counts on 14-May-91 to 14 and on 29-May-91 to 8. This results in a baseline IB+IC seizure rate of 13, and a twofold decrease at endstudy.
	29-May-91 S1V2	2 IB2C		

b(6)

Patients Identified in Audit of Protocol 71754-3-C-024				
Patient #/ Treatment	Date/ Segment Visit	Seizures Recorded in Daily Seizure Record	Reason Patient was Flagged	Action
054-008 3 g VGB	7-Jul-91 S1V1	0	Seizure record comment indicates lightheadedness, blurred vision, impaired awareness, wandering, fumbling with hands	Before baseline period--No Change
	28-Nov-91 S3V3		Twofold increase in IC seizures	Drop on 28-Nov-91
054-011 Placebo	██████ S1V3	1 IB1C	Hospitalized due to seizure	Drop on ██████, eliminates patient from analysis
055-002 Placebo	27-Aug-91 S3V4	0	Twofold increase in IB	Drop on 27-Aug-91
055-007 Placebo	S3V4	7 Total	Seizure record comment indicates patient had one additional seizure but cannot recall the day.	Vigabatrin worst case--No Change
055-009 Placebo	13-Dec-91 S2V1	0	Concomitant medication record indicates lorazepam 2-4 mg PRN for seizure flurries	Drop on 13-Dec-91, eliminates patient from analysis
056-006 3 g VGB	5-Nov-91 S3V4	1 IC	Concomitant AED record indicates carbamazepine decrease from 1900 to 1700 mg	Vigabatrin worst case--No Change
056-010 3 g VGB	1-Jan-92 S3V3	0	Seizure record comment indicates patient was sent to the ER for status epilepticus.  Concomitant medication record indicates lorazepam 1 mg for status	Change IB seizure count on 1-Jan-92 to 51 and drop on that day. This results in an endstudy IB+IC seizure rate of 27 and a twofold increase from baseline.
056-011 Placebo	7-Dec-91 S2V2	6 IB2C	Concomitant medication record indicates diazepam 5 mg 12/7/91 - 3/10/92 PRN for increased seizures	Drop on 7-Dec-91
057-002 Placebo	3-Jan-91 S1V1	0	Adverse event comment indicates patient fell during seizure against bathtub.	Before baseline period--No Change
057-007 Placebo	9-Sep-91 S3V3	0	Twofold increase in IC seizures	Drop on 9-Sep-91
058-001 Placebo	10-Jan-92 S1V3	10 IC	Patient hospitalized due to frequent seizures. Concomitant medication record indicates chlorazepate 7.5 mg and phenytoin 1100 mg for seizures	Drop on 10-Jan-92, eliminates patient from analysis

b(6)

Patients Identified in Audit of Protocol 71754-3-C-024				
Patient #/ Treatment	Date/ Segment Visit	Seizures Recorded in Daily Seizure Record	Reason Patient was Flagged	Action
058-005 Placebo	13-Mar-91 S1V2	14 IB2C	Concomitant medication record indicates chlorazepate 7.5 mg for flurry	Drop on 13-Mar-91, eliminates patient from analysis
	26-May-91 S3V1	12 IB2C	Concomitant medication record indicates chlorazepate 7.5 mg for flurry	Previously dropped
	23-Jul-91 S3V4	16 IB2C	Concomitant medication record indicates chlorazepate 7.5 mg for flurry	Previously dropped
058-008 3 g VGB	10-Mar-91 S1V1	2 IB2C 1 IC	Comment indicates patient was given diazepam 10 mg and haloperidol 5 mg IM in ER for seizure and postictal agitation. Concomitant medication record indicates diazepam 10 mg for postictal agitation	Drop on 10-Mar-91, eliminates patient from analysis
	8-Aug-91 S3V3	0	Twofold increase in IC seizures	Drop on this date in "Unfavorable Changes" analysis
058-009 Placebo	31-Aug-91 S3V2	3 IC	Concomitant medication record indicates diazepam 10 mg for status epilepticus	Drop on 31-Aug-91
058-013 Placebo	31-Dec-91 S2V2	0	Investigator comment indicates phenytoin was decreased from 225 to 200 mg	Drop on 31-Dec-91
059-001 3 g VGB	1-May-91 S3V3	1 IB2A	Seizure comment indicates patient clustered on and off for 30 minutes.	Drop on 1-May-91, which results in patient being a twofold increase from baseline.
	22-May-91 S3V4	0	Twofold increase in IB seizures	Previously dropped
059-009 Placebo	15-Sep-91 S3V1	1 IB2A	Comment indicate seizures were brief and clustered in a very brief time frame. These were recorded as one seizure.	Vigabatrin worst case—No Change
059-015 3 g VGB	31-Oct-91 S2V1	0	Seizure comment indicates patient discontinued carbamazepine and taking study drug only.	Vigabatrin worst case—No Change

Patients Identified in Audit of Protocol 71754-3-C-024				
Patient #/ Treatment	Date/ Segment Visit	Seizures Recorded In Daily Seizure Record	Reason Patient was Flagged	Action
060-004 Placebo	5-May-91 S1V3	1 IB1C 1 IC	Comment indicates patient experienced three flurries.	Change seizure count on 5-May-91 to 53 IB and 53 IC. This results in a baseline IB+IC seizure rate of 59 and creates a twofold decrease at endstudy.
	5-Aug-91 S3V3	1 IA2	Twofold increase in IC seizures	Previously modified to create a twofold endstudy decrease
060-005 Placebo	11-Mar-91 S1V1	48 IB	Seizure record comment indicates patient experienced approximately 12 seizures/hour from 10 am-2 pm.	Before baseline period--No Change
060-007 3 g VGB	18-Jun-91 S1V1	0	Adverse event comment indicates patient fell during seizure.	Before baseline period--No Change
	7-Nov-91 S3V4	1 IA1 1 IC	Twofold increase in IC seizures	Drop on 7-Nov-91
061-003 Placebo	30-Mar-91 S1V2	0	Carbamazepine increase to 1800 mg and phenytoin increased to 500 mg	Vigabatrin worst case--No Change
061-004 3 g VGB	██████████ S3V2	7 IB2C	Hospitalized to rule out status epilepticus	Change IB seizure count on ██████████ to 24 and drop on that day. This results in an endstudy IB+IC seizure rate of 17 and a twofold increase over baseline.
061-008 Placebo	3-Feb-92 S3V2	0	Adverse event comment indicates methsuximide dose decreased	Drop on 3-Feb-92
061-009 Placebo	26-Sep-91 S1V1	4 IA4 5 IB1B	Comment indicates patient took extra methsuximide 15 mg (liquid) at noon and 11pm due to increased seizures.	Drop on 26-Sep-91, eliminates patient from analysis
062-008 3 g VGB	22-Aug-91 S2V1	0	Adverse event comment indicates hand abrasion due to seizure fall	Change IB seizure count on 22-Aug-91 to 2 and drop on that date. This results in an endstudy IB+IC seizure rate of 28, making a twofold increase over baseline.
062-009 Placebo	26-Nov-91 S3V3	0	Twofold increase in IC seizures	Drop on 26-Nov-91

b(6)

Patients Identified in Audit of Protocol 71754-3-C-024				
Patient #/ Treatment	Date/ Segment Visit	Seizures Recorded in Daily Seizure Record	Reason Patient was Flagged	Action
062-011 3 g VGB	20-Feb-92 S3V4	2 IB1A	Comment indicates patient decreased phenytoin dose to 200 mg due to involuntary twitching.	Vigabatrin worst case--No Change
062-012 Placebo	29-Sep-1- Oct-91 S1V1	Missing	Seizure record comments indicates patient forgot to mark seizures on calendar.	Before baseline period--No Change
063-002 3 g VGB	20-Feb-91 S1V1	0	Concomitant medication record indicates lorazepam 2 mg PRN 10/29/90 - 9/18/91 for seizure clusters	Drop on 20-Feb-91, eliminates patient from analysis
063-003 3 g VGB	22-Feb-91 S1V1	2 IB1B	Concomitant medication record indicates lorazepam 1 mg PRN 2/22/91 - 9/9/91 for seizure clusters	Drop on 22-Feb-91, eliminates patient from analysis
063-006 3 g VGB	17-Apr-91 S1V1	1 IB1C	Concomitant medication record indicates lorazepam 2 mg PRN 4/17/91 - 11/5/91 for seizure clusters	Drop on 17-Apr-91, eliminates patient from analysis
063-008 3 g VGB	11-Aug-91 S1V3	2 IB2B	Concomitant medication record indicates lorazepam 2 mg 8/11/91 for seizure coverage secondary to vomiting	Drop on 11-Aug-91, eliminates patient from analysis
	4-Nov-91 S3V3	1 IA2	Twofold increase in IB	Previously dropped
064-003 3 g VGB	19-Jun-91 S3V4	14 IB1B	Seizure record comment indicates "...patient had approximately 10-15 minis. These are the B1B without postictal state. We used an average of 12 plus 2 complex partials with postictal state."	Vigabatrin worst case--Change seizure count on 19-Jun-91 from 14 to 17
064-010 Placebo	20-Jan-92 S3V3	0	Twofold increase in IC	Drop on 20-Jan-92
065-001 3 g VGB	24-Dec-90 S1V1	4 IB1B	Seizure comment indicates patient took phenytoin 100 mg for seizure flurry.	Drop on 24-Dec-90, eliminates patient from analysis
065-005 Placebo	13-Sep-91 S2V2	0	Investigator comment indicates phenytoin dose decreased by 50 mg	Drop on 13-Sep-91

Patients Identified in Audit of Protocol 71754-3-C-024				
Patient #/ Treatment	Date/ Segment Visit	Seizures Recorded in Daily Seizure Record	Reason Patient was Flagged	Action
065-006 3 g VGB	18-Jun-91 S1V1	7 IB2B	Seizure record indicates patient lost count after 7 seizures.	Before baseline period--No Change
	11-Jul-91 S1V2	11 IB2A	Seizure record indicates patient lost count after 11 seizures.	Vigabatrin worst case--No Change
	31-Oct-91 S3V2	1 IB2B	Seizure comment indicates patient lost count of seizures.	Change IB seizure count on 31-Oct-91 to 1437 and drop on that day. This results in an endstudy IB+IB seizure rate of 1326 and a twofold increase over baseline.
	17-Nov-91 S3V3	1 IB2B	Seizure comment indicates patient lost count of seizures.	Previously dropped
	1-Dec-91 S3V3	27 IB2B 3 IC	Seizure record indicates patient had more than 27 seizures.	Previously dropped
065-007 Placebo	15-Jul-91 S1V1	0	Concomitant medication record indicates decreasing valproic acid dose throughout: 7/12-17 3500 mg, 7/18-24 3000 mg, 7/25 - 8/5 2500 mg, 8/6-18 2000 mg, 8/19 1500 mg	Drop on 15-Jul-91, eliminates patient from analysis
	12-Jan-92 S3V3	2 IA2	Twofold increase in IC seizures	Previously dropped
065-008 3 g VGB	11-Nov-91 S1V2	0	Investigator comment indicates patient took additional 25 mg of phenytoin because she needed it.	Drop on 11-Nov-91, eliminates patient from analysis
	13-Jan-92 S2V1	Missing	Seizure record indicates patient seized on and off all day.	Previously dropped
	1-Feb-92 S2V3	0	Concomitant AED record indicates phenytoin dose decreased from 200 mg to 150 mg	Previously dropped
066-004 3 g VGB	7-Jun-91 S3V3	5 IB1C	Investigator comment indicates carbamazepine dose increased	Drop on 7-Jun-91
	30-Jun-91 S3V4	1 IB1C	Concomitant medication record indicates lorazepam 1 mg for flurry	Previously dropped

<b>Patients Identified In Audit of Protocol 71754-3-C-024</b>				
<i>Patient #/ Treatment</i>	<i>Date/ Segment Visit</i>	<i>Seizures Recorded in Daily Seizure Record</i>	<i>Reason Patient was Flagged</i>	<i>Action</i>
066-006 3 g VGB	5-Jun-91 S1V2	1 IC 40 IB1B	Concomitant medication record indicates lorazepam 1 mg for seizure flurry	Drop on 5-Jun-91, eliminates patient from analysis
	9-Jun-91 S1V2	40 IB1B	Concomitant medication record indicates lorazepam 1 mg for seizure flurry	Previously dropped
	S3V2	Missing	Patient did not keep track of seizures.	Previously dropped
066-007 Placebo	4-Dec-91 S3V3	0	Twofold increase in IB seizures	Drop on 4-Dec-91
066-008 3 g VGB7	13-Dec-91 S3V3	0	Concomitant AED record indicates carbamazepine dose decreased from 1600 mg to 1400 mg	Vigabatrin worst case--No Change
066-009 Placebo	18-Oct-91 S1V1	2 IB1A	Concomitant medication record indicates lorazepam 0.5 mg PRN 10/18/91 - 4/2/92 for after strong seizure	Drop on 18-Oct-91, eliminates patient from analysis
066-014 3 g VGB	18-Mar-92 S3V4	0	Carbamazepine decreased to 1000 mg	Vigabatrin worst case--No Change
067-011 Placebo	22-Aug-91 S1V2	1 IB2A	Seizure record comment indicates patient taken to hospital in Puerto Rico for seizure.	Drop on 22-Aug-91, eliminates patient from analysis
	30-Dec-91 S3V3	0	Twofold increase in IC seizures	Previously dropped

**MEMORANDUM****DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** March 28, 1995

**FROM:** Group 2 Leader, Statistical Evaluation & Research Branch (HFD-713)

**SUBJECT:** Statistical review dated March 7, 1995

**TO:** File (NDA 20-427, Sabril)

The statistical reviewer has stated that he has analyzed the "patients' mean monthly (28 day) frequency" of seizures in the Statistical Reviewer's Independent Analyses section of the NDA review. It needs to be made clear that "mean monthly frequency" refers to the per-patient variable analyzed, not to the method of analysis for comparing treatment groups for this variable. The "mean monthly frequency" is Dr. Taneja's terminology for the number of seizures per unit time adjusted for a one-month time period. His analyses of this variable utilized nonparametric techniques (as did the sponsor's), so there was no assumption made that this variable was normally distributed or that an arithmetic mean is the appropriate descriptive summary statistic to represent a group measure of location for this variable.

*S. Edward Nevius*  
S. Edward Nevius, Ph.D.

cc: Arch NDA 20-427  
HFD-120  
HFD-120/PLeber  
HFD-120/RKatz  
HFD-120/CMcCormick  
HFD-120/RPitts  
HFD-713/SDubey [File: DRU 1.3.2]  
HFD-713/Group 2 file  
HFD-344/Dr. Lisook

**Statistical Review and Evaluation**

NDA: NDA 20-427 (IND 17,213)  
Applicant: Marion Merrell Dow Inc.  
Name of Drug: Sabril (Vigabatrin)  
Documents Reviewed: IND 17,213 Vols. 1-4.  
 Data on floppy diskette supplied by the sponsor.

Date: MAR 13 1995  
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I. Background: In this NDA submission two animal carcinogenicity studies, one in mice and one in rats, were included. These two studies were intended to assess the carcinogenicity potential of Sabril in mice and rats when administered orally mixing with diet at some selected dose levels. The length of the mouse study was 18 months and that of the rat study was 2 years. The reviewing pharmacologist Dr. Barry Rosloff, HFD-120, requested the Division of Biometrics to perform the statistical review and evaluation of these studies. The results of the review have been discussed with Dr. Rosloff.

**II. The mouse study**

IIa. Design: Two separate experiments, one in male and one in female mice, were conducted. In these two experiments there were three treated groups known as low, medium, and high dose groups, and one control group. Two hundred male and two hundred female CD-1(ICR)BR  mice were randomly divided into equal size of 50 animals to form the four treatment groups. The dose levels for the treated groups were 50, 100, and 150 mg/kg/day for low, medium, and high dose groups, respectively. The animals in the control group remained untreated.

b(4)

The animals were checked regularly for mortality, morbidity and presence of any palpable masses. A complete pathological examination was performed on all animals found dead, killed moribund during the experiment or sacrificed at the end of the experiment. Selected tissues were retained for histopathological evaluation.

**IIb. Sponsor's analysis**

Survival data analysis: Survival data were analyzed using the longrank tests to assess any differences in survival among the treatment groups. The Cox proportional hazards model (Regression Models and Life Tables, Journal of Royal Statistical Society, B, 34, pp 187-220, Cox D. R., 1972) was used to test for a linear dose related trend. The tests did not show any statistically significant (at .05 level) linear trend or differences in mortality among the treatment groups.

Tumor data analysis: Tumor data were analyzed using the Cochran-Armitage test (Cochran W., Some Methods for Strengthening the Common Chi-Square Tests, Biometrics, 10, pp 417-451, 1954 and Armitage, P., Tests for Linear Trend in Proportions and Frequency, Biometrics, 11, pp 375-386, 1955) for the presence of positive linear trend along dose levels in the incidences of observed tumor types. The Westfall and Young's method (Westfall P. H. and Yong S. S., P-value Adjustments for Multiple Tests in Multivariate Binomial Models, Journal of the American Statistical Association, 1989) was used for multiple testing adjustment. The test did not show statistically significant positive linear trend in incidence of any of the tested tumor types.

### Iic. Reviewer's analysis

The reviewer independently performed analyses on the survival and the tumor data. For survival data analysis the methods described in the papers of Cox (Regression models and life tables, Journal of the Royal Statistical Society, B, 34 187-220, 1972), and of Gehan (A generalized Wilcoxon test for comparing arbitrarily singly censored samples, Biometrika, 52 203-223, 1965) were used. The tumor data were analyzed using the methods described in the paper of Peto et al. (Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments, Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, Annex to supplement, World Health Organization, Geneva, 311-426, 1980) and the method of exact permutation trend test, developed by the Division of Biometrics. All data used in the reviewer's analysis were provided by the sponsor on a floppy diskette, except for the body weight data which were taken from the sponsor's hard copy submission.

Survival analysis: The intercurrent mortality data of mouse study are given in Table 1. The plots of Kaplan-Meier estimates of the survival distributions of male and female mice are given in Figures 1a and 1b, respectively. The homogeneity of survival distributions of four groups (Control, Low, Medium, High) was tested separately for male and female mice using the Cox test and the Generalized Wilcoxon test. The tests did not show any statistically significant (at .05 level) positive linear trend or differences among treatment groups in either sex.

The p-values of the positive linear trend and the pairwise tests are given in Tables 2a and 2b, respectively.

Tumor data analysis: The reviewer performed the positive linear trend test on data of all tumor types and the pairwise comparisons of the treated groups with the control for some selected tumor types. Since the sponsor classified the tumor types as 'cause of death' or 'not a cause of death', following Peto et al. (1980), the reviewer applied the 'death rate method' and the 'prevalence method' for testing positive linear trend in these two categories of tumor types, respectively. For tumor types occurring in both categories (i.e. same tumor found as cause of death for some animals and not cause of death for some other animals) a combined test was performed. The exact permutation trend test was used to calculate the p-values of all trend tests,

except when the tumors were found in the both categories, in which cases the continuity corrected normal test was used. The scores used were 0, 50, 100, and 150 for control, low, medium, and high dose groups, respectively. The time intervals used were 0-365, 366-551 days, and terminal sacrifice for males and 0-365, 366-549 days, and terminal sacrifice for females. None of the tested tumor types showed a statistically significant positive linear trend in either sex.

The P-values of the tested tumor types are given in Table 3.

### **III. The rat study**

**IIIa. Design:** Two separate experiments, one in male and one in female rats were conducted. In each of these experiments there were three treated groups, known as low, medium, and high dose groups and a control group. Two hundred male and two hundred female Long Evans rats were randomly divided into equal size of 50 animals to form the four treatment groups. The dose levels for the treated groups were 50, 100, and 150 mg/kg/day for low, medium, and high dose groups, respectively. The animals in the control group remained untreated.

The animals were checked regularly for mortality, morbidity and presence of any palpable masses. A complete pathological examination was performed on all animals found dead, killed moribund during the experiment or sacrificed at the end of the experiment. Selected tissues were retained for histopathological evaluation.

### **IIIb. Sponsor's analysis**

**Survival data analysis:** Survival data were analyzed using the longrank tests to assess any differences in survival among the treatment groups. The Cox proportional hazards model (1972) was used to test for a linear dose related trend. The tests did not show any statistically significant (at .05 level) linear trend or differences in mortality among the treatment groups.

**Tumor data analysis:** Tumor data were analyzed using the Cochran-Armitage test (1955) for the presence of positive linear trend along dose levels in the incidences of observed tumor types. The Westfall and Young's method (1989) was used for multiple testing adjustment. The smallest calculated P-value for positive linear trend test was .0157 for Liposarcoma in Abdominal cavity in male rats. The adjusted P-value for this, calculated from 1,000 bootstrap sample, was .24. Therefore, it was concluded that no statistically significant positive linear trend was detected in the incidence of any of the tested tumor types.

### **IIIc. Reviewer's analysis**

The reviewer independently performed analyses on the survival and the tumor data. For survival data analysis the methods described in the papers of Cox (1972) and of Gehan (1965) were used.

The tumor data were analyzed using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test, developed by the Division of Biometrics. All data used in the reviewer's analysis were provided by the sponsor on a floppy diskette.

Survival analysis: The intercurrent mortality data of the rat study are given in Table 4. The plots of Kaplan-Meier estimates of the survival distributions for male and female rats are given in Figures 2a and 2b, respectively. The homogeneity of survival distributions of four groups (Control, Low, Medium, and High) was tested separately for male and female rats using the Cox test and the Generalized Wilcoxon test. The test did not show any statistically significant (at .05 level) positive linear trend or differences in the mortality among the treatment groups in either sex.

The p-values of the trend and the pairwise tests are given in Tables 5a and 5b.

Tumor data analysis: The reviewer performed the trend test on data of all tumor types and the pairwise comparisons of the treated groups with the control for some selected tumor types. Since the sponsor classified the tumor types as 'cause of death' or 'not a cause of death', following Peto et al.(1980), the reviewer applied the 'death rate method' and the 'prevalence method' for testing the positive linear trend in these two categories of tumor types, respectively. For tumor types occurring in both categories a combined test was performed. The exact permutation trend test was used to calculate the p-values of all trend tests, except when the tumors were found in the both categories, in which cases the continuity corrected normal test was used. The scores used were 0, 50, 100, and 150 for control, low, medium, and high dose groups, respectively. The time intervals used were 0-365, 366-550, 551-660, 661-734 days, and terminal sacrifice for males and 0-365, 366-550, 551-660, 661-732 days, and terminal sacrifice for females. None of the tested tumor types showed a statistically significant positive linear trend in either sex.

The P-values of the tested tumor types are given in Table 6.

#### **IV. Evaluation of validity of the design**

The reviewer's analysis did not show any statistically significant positive linear trend or increased tumor incidence in the treatment groups in the tested tumor types in the mouse or rat study. However, before drawing the conclusion that the drug is not carcinogenic in mice and rats, it is important to look into the following two issues as having been pointed out in the paper by Haseman (Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies, Environmental Health Perspectives, Vol. 58, pp 385-392, 1984).

(i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumor?

(ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman (Issues in carcinogenicity testing: Dose selection, Fundamental and Applied Toxicology, Vol. 5, pp 66-78, 1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on an average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Statistical Application and Research Branch, Division of Biometrics, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would be considered as a sufficient number and adequate exposure.

In addition Chu, Cueto and Ward (Factors in the evaluation of 200 national cancer institute carcinogen bioassay, Journal of Toxicology and environmental Health. Vol. 8, pp 251-280, 1981), suggested that " To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources, that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy.

i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."

ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the experimental designs of the Sabril mouse and rat carcinogenicity studies, in the light of the above guidelines.

### Mouse study

The following are the summary survival data of mice in high dose group.

	End of 52 weeks	End of 78 weeks (End of the study)
Male	96.00%	82.00%
Female	82.00%	64.00%

From this summary data, and the survival criteria mentioned above, it can be concluded that there were enough number of mice exposed for sufficient amount of time to the drug in both sexes.

The following are summary body weight gains data of the mouse study.

		Mean body weight(gms)			
<u>Sex</u>	<u>Group</u>	<u>Beginning of study</u>	<u>End of study</u>	<u>Weight gain</u>	<u>Percentage of Control</u>
Male	Control	25.3	45.03	19.73	
	Low	25.3	44.12	18.82	95.39
	Medium	25.3	40.93	15.63	79.21
	High	25.3	39.22	13.92	70.55
Female	Control	19.6	35.49	15.89	
	Low	19.6	36.47	16.87	106.16
	Medium	19.6	33.48	13.88	87.35
	High	19.6	32.74	12.87	80.99

Therefore, relative to the control, decrement of body weight gain in the high dose group equals to 29.45% for males and 19.01 for females.

The mortality rates at the end of the experiment are as follows:

	<u>Control</u>	<u>Low</u>	<u>Medium</u>	<u>High</u>
Male	12.00%	18.00%	18.00%	18.00%
Female	22.00%	34.00%	30.00%	36.00%

The above table shows that compared to the control, the mortality rate in the high dose group is 6% and 14% higher in males and females respectively.

Thus, from the weight gain and mortality criteria it appears that the high dose used in mouse study was over MTD. However, to draw any final conclusion in this regard all clinical signs and histopathological effects must be taken into consideration.

### Rat study

The following are the summary survival data of mice in high dose group.

	End of 52 <u>weeks</u>	End of 78 <u>weeks</u>	End of 104 <u>weeks</u> (End of the study)
Male	90.00%	84.00%	62.00
Female	96.00%	92.00%	76.00

From this summary data, and the survival criteria mentioned above, it can be concluded that there were enough number of mice exposed for sufficient amount of time to the drug in both sexes.

The following are summary body weight gains data of the mouse study.

<u>Sex</u>	<u>Group</u>	Mean body weight(gms)			
		<u>Beginning of study</u>	<u>End of study</u>	<u>Weight gain</u>	<u>Percentage of Control</u>
Male	Control	175.5	654.86	470.36	
	Low	176.5	638.40	461.90	98.20
	Medium	176.3	550.10	373.80	79.49
	High	176.5	454.29	277.79	59.05
Female	Control	145.8	372.24	226.44	
	Low	145.5	358.80	213.30	94.19
	Medium	145.0	356.76	211.76	93.51
	High	145.7	316.16	170.46	75.28

Therefore, relative to the control, decrement of body weight gain in the high dose group equals to 40.95% for males and 24.72% for females.

The mortality rates at the end of the experiment are as follows:

	<u>Control</u>	<u>Low</u>	<u>Medium</u>	<u>High</u>
Male	40.00%	38.00%	24.00%	38.00%
Female	28.00%	30.00%	32.00%	24.00%

The above table shows that compared to the control, the mortality rate in the high dose group is 2% and 4% lower in males and females respectively.

Thus, from the weight gain criterion it appears that the high dose used in mouse study is over MTD. However, the mortality criteria does not support it. To draw any final conclusion in this regard all clinical signs and histopathological effects must be taken into consideration.

## V. Summary

Mouse study: No statistically significant (at .05 level) positive linear trend or differences in the mortality among treatment groups was detected in either sex.

None of the tested tumor types showed a statistically significant positive linear trend in either sex.

From the weight gain and mortality criteria it appears that the high dose used in mouse study is over MTD. However, to draw any final conclusion in this regard all clinical signs and histopathological effects must be taken into consideration.

The rat study: No statistically significant (at .05 level) positive linear trend or difference in the mortality among treatment groups was detected in either sex.

None of the tested tumor types showed a statistically significant positive linear trend in either sex.

From the weight gain criterion it appears that the high dose used in mouse study is over MTD. However, the mortality criteria does not support it. To draw any final conclusion in this regard all clinical signs and histopathological effects must be taken into consideration.

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HFD-120/Dr. Leber  
HFD-120/Dr. Rosloff  
HFD-710/Chron  
HFD-715/Dr. K. Lin  
HFD-715/Dr. Rahman  
HFD-715/SARB Chron  
HFD-715/DRU 2.1.1 NDA 20-427 Mouse and Rat  
carcinogenicity studies  
HFD-502/Assistant Director (Pharmacology)  
HFD-715/Diskette Rahman-2/SABRIL.CAR  
HFD-400/Dr. Contrera

**Table 1**

Intercurrent mortality rates in the mouse study

<u>Sex</u>	<u>Time (Days)</u>	<u>Control</u>	<u>Low</u>	<u>Medium</u>	<u>High</u>
Male	0- 365	2/50 (4.00)	1/50 (2.00)	4/50 (8.00)	2/50 (4.00)
	366-551	4/48 (12.00)	8/49 (18.00)	5/46 (18.00)	7/48 (18.00)
	Term. Sac.	44/50 (88.00)	41/50 (82.00)	41/50 (82.00)	41/50 (82.00)
Female	0- 365	8/50 (16.00)	12/50 (24.00)	9/50 (18.00)	9/50 (18.00)
	366-549	3/42 (22.00)	5/38 (34.00)	6/41 (30.00)	9/41 (36.00)
	Term. Sac.	39/50 (78.00)	33/50 (66.00)	35/50 (70.00)	32/50 (64.00)

Note: Except the TERM. SAC. row, an entry of this table =number of animals died or sacrificed in the time interval/number of animals entering the time interval. An entry in parenthesis =cumulative mortality rate; i.e. cumulative percent of animals dying up to the end of the time interval. An entry in the TERM. SAC. row =number of animals surviving to terminal sacrifice/initial number of animals. An entry in parenthesis in this row =percent of animals (of the initial number) surviving to terminal sacrifice.

**Table 2a**

P-values of tests for positive linear trend in mortality  
in the mouse study

Test of homogeneity

<u>Sex</u>	<u>Test</u>	<u>P-value</u> (One tail Chi-Sqr.)
Male	Cox	.8056
	Wilcoxon	.7992
Female	Cox	.4606
	Wilcoxon	.4621

Test of Positive linear trend

<u>Sex</u>	<u>Test</u>	<u>P-value</u> (One tail Normal)
Male	Cox	.2238
	Wilcoxon	.2234
Female	Cox	.1105
	Wilcoxon	.1219

Table 2b

P-values of pairwise tests for the differences in mortality  
between treatment groups in the mouse study

## Male mouse

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PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR) DSNAME: A:LTB.MMS

GROUP	EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST		GENERALIZED K/W ANALYSIS	
				EXACT INVERSE	CONSERVATIVE	EXACT INVERSE	CONSERVATIVE
0 VS. 1	CHISO	.3137	POS	.3643	.3642	.7833	.7830
	PROB	.2883		.5451	.5452	.3761	.3762
0 VS. 2	CHISO	.3137	POS	.3449	.3448	.7252	.7251
	PROB	.2883		.5570	.5570	.3944	.3945
0 VS. 3	CHISO	.3137	POS	.3318	.3318	.6878	.6878
	PROB	.2883		.5646	.5646	.4069	.4069
1 VS. 2	CHISO	.0000	POS	.0003	.0003	.0011	.0011
	PROB	.6024		.9853	.9853	.9733	.9733
1 VS. 3	CHISO	.0000	POS	.0000	.0000	.0000	.0000
	PROB	.6024		.9974	.9974	.9979	.9979
2 VS. 3	CHISO	.0000	POS	.0002	.0002	.0005	.0005
	PROB	.6024		.9855	.9855	.9815	.9815

## Female mouse

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR) DSNAME: A:LTB.FMS

GROUP	EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST		GENERALIZED K/W ANALYSIS	
				EXACT INVERSE	CONSERVATIVE	EXACT INVERSE	CONSERVATIVE
0 VS. 1	CHISO	1.2401	POS	1.4817	1.4812	2.1877	2.1869
	PROB	.2655		.2235	.2236	.1391	.1392
0 VS. 2	CHISO	.4878	POS	.5511	.5509	.9534	.9532
	PROB	.2473		.4579	.4579	.3288	.3289
0 VS. 3	CHISO	1.7484	POS	1.6117	1.6105	1.9241	1.9229
	PROB	.1661		.2043	.2044	.1654	.1655
1 VS. 2	CHISO	.0460	NEG	.0703	.0703	.1963	.1963
	PROB	.4152		.7909	.7910	.6577	.6578
1 VS. 3	CHISO	.0000	POS	.0080	.0080	.0002	.0002
	PROB	.5000		.9286	.9286	.9887	.9887
2 VS. 3	CHISO	.1609	POS	.1550	.1549	.2505	.2504
	PROB	.3355		.6938	.6939	.6167	.6168

Table 3

Tumor rates and p-values of the tested tumor types for positive linear trend in mouse study

MALE MOUSE

<u>Organ Name</u>	<u>Tumor Name</u>	<u>MSFLG</u>	<u>Exact P-Value</u>	<u>Asymptotic P-value</u>	<u>C</u>	<u>L</u>	<u>M</u>	<u>H</u>
ADRENAL(S)	B CORTICAL NODULAR HYPE	S	0.2208	0.17340	2	0	3	3
EAR	M SQUAMOUS CELL CARCINO	S	1.0000	0.93505	1	0	0	0
LACRIMAL GL. POS	B PAPILLARY ADENOMA	S	0.7266	0.65540	1	2	0	1
LACRIMAL GL. POS	M FIBROSARCOMA	S	0.7778	0.73645	0	1	0	0
LACRIMAL GL. POS	M PULMONARY CARCINOMA	S	0.2222	0.10295	0	0	0	1
LARGE INTESTINE	B POLYPS	S	0.4910	0.31985	0	0	1	0
LIVER	B ANGIOMATOUS FOCI	S	0.7365	0.66285	0	1	0	0
LIVER	B BASOPHILIC FOCI	S	0.6123	0.48645	1	0	0	1
LIVER	B CLEAR CELL FOCI	S	0.8016	0.72445	1	0	1	0
LIVER	B HEMANGIOMA	S	1.0000	0.90465	1	0	0	0
LIVER	B HEPATOCELLULAR ADENOM	S	0.7887	0.75315	5	2	5	2
LIVER	B HYPERPLASTIC NODULE	S	1.0000	0.90465	1	0	0	0
LIVER	M HEMANGIOSARCOMA~	S	1.0000	0.90465	1	0	0	0
LIVER	M HEPATOCELLULAR CARCIN	S	0.8819	0.85575	6	1	4	2
LUNG	B PULMONARY ADENOMA	S	0.8194	0.79035	4	8	3	3
LUNG	M PULMONARY CARCINOMA	S	0.6497	0.52515	1	0	0	1
LYM.-HEMPOIETIC	M FIBROUS HISTIOCYTOMA	S	0.7365	0.66285	0	1	0	0
LYM.-HEMPOIETIC	M LYMPHOSARCOMA/LEUKEMI	S	0.4531	0.37965	0	4	1	2
TESTIS	B INTERSTITIAL CELL TUM	S	0.2455	0.08750	0	0	0	1
TESTIS	B SERTOLI CELL TUMOR	S	0.4910	0.31985	0	0	1	0
URINARY BLADDER	M LEIOMYOSARCOMA	S	0.4910	0.31985	0	0	1	0

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FEMALE MOUSE

<u>Organ Name</u>	<u>Tumor Name</u>	<u>MSFLG</u>	<u>Exact P-Value</u>	<u>Asymptotic P-value</u>	<u>C</u>	<u>L</u>	<u>M</u>	<u>H</u>
LACRIMAL GL. POS B	ENDOMETRIAL STROMAL P	S	0.4737	0.32015	0	0	1	0
LACRIMAL GL. POS B	HYPERPLASTIC NODULE	S	0.2368	0.08045	0	0	0	1
LACRIMAL GL. POS B	LEIOMYOMA	S	0.7895	0.67985	0	1	0	0
LACRIMAL GL. POS B	PAPILLARY ADENOMA	S	0.1685	0.08895	0	0	1	1
LACRIMAL GL. POS M	LEIOMYOSARCOMA	S	0.4737	0.32015	0	0	1	0
LIVER	B HEPATOCELLULAR ADENOM	S	1.0000	0.89830	1	0	0	0
LIVER	M HEPATOCELLULAR CARCIN	S	0.7194	0.64930	0	1	0	0
LUNG	B PULMONARY ADENOMA	S	0.9753	0.96620	4	5	4	0
LUNG	M PULMONARY CARCINOMA	S	1.0000	0.89830	1	0	0	0
LYM.-HEMOPOIETIC M	FIBROUS HISTIOCYTOMA	S	0.3913	0.15250	0	0	0	1
LYM.-HEMOPOIETIC M	LYMPHOSARCOMA/LEUKEMI	S	0.9782	0.97030	5	5	4	1
MAMMARY GLAND	M ADENOCARCINOMA	S	0.9634	0.93535	1	1	0	0
PAW/FOOT	M FIBROSARCOMA	S	0.3913	0.15250	0	0	0	1
SKIN/SUBCUTIS	M FIBROSARCOMA	S	0.7194	0.64930	0	1	0	0
SKIN/SUBCUTIS	M SUDORIFEROUS ADENOCAR	S	0.6604	0.55550	0	2	0	1
SPLEEN	B HEMANGIOMA	S	0.4820	0.30680	0	0	1	0
UTERUS	B ENDOMETRIAL STROMAL P	S	0.9919	0.98125	4	0	1	0
UTERUS	B HEMANGIOMA	S	1.0000	0.96450	2	0	0	0
UTERUS	B LEIOMYOMA	S	0.4820	0.30680	0	0	1	0
UTERUS	M ENDOMETRIAL STROMAL S	S	0.7886	0.70690	0	2	0	0
UTERUS	M LEIOMYOSARCOMA	S	0.6522	0.46730	0	0	1	0

**Table 4**

Intercurrent mortality rates in the rat study

<u>Sex</u>	<u>Time (Days)</u>	<u>Control</u>	<u>Low</u>	<u>Medium</u>	<u>High</u>
Male	0- 365	4/50 (8.00)	2/50 (4.00)	2/50 (4.00)	5/50 (10.00)
	366-550	3/46 (14.00)	3/48 (10.00)	3/48 (10.00)	3/45 (16.00)
	551-660	8/43 (30.00)	5/45 (20.00)	4/45 (18.00)	5/42 (26.00)
	661-734	5/35 (40.00)	9/40 (38.00)	3/41 (24.00)	6/37 (38.00)
	Term. Sac.	30/50 (60.00)	31/50 (62.00)	38/50 (76.00)	31/50 (62.00)
Female	0- 365	0/50 (0.00)	1/50 (2.00)	2/50 (4.00)	2/50 (4.00)
	366-550	2/50 (4.00)	3/49 (8.00)	1/48 (6.00)	2/48 (8.00)
	551-660	4/48 (12.00)	7/46 (22.00)	7/47 (20.00)	2/46 (12.00)
	661-732	8/44 (28.00)	4/39 (30.00)	6/40 (32.00)	6/44 (24.00)
	Term. Sac.	36/50 (72.00)	35/50 (70.00)	34/50 (68.00)	38/50 (76.00)

Note: Except the TERM. SAC. row, an entry of this table =number of animals died or sacrificed in the time interval/number of animals entering the time interval. An entry in parenthesis =cumulative mortality rate; i.e. cumulative percent of animals dying up to the end of the time interval. An entry in the TERM. SAC. row =number of animals surviving to terminal sacrifice/initial number of animals. An entry in parenthesis in this row =percent of animals (of the initial number) surviving to terminal sacrifice.

**Table 5a**

P-values of tests for positive linear trend in mortality  
in the mouse study

Test of homogeneity

<u>Sex</u>	<u>Test</u>	<u>P-value</u> (One tail Chi-Sqr.)
Male	Cox	.3516
	Wilcoxon	.3714
Female	Cox	.8229
	Wilcoxon	.8104

Test of Positive linear trend

<u>Sex</u>	<u>Test</u>	<u>P-value</u> (One tail Normal)
Male	Cox	.2918
	Wilcoxon	.3330
Female	Cox	.4026
	Wilcoxon	.4419

**Table 5b**

P-values of pairwise tests for the differences in mortality  
between treatment groups in the rat study

**Best Possible Copy****Male rat**

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR) DSNAME: A:LTA.MRT

GROUP	EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST		GENERALIZED K/W ANALYSIS	
				EXACT	INVERSE CONSERVATIVE	EXACT	INVERSE CONSERVATIVE
0 VS. 1	CHISQ	.0000	NEG	.0515	.0515	.2904	.2903
	PROB	.5000	1.0000	.8205	.8205	.5900	.5901
0 VS. 2	CHISQ	2.2518	NEG	2.2385	2.2344	2.6310	2.6287
	PROB	.3664	.1335	.1346	.1348	.1048	.1050
0 VS. 3	CHISQ	.0000	NEG	.0171	.0271	.0042	.0042
	PROB	.5000	1.0000	.8958	.8959	.9485	.9485
1 VS. 2	CHISQ	1.6830	NEG	1.3759	1.3751	1.4407	1.4400
	PROB	.0971	.1945	.2408	.2409	.2300	.2301
1 VS. 3	CHISQ	.0000	POS	.0090	.0050	.2302	.2301
	PROB	.5815	1.0000	.9245	.9246	.6313	.6314
2 VS. 3	CHISQ	1.6830	POS	1.7219	1.7202	2.1378	2.1357
	PROB	.0971	.1945	.1894	.1897	.1437	.1439

**Female rat**

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR) DSNAME: A:LTA.FRT

GROUP	EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST		GENERALIZED K/W ANALYSIS	
				EXACT	INVERSE CONSERVATIVE	EXACT	INVERSE CONSERVATIVE
0 VS. 1	CHISQ	.0000	POS	.0256	.0256	.2177	.2177
	PROB	.5000	1.0000	.8729	.8729	.6408	.6408
0 VS. 2	CHISQ	.0476	POS	.1404	.1404	.4428	.4427
	PROB	.4138	.8273	.7079	.7079	.5058	.5058
0 VS. 3	CHISQ	.0520	NEG	.0297	.0297	.0780	.0779
	PROB	.4100	.8197	.8632	.8632	.7801	.7801
1 VS. 2	CHISQ	.0000	POS	.0002	.0002	.0262	.0262
	PROB	.5000	1.0000	.9890	.9890	.8714	.8715
1 VS. 3	CHISQ	.2029	NEG	.2170	.2169	.4057	.4055
	PROB	.3264	.6524	.6414	.6414	.5242	.5243
2 VS. 3	CHISQ	.4464	NEG	.4787	.4783	.7392	.7386
	PROB	.2522	.5040	.4890	.4892	.3899	.3901

Table 6

Tumor rates and p-values of the tested tumor types for positive linear trend in rat study

## MALE RAT

Organ Name	Tumor Name	MSFLG	Exact Asymptotic		C	I	M	H
			P-Value	P-value				
ABDOMINAL CAVITY	M FIBROSARCOMA	S	0.9423	0.90420	1	1	0	0
ABDOMINAL CAVITY	M LIPOSARCOMA	S	0.0568	0.02330	0	0	0	2
ABDOMINAL CAVITY	M MYXOSARCOMA	S	0.6458	0.52000	1	0	0	1
ABDOMINAL CAVITY	M RETICULUM CELL SARCOM	S	0.5000	0.32735	0	0	1	0
ADRENAL	B CORTICAL ADENOMA	S	0.2385	0.08990	0	0	0	1
ADRENAL	B MEDULLARY NODULAR HYP	S	0.4658	0.40640	1	4	2	2
ADRENAL	B PHEOCHROMOCYTOMA	S	0.9018	0.87465	2	6	1	1
ADRENAL	M CORTICAL CARCINOMA	S	0.2385	0.08990	0	0	0	1
BRAIN	M ASTROCYTOMA	S	0.8250	0.74705	1	0	1	0
EAR	B SQUAMOUS PAPILLOMA	S	0.5308	0.33590	0	0	1	0
EAR	M MALIGNANT MELANOMA	S	0.2273	0.07075	0	0	0	1
KIDNEY	B LIPOMA	S	0.1959	0.10510	0	0	1	1
LIVER	B BASOPHILIC FOCI	S	0.2385	0.08990	0	0	0	1
LIVER	B CLEAR CELL FOCI	S	0.6458	0.52000	1	0	0	1
LIVER	B EOSINOPHILIC FOCI	S	0.9404	0.92200	2	7	1	1
LIVER	B HEPATOCELLULAR ADENOM	S	0.3944	0.27375	0	1	0	1
LIVER	B NODULAR HYPERPLASIA	S	1.0000	0.97750	2	0	0	0
LIVER	M HEPATOCELLULAR CARCIN	S	0.1923	0.10445	0	0	1	1
LUNG	B PULMONARY ADENOMA	S	0.9481	0.91200	1	1	0	0
LUNG	M BRONCHOGENIC CARCINOM	S	1.0000	0.92105	1	0	0	0
LYM./HEMOPOIETIC	M LYMPHOCYTIC LEUKEMIA/	S	0.7387	0.68945	3	2	2	2
LYMPH N., MAND.	M FIBROUS HISTIOCYTOMA	S	1.0000	0.92105	1	0	0	0
MAMMARY GLAND	B LIPOMA	S	1.0000	0.92105	1	0	0	0
MAMMARY GLAND	M FIBROSARCOMA	S	0.7693	0.68945	0	1	0	0
NOSE/TURBINATE	B PAPILLOMA OF THE NOSE	S	0.2385	0.08990	0	0	0	1
PANCREAS	B ISLET CELL ADENOMA	S	0.9481	0.91200	1	1	0	0
PITUITARY	B ADENOMA	S	0.9959	0.99460	19	13	10	9
SALIVARY GLAND	M FIBROSARCOMA	S	0.7769	0.69365	1	0	1	0
SKIN/SUBCUTIS	B FIBROMA	S	0.8973	0.85795	3	0	1	1
SKIN/SUBCUTIS	B LIPOMA	S	0.5693	0.48315	1	1	1	1
SKIN/SUBCUTIS	B PAPILLOMA	S	0.9481	0.91200	1	1	0	0
SKIN/SUBCUTIS	M FIBROSARCOMA	S	0.7407	0.66965	1	1	2	0
SKIN/SUBCUTIS	M FIBROUS HISTIOCYTOMA	S	0.9424	0.91595	2	3	1	0
SKIN/SUBCUTIS	M LIPOSARCOMA	S	1.0000	0.90465	1	0	0	0
SKIN/SUBCUTIS	M MYXOSARCOMA	S	0.9187	0.87635	2	0	1	0
SKIN/SUBCUTIS	M NEUROFIBROSARCOMA	S	0.5000	0.32735	0	0	1	0
SKIN/SUBCUTIS	M SQUAMOUS CELL CARCINO	S	0.1304	0.07985	0	0	1	1
SPLEEN	M HEMANGIOSARCOMA	S	0.2385	0.08990	0	0	0	1
STOMACH	B LEIOMYOMA	S	0.5308	0.33590	0	0	1	0
TESTIS	B INTERSTITIAL CELL TUM	S	0.2385	0.08990	0	0	0	1
TESTIS	B SERTOLI CELL TUMOR	S	0.2385	0.08990	0	0	0	1
THYMUS	M ADENOCARCINOMA	S	0.6364	0.59180	0	1	0	0
THYMUS	M FIBROUS HISTIOCYTOMA	S	0.9679	0.94340	3	1	1	0
THYROID	B C-CELL ADENOMA	S	0.7784	0.74215	4	5	3	3
TONGUE	B FIBROMA	S	0.5308	0.33590	0	0	1	0

Table 6 continued to the next page

Table 6 continued from the previous page

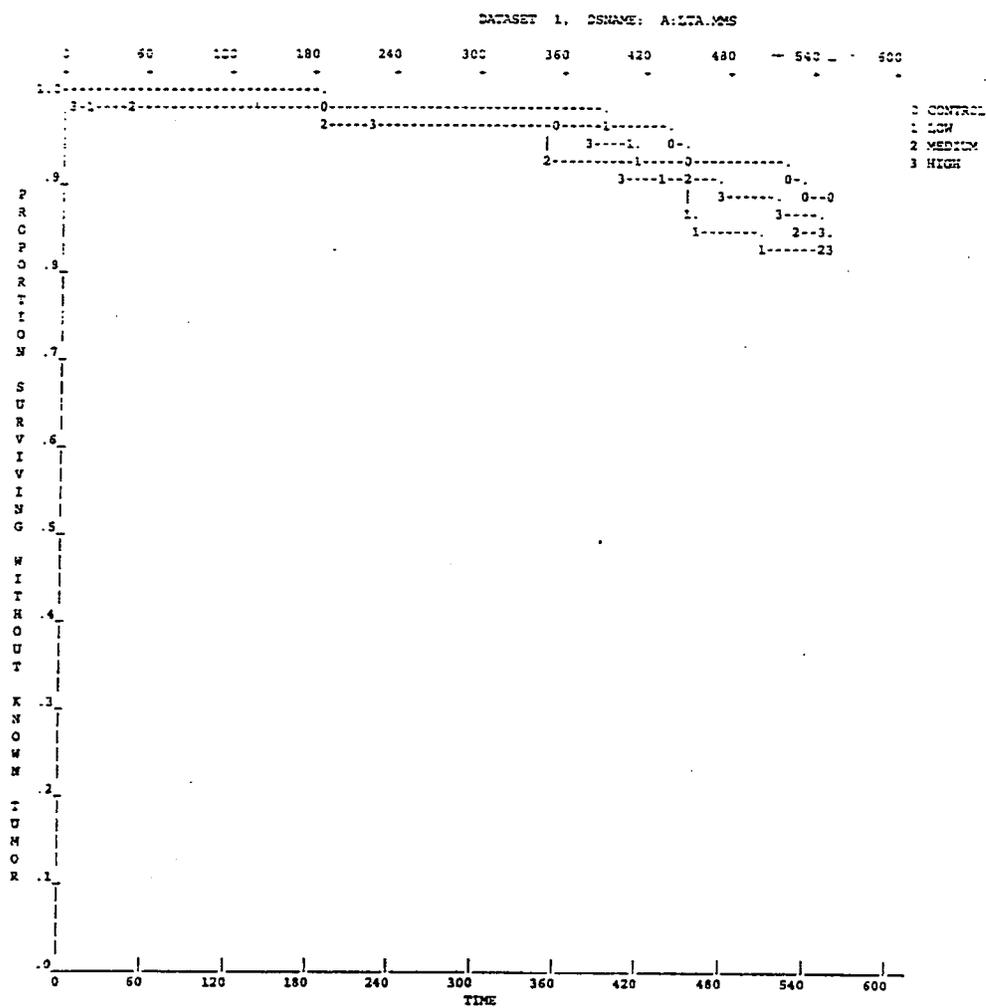
Female rats

<u>Organ Name</u>	<u>Tumor Name</u>	<u>MSFLG</u>	<u>Exact P-Value</u>	<u>Asymptotic P-value</u>	<u>C</u>	<u>L</u>	<u>M</u>	<u>H</u>
ABDOMINAL CAVITY	M FIBROSARCOMA	S	1.0000	0.89205	1	0	0	0
ABDOMINAL CAVITY	M UNDIFFERENTIATED ADEN	S	1.0000	0.88360	1	0	0	0
ADRENAL	B CORTICAL ADENOMA	S	0.2657	0.09545	0	0	0	1
ADRENAL	B MEDULLARY NODULAR HYP	S	0.6667	0.63720	0	1	0	0
ADRENAL	B PHEOCHROMOCYTOMA	S	1.0000	0.90970	1	0	0	0
EAR	M MALIGNANT MELANOMA	S	1.0000	0.90970	1	0	0	0
HEART	M HEMANGIOSARCOMA	S	0.2500	0.09120	0	0	0	1
JEJUNUM	M ADENOCARCINOMA	S	1.0000	0.90970	1	0	0	0
KIDNEY	B LIPOMA	S	0.7483	0.67600	0	1	0	0
LIVER	B CLEAR CELL FOCI	S	0.7180	0.65730	2	1	2	1
LIVER	B EOSINOPHILIC FOCI	S	0.7831	0.74535	4	2	6	1
LIVER	B HEPATOCELLULAR ADENOM	S	0.5793	0.49460	2	0	0	2
LIVER	B NODULAR HYPERPLASIA	S	1.0000	0.93110	1	0	0	0
LIVER	M HEPATOCELLULAR CARCIN	S	1.0000	0.90970	1	0	0	0
EMOPOIETIC	M LYMPHOCYTIC LEUKEMIA/	S	0.2429	0.17655	0	2	1	2
N., MAND.	M FIBROUS HISTIOCYTOMA	S	0.2657	0.09545	0	0	0	1
L. of N., MESEN.	B HEMANGIOMA	S	0.2657	0.09545	0	0	0	1
MAMMARY GLAND	B ADENOMA	S	0.9445	0.91445	2	1	1	0
MAMMARY GLAND	B FIBROADENOMA	S	0.9820	0.97290	3	6	1	0
MAMMARY GLAND	B LIPOMA	S	0.3827	0.27285	0	0	2	0
MAMMARY GLAND	M ADENOCARCINOMA	S	0.9401	0.92385	7	1	4	2
OVARY	M FIBROSARCOMA	S	0.4500	0.23745	0	0	1	0
OVARY	M GRANULOSA CELL TUMOR	S	0.5913	0.46365	0	1	1	0
PANCREAS	M ACINAR ADENOCARCINOMA	S	0.8985	0.86785	1	1	0	0
PAW/FOOT	M OSTEOGENIC OSTEOSARCO	S	1.0000	0.90970	1	0	0	0
PITUITARY	B ADENOMA	S	0.9991	0.99885	31	21	17	16
PITUITARY	B PHEOCHROMOCYTOMA	S	0.8000	0.60535	0	0	1	0
PITUITARY	M CARCINOMA	S	0.7483	0.67600	0	1	0	0
RECTUM	M SQUAMOUS CELL CARCINO	S	0.7483	0.67600	0	1	0	0
SALIVARY GLAND	M FIBROSARCOMA	S	1.0000	0.88360	1	0	0	0
SALIVARY GLAND	M FIBROUS HISTIOCYTOMA	S	0.2657	0.09545	0	0	0	1
SKIN/SUBCUTIS	B FIBROMA	S	0.7833	0.69585	1	0	1	0
SKIN/SUBCUTIS	B LIPOMA	S	1.0000	0.88360	1	0	0	0
SKIN/SUBCUTIS	M FIBROSARCOMA	S	0.9167	0.87800	2	0	1	0
SKIN/SUBCUTIS	M FIBROUS HISTIOCYTOMA	S	0.1000	0.03485	0	0	0	1
SKIN/SUBCUTIS	M SQUAMOUS CELL CARCINO	S	0.7483	0.67600	0	1	0	0
THYMUS	M THYMOMA	S	1.0000	0.90970	1	0	0	0
THYROID	B C-CELL ADENOMA	S	0.8536	0.81420	2	2	3	0
THYROID	B FOLLICULAR ADENOMA	S	0.2657	0.09545	0	0	0	1
UTERUS	B ENDOMETRIAL GLAND POL	S	1.0000	0.90970	1	0	0	0
UTERUS	B STROMAL POLYP	S	0.1133	0.08585	2	1	1	5
UTERUS	M ADENOCARCINOMA	S	0.6657	0.62400	5	4	3	4
UTERUS	M STROMAL CELL SARCOMA	S	0.8400	0.77440	1	1	1	0
VAGINA	M LEIOMYOSARCOMA	S	0.8000	0.64980	0	1	0	0

**Figure 1a**

Kaplan-Meier Estimates of the survival distributions  
(Male mice)

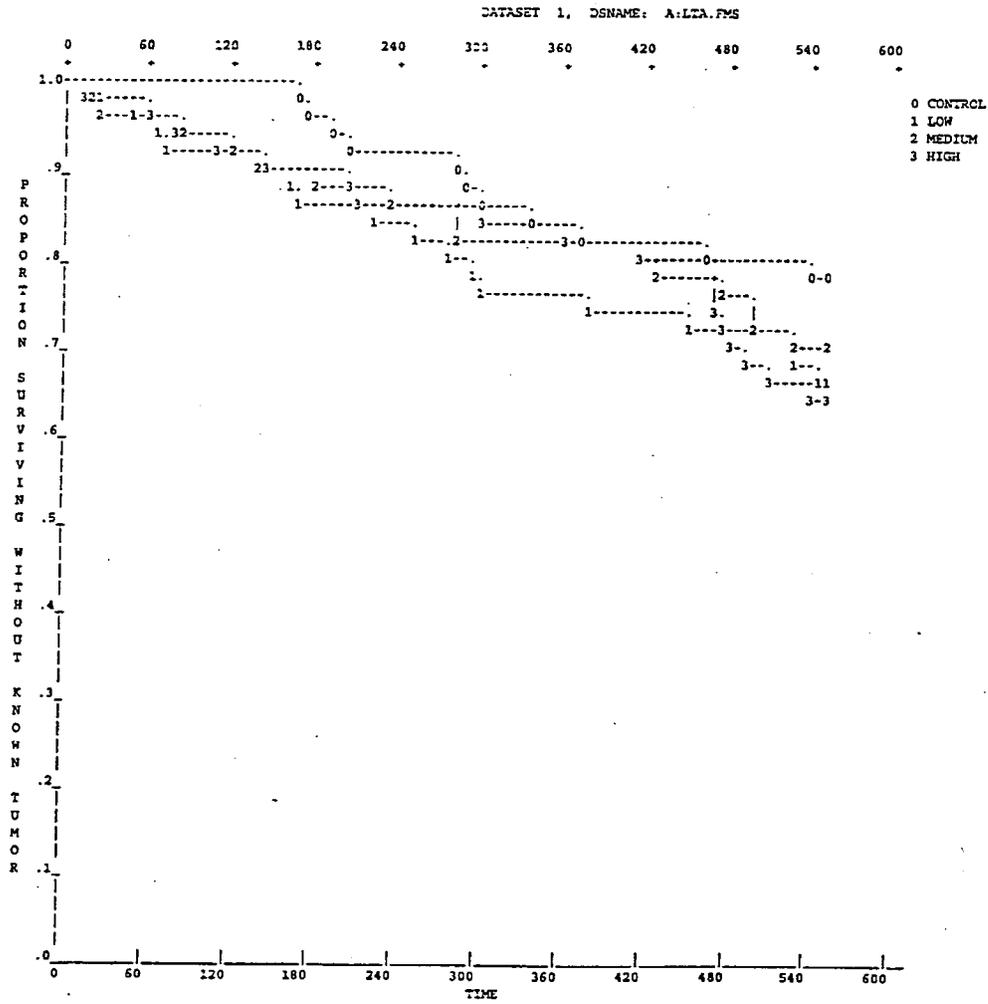
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**Figure 1b**

Kaplan-Meier Estimates of the survival distributions  
(Female mice)

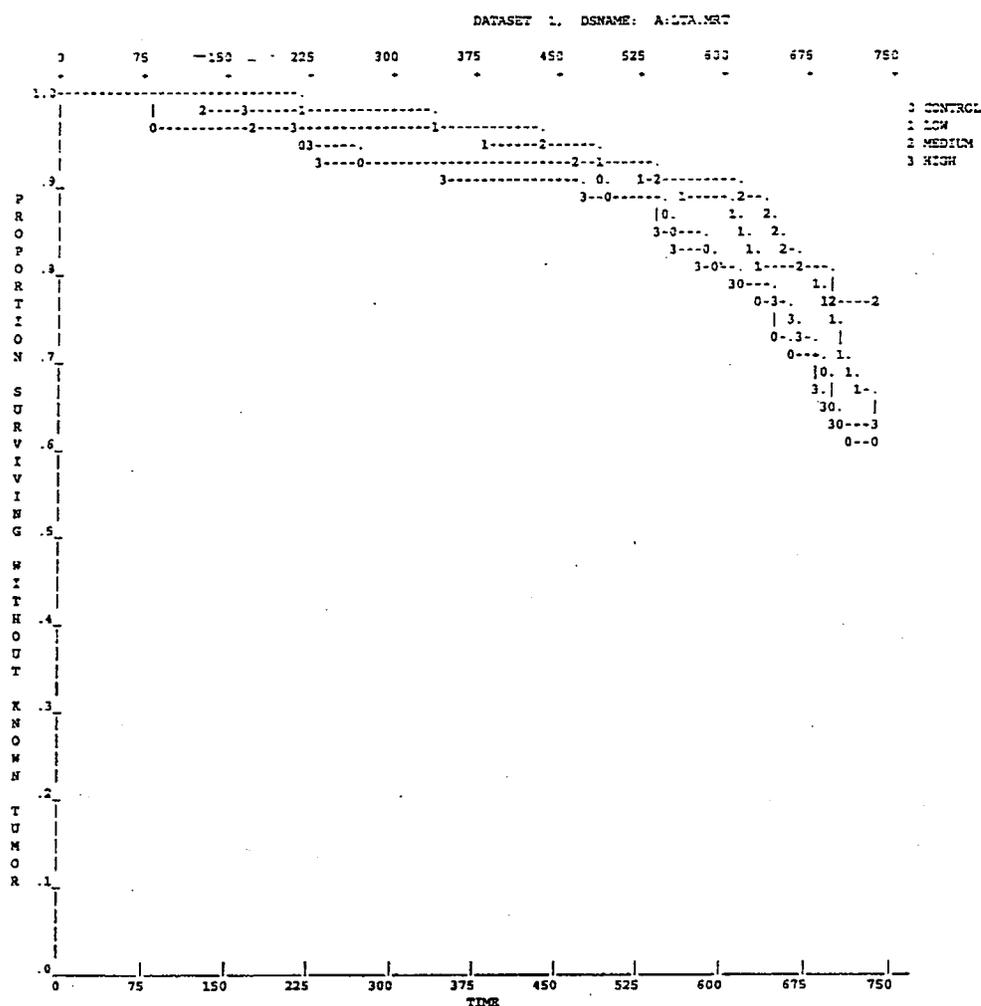
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**Figure 2a**

Kaplan-Meier Estimates of the survival distributions  
(Male rats)

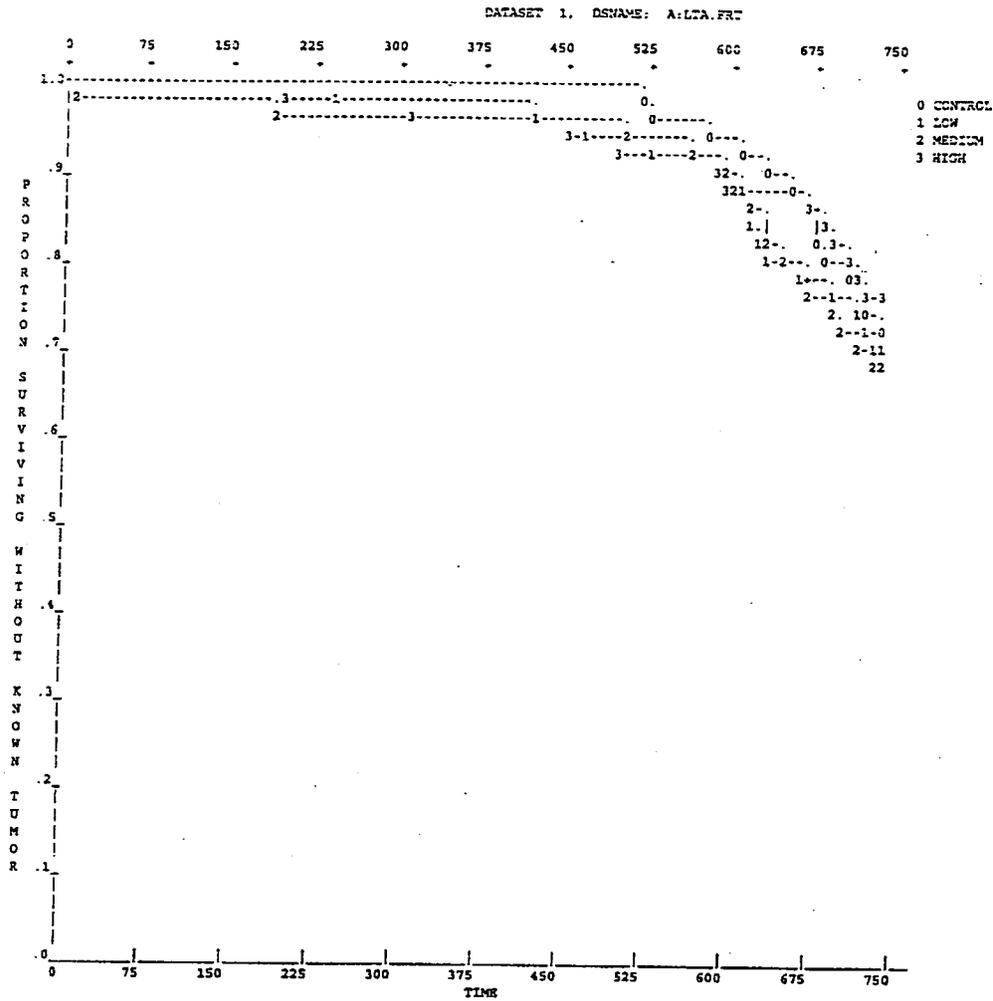
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**Figure 2b**

Kaplan-Meier Estimates of the survival distributions  
(Female rats)

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## STATISTICAL REVIEW AND EVALUATION

**NDA #:** 20-427 / Drug Class 1-S

MAR 7 1995

**Applicant:** Marion Merrell Dow Inc.

**Name of Drug:** Sabril®(vigabatrin)

DECISION

MAR 10 1995

**Indication:** Treatment of Epilepsy

**Documents Reviewed:** Volumes 1.94 thru 1.136, dated April 29, 1994; Amendments dated September 21, 1994, January 25, 1995 and February 15, 1995.

**Medical Reviewer:** Cynthia McCormick, M.D. (HFD-120). This review has been discussed with the medical reviewer who is in agreement with the conclusions stated.

This review is arranged in four sections. Section I gives a brief introduction of the studies under this submission. The two US studies are described along with sponsor's efficacy results, efficacy discussions and conclusions in Section II. This reviewer's independent evaluation of these studies is contained in Section III. Section IV contains the sponsor's response to the FDA-requested analysis of the data. Section V contains reviewer's conclusions that may be conveyed to the sponsor.

### **I. INTRODUCTION**

Two US placebo-controlled studies and 13 non-US placebo-controlled studies were conducted to evaluate the effectiveness of add-on vigabatrin (VGB) for the treatment of focal epilepsy. In this review, the two US completed placebo-controlled studies:

- Protocol 71754-3-C-024 (024)
- Protocol 71754-3-C-025 (025)

are evaluated for sponsor's claim. Protocol 024 evaluated the effectiveness of 3g vigabatrin daily compared to placebo. Protocol 025 assessed the presence of a dose response across the daily doses of placebo, 1g, 3g, and 6g vigabatrin.

### **II. DESCRIPTION OF STUDIES AND SPONSOR'S RESULTS**

#### **Protocol 71754-3-C-024**

#### **Study Objective**

The primary objective of this study was to evaluate the therapeutic efficacy and tolerance of vigabatrin 3 g/day, compared to placebo, when added to currently prescribed antiepilepsy drug (AED) therapy in patients with focal epilepsy whose complex partial seizures were difficult to control.

**KEY WORDS:** Epilepsy, Parallel Group, Dose-Response, Rank Transformation.

## Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel study in patients with focal epilepsy whose complex partial seizures were difficult to control with currently available therapy. Patients' seizures were classified according to the 1981 Revision of the International Classification of Epileptic Seizures (see Appendix I). The study was conducted in the following segments:

- **Initial Evaluation:**  
Patients were evaluated to determine eligibility for participation in the study.
- **Segment I:**  
Patients meeting entrance criteria for participation in the study were evaluated during a 12 week period. Patients were to be seen at three clinic visits during Segment I; Visit 1 (Week 4), Visit 2 (Week 8) and Visit 3 (Week 12).

The last 8 weeks during Segment I was considered Baseline.

- **Segment II:**  
Patients who met entry criteria at the end of Segment I were randomized to receive vigabatrin or placebo. Segment II was a 4 week Titration Period during which vigabatrin or placebo was started and the dose was increased as specified:
  - Week 1: One tablet BID (1g/day vigabatrin or placebo)
  - Week 2: One tablet in the a.m. and three tablets in the p.m. (1.5g/day vigabatrin or placebo)
  - Week 3: Two tablets BID (2g/day vigabatrin or placebo)
  - Week 4: Two tablets in the a.m. and three tablets in the p.m. (2.5g/day vigabatrin or placebo)

Patients were to be seen at two clinic visits during Segment II; Visit 1 (Week 2) and Visit 2 (Week 4).

- **Segment III:**  
Patients entered a 12 week Treatment Period at maintenance dosage (3g/day vigabatrin or placebo). Patients were to increase their study medication to three tablets twice daily at the start of Week 1 of Segment III and maintain this dose level throughout the segment.

Patients were to be seen at four clinic visits during Segment III; Visit 1 (Week 2), Visit 2 (Week 4), Visit 3 (Week 8) and Visit 4 (Week 12). Upon study completion, patients were allowed to enroll in a long-term, open-label study, Protocol No. 71754-3-C-020.

- **Taper Segment:**  
Patients discontinuing the study during Segment II or III, and patients not entering the long-term (1 year) study upon completion, had study drug tapered downward by decreasing the daily dose 1g/day (one tablet BID) on a weekly basis until study drug was discontinued.

The study design for Segments I, II and III is depicted in Figure 1 (in the Appendix II).

### **Primary Assessment of Efficacy**

The primary assessment of efficacy was the patients' mean monthly (28 day) 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).

### **Secondary Assessment of Efficacy**

Secondary efficacy assessments were performed using each of the following:

- Therapeutic success: A patient who experienced a >50% decrease in the frequency of complex partial seizures plus partial seizures secondarily generalized was considered a therapeutic success.
- Frequency of complex partial seizures (IB).
- Frequency of partial seizures secondarily generalized (IC).
- Frequency of simple partial seizures (IA).
- Frequency of seizure-free days (number per 28 days).
- Physician's global evaluation (completed at the final visit).
- Physician's evaluation of therapeutic effect (completed at the final visit).
- Physician's overall assessment of tolerability (completed at the final visit).

### **Sponsor's Efficacy Results**

#### **Subject Disposition**

A total of 203 patients were entered into the Baseline Period (Segment I) of the study. There were 20 patients who discontinued during the Baseline Period. Of the remaining 183 patients, 90 were randomized to receive placebo and 93 were randomized to receive vigabatrin. One patient randomized to vigabatrin group (060-903) discontinued prior to study drug administration. The distribution of randomized patients by investigative site and treatment group is summarized below.

Investigative Site	Number of Randomized Patients		Total
	Placebo	3 g/day VGB	
005	7	6	13
054	6	6	12
055	5	5	10
056	7	7	14
057	6	7	13
058	7	7	14
059	8	8	16
060	4	6 #	10 #
061	5	5	10
062	7	7	14
063	5	5	10
064	7	7	14
065	3	4	7
066	7	7	14
067	6	6	12
<b>Total</b>	<b>90</b>	<b>93 #</b>	<b>183 #</b>

# Patient 060-903 randomized to 3 g/day VGB did not consume study medication.

Of the 182 patients who were randomized and consumed study medication, 13 were considered to have major protocol violations and therefore were classified as Not Protocol Correct. The most common major protocol violations were changes in concurrent AED dosing after randomization (3 placebo, 3 vigabatrin) and failure to satisfy entry seizure frequency requirements (1 placebo, 3 vigabatrin).

### Analysis Datasets

Efficacy analyses used the Intent-to-Treat dataset composed of 182 patients who were exposed to double-blind study medication. Supportive efficacy analyses included the following datasets (all of these datasets were subsets of the Intent-to-Treat dataset.):

- Protocol Correct Completers: All patients who completed the 12-week Maintenance Period and had no major protocol violations.
- Protocol Correct: All patients with no major protocol violations.
- Study Completers: All patients who completed the 12-week Maintenance Period.
- 8-Week Completers: All patients with at least 8 weeks of post-randomization seizure data.

The following table gives a summary of the number of patients in each of these datasets across treatment groups.

Analysis Datasets	Number of Patients		Total
	Placebo	3 g/day VGB	
Intent-to-Treat	90	92	182
Protocol Correct Completers	84	76	160
Protocol Correct	86	83	169
Study Completers	88	82	170
8-Week Completers	88	86	174

## Baseline Comparisons

The Table 2 in Appendix III gives a summary of the 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, and duration of epilepsy. Concurrent AED use was similar in both treatment groups with a slightly higher percentage of vigabatrin patients than placebo patients using valproic acid (30% versus 19%, P=0.071).

## Efficacy Results

### 1. Analysis of Primary Efficacy Parameters

#### a. Primary Analysis of Complex Partial Seizures Plus Partial Seizures Secondarily Generalized (Intent-to-Treat Dataset)

The primary assessment of efficacy used an *intent-to-treat analysis* of patient's mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized (IB + IC). This analysis included all patients who were randomized and ingested study medication.

The Endstudy seizure frequencies were analyzed using analysis of covariance. A rank transformation was applied to the data prior to statistical analysis. A model adjusting for investigative site and Baseline seizure frequency was used to compare patient response across treatments.

The test for a difference in response to vigabatrin versus placebo was statistically significant (P=.0002). This indicates there was a lower Endstudy frequency of seizures for patients receiving vigabatrin than for patients receiving placebo. The median monthly frequency of seizures was reduced by three seizures per 28 days in the vigabatrin group versus 0.8 seizures per 28 days in the placebo group. The following table (which is a portion of Sponsor's Table 8-25 on page 8-1391, v1.94) gives the median Baseline and Endstudy seizure frequencies (IB + IC) together with the 95% confidence intervals for the medians for each treatment group.

<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	90	8.3 ( 6.5, 10.0)	7.5 ( 6.0, 9.0)
3 g VGB	92	8.3 ( 6.5, 10.0)	5.3 ( 3.5, 6.0)

The test for treatment by investigative site interaction was not statistically significant (P=.6634), indicating there were not significant differences in the vigabatrin effect relative to placebo across sites.

The Baseline seizure frequency was a significant predictor of response (P=.0001). 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=.3450), indicating that the vigabatrin effect relative to placebo was not significantly affected by Baseline seizure frequency.

*b. Supportive Analyses of Complex Partial Seizures Plus Partial Seizures  
Secondarily Generalized*

Supportive analyses used the Protocol Correct Completer, the Protocol Correct, the Study Completer, and the 8 week Completer datasets. These analyses used the same model used in the Intent-to-treat analysis.

The results of the Intent-to-treat analysis and all supportive analyses are summarized in the following table (which is a portion of Sponsor's Table 8-27 on page 8-1393, v1.94). The results of all four analyses were consistent with the Intent-to-treat analysis. In each case the comparison of placebo with vigabatrin was highly statistically significant (P<.0006).

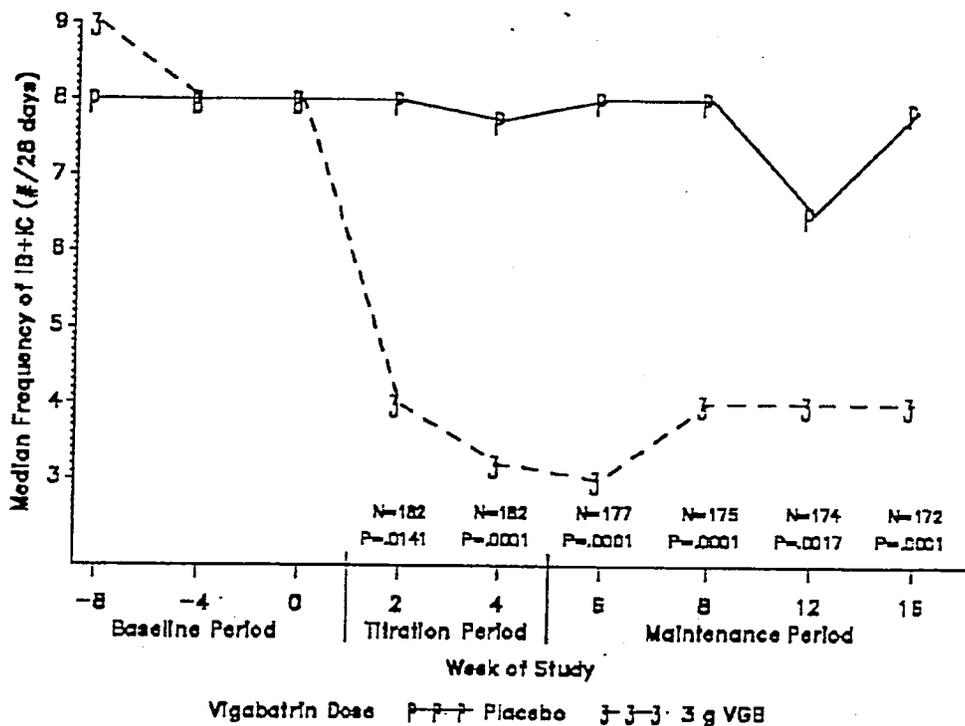
<b>Analysis Datasets</b>	<b>Total N</b>	<b>Treatment Comparison p-Value*</b>
Intent-to-Treat	182	0.0002
Protocol Correct Completers	160	0.0006
Protocol Correct	169	0.0002
Study Completers	170	0.0002
8-Week Completers	174	0.0003

\* : P-values from analysis of covariance of the ranked endstudy seizure frequencies using model which adjusted for treatment, site and ranked baseline seizure frequency

c. *By-Visit Analysis of Seizure Frequencies*

A separate analysis of complex partial seizures plus partial seizures secondarily generalized was performed for each visit following the start of study medication. The analysis of each study visit included only patients who had data in that visit window (see "IV, Biostatistical Approaches, b. Statistical Plan" on page 8-1361, v1.94). There were two patients (058-014, 060-007) who had data in the Segment III Visit 4 window, but were not study completers. Each analysis used the rank transformed data and the same statistical model as the Endstudy Intent-to-treat analysis.

Figure 8-3 on page 8-1394, v1.94, displayed below, presents a graphical display of the median frequencies of IB + IC seizures at each study visit. Included are the P values from the treatment comparisons at each visit. A statistically significant difference in seizure reduction between vigabatrin and placebo was observed following 2 weeks of treatment (P=.014) and at each subsequent visit.



Treatment Comparison 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.

Figure 8-3. Median Frequency of Complex Partial Seizures Plus Partial Seizures Secondarily Generalized, By Study Visit.

## 2. Analysis of Secondary Efficacy Parameters

### a. Analysis of Therapeutic Success

#### 1.) Intent-to-treat Patients

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. The following table gives the results of the Intent-to-treat patients analysis. A significantly greater percentage of patients in the vigabatrin group achieved therapeutic success than in the placebo group.

Treatment	N	Therapeutic Success	Treatment Comp. p-Value
		% (N)	
Placebo	90	19% (17)	<0.001
3 g VGB	92	43% (40)	

#### 2.) Protocol Correct Completer Patients

Results for the protocol Correct Completer patient population, the most restrictive subset of the Intent-to-treat population, are given in the following table. The results are consistent with the Intent-to-treat analysis, showing a significantly higher percentage of therapeutic successes in the vigabatrin group than in the placebo group.

Treatment	N	Therapeutic Success	Treatment Comp. p-Value
		% (N)	
Placebo	84	19% (16)	<0.001
3 g VGB	76	46% (35)	

### b. Analysis of Each Partial Seizure Type

Separate analyses were performed for the three types of partial seizures: simple partial (IA), complex partial (IB), and partial seizures secondarily generalized (IC). Analyses for each seizure type were first performed using all Intent-to-treat patients. Results of these analyses are not given here. Then, each analysis was repeated using Intent-to-Treat patients after excluding patients who had zero Baseline frequency of that seizure type. Results of these analyses are given here.

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 following table (which is a portion of Sponsor's Table 8-30 on page 8-1398, v1.94) gives the results of the analysis 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 versus 1.0 seizures per 28 days in the placebo group.

<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	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 )

The following table (which is a portion of Sponsor's Table 8-31 on page 8-1399, v1.94) gives the results of the analysis of partial seizures secondarily generalized (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 not statistically significant difference between the treatment groups ( $P=.3881$ ). The lack of statistical significance may be because the Baseline frequencies of partial seizures secondarily generalized was low, thus allowing only small differences between groups at Endstudy.

<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	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 )

The following table (which is a portion of Sponsor's Table 8-91 on page 8-3852, v1.101) gives the results of the analysis of simple partial seizures (IA). The analysis of simple partial seizures (IA) was performed using the 65 Intent-to-treat patients who had a nonzero Baseline frequency of simple partial seizures. The median monthly rate of simple partial seizures was increased by 1.0 seizure per 28 days in the vigabatrin

group versus 2.2 seizures per 28 days in the placebo group. However, there was not statistically significant difference between the treatment groups (P=.3951).

<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	34	4.3 ( 3.0, 11.5)	6.5 ( 4.0, 10.5)
3 g VGB	31	9.0 ( 3.5, 13.5)	10.0 ( 1.5, 14.0)

*c. Analysis of Seizure-Free Days*

The mean monthly frequency of seizure-free days was compared for the two treatment groups. The following table (which is a portion of Sponsor's Table 8-32 on page 8-1400, v1.94) gives the results of the Intent-to-treat analysis of seizure-free days. 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>Treatment</i>	<i>N</i>	<i>Mean Monthly Frequency of Seizure-Free Days</i>		<i>Adjusted Change From Baseline Mean ± SE</i>	<i>Treatment Comparison p-Value*</i>
		<i>Baseline Mean ± SE</i>	<i>Endstudy Mean ± SE</i>		
Placebo	90	18.4 ± 0.7	19.1 ± 0.7	0.5 ± 0.4	0.0024
3 g VGB	92	18.6 ± 0.7	20.8 ± 0.7	2.2 ± 0.4	

\* : Adjusted means and associated SEs from two-way ANCOVA of change from Baseline to Endstudy in rate of seizure-free days. P-value was estimated using the model adjusted for site and Baseline rate of seizure-free days.

*d. 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.

1.) Physician's Evaluation of Therapeutic Effect

The following table (which is a portion of Sponsor's Table 8-33 on page 8-1401, v1.94) gives the analysis of the Physician's Evaluation of Therapeutic Effect. Patients

receiving vigabatrin had significantly greater improvement than placebo patients (P<.001 from Mantel-Haenszel stratified by investigative site).

<b>Evaluation</b>	<b>Placebo % (N)</b>	<b>3 g VGB, % (N)</b>
Seizure Free	0% (0)	5% (5)
Markedly Improved	1% (1)	9% (8)
Moderately Improved	19% (17)	29% (27)
Minimally Improved	10% (9)	21% (19)
Unchanged	58% (52)	34% (31)
Minimally Worse	11% (10)	1% (1)
Moderately Worse	1% (1)	1% (1)
Markedly Worse	0% (0)	0% (0)
<b>TOTAL</b>	<b>N=90</b>	<b>N=92</b>

For purposes of summarization, the eight categories of response in the Physician's Evaluation of Therapeutic Effect, presented in the previous table were collapsed into three: improved, unchanged and worsened. There were 64% (59/92) of the vigabatrin patients and 30% (27/90) of the placebo patients who showed at least some improvement, as shown in the following table.

<b>Evaluation*</b>	<b>Placebo % (N)</b>	<b>3 g VGB % (N)</b>
Improved	30% (27)	64% (59)
Unchanged	58% (52)	34% (31)
Worsened	12% (11)	2% (2)
<b>TOTAL</b>	<b>N=90</b>	<b>N=92</b>

\*: Improved=seizure-free, markedly improved, moderately improved, and minimally improved

Unchanged=unchanged

Worsened=minimally worse, moderately worse, and markedly worse.

## 2.) Physician's Global Evaluation

The following table (which is a portion of Sponsor's Table 8-35 on page 8-1403, v1.94) gives the analysis of the Physician's Global Evaluation. There are nine categories of response: marked improvement, moderate improvement, mild improvement, minimal improvement, unchanged, minimal deterioration, mild deterioration, moderate deterioration, and severe deterioration. Again, patients receiving vigabatrin had significantly greater improvement than placebo patients (P=.015).

<b>Evaluation</b>	<b>Placebo % (N)</b>	<b>3 g VGB % (N)</b>
Marked Improvement	3% (3)	11% (10)
Moderate Improvement	9% (8)	16% (15)
Mild Improvement	2% (2)	13% (12)
Minimal Improvement	7% (6)	9% (8)
Unchanged	73% (66)	41% (38)
Minimal Deterioration	2% (2)	1% (1)
Mild Deterioration	2% (2)	3% (3)
Moderate Deterioration	1% (1)	3% (3)
Severe Deterioration	0% (0)	2% (2)
<b>TOTAL</b>	<b>N=90</b>	<b>N=92</b>

For purposes of summarization, the nine categories of response in the Physician's Global Evaluation, presented in the previous table were collapsed into three: improved, unchanged and worsened. There were 49% (45/92) of the vigabatrin patients and 21% (19/90) of the placebo patients who had at least some improvement, as given in the following table.

<b>Evaluation*</b>	<b>Placebo % (N)</b>	<b>3 g VGB % (N)</b>
Improved	21% (19)	49% (45)
Unchanged	73% (66)	41% (38)
Worsened	6% (5)	10% (9)
<b>TOTAL</b>	<b>N=90</b>	<b>N=92</b>

\*: Improved=marked improvement, moderate improvement, mild improvement, and minimal improvement  
 Unchanged=unchanged  
 Worsened=minimal deterioration, mild deterioration, moderate deterioration, and severe deterioration.

### 3.) Physician's Overall Assessment of Tolerability

The investigators also performed an Endstudy Physician's Overall Assessment of Tolerability of study drug, which is summarized in the following table (which is a

<b>Evaluation</b>	<b>Placebo % (N)</b>	<b>3 g VGB % (N)</b>
Extremely Well Tolerated	47% (42)	34% (31)
Well Tolerated	38% (34)	35% (32)
Fairly Well Tolerated	13% (12)	22% (20)
Poorly Tolerated	1% (1)	5% (5)
Very Poorly Tolerated	1% (1)	4% (4)
<b>TOTAL</b>	<b>N=90</b>	<b>N=92</b>

portion of Sponsor's Table 8-37 on page 8-1405, v1.94). Placebo was significantly better tolerated than vigabatrin (P=.004).

For purposes of summarization, the three categories of positive response in the Physician's Overall Assessment of Tolerability, presented in the previous table were collapsed into one, labelled tolerated. There were 90% (83/92) vigabatrin patients and 98% (88/90) placebo patients who had a tolerability assessment of "fairly well tolerated" or better, as given in the following table.

<b>Evaluation*</b>	<b>Placebo % (N)</b>	<b>3 g VGB % (N)</b>
Tolerated	98% (88)	90% (83)
Poorly Tolerated	1% (1)	5% (5)
Very Poorly Tolerated	1% (1)	4% (4)
<b>TOTAL</b>	<b>N=90</b>	<b>N=92</b>

\*: Tolerated=Extremely Well Tolerated, Well Tolerated, Fairly Well Tolerated.

### **Sponsor's Discussion of Efficacy**

The sponsor stated that the primary assessment of efficacy was an Intent-to-Treat (ITT) Analysis of the frequency of complex partial seizures plus partial seizures secondarily generalized. A highly statistically significant reduction in seizures was observed in vigabatrin patients versus placebo patients ( $P=0.0002$ ). The median monthly frequency of seizures was reduced by 3 seizures per 28 days in the vigabatrin group versus 0.8 seizures per 28 days in the placebo group. A statistically significant difference in seizure reduction between vigabatrin and placebo was observed following 2 weeks of treatment ( $P=0.0141$ ) and at each subsequent visit. Results obtained in Protocol Correct patients (86 placebo, 83 vigabatrin) and Protocol Correct Completers (84 placebo, 76 vigabatrin) were similar.

The sponsor also stated that vigabatrin was also effective when considering the secondary efficacy assessment of therapeutic success. A significantly greater percentage of patients in the vigabatrin group achieved  $\geq 50\%$  reduction in seizures than in the placebo group (43% versus 19%,  $P < 0.001$ ).

The sponsor further stated that vigabatrin was also superior to placebo in the Physician's Evaluation of Therapeutic Effect ( $P < 0.001$ ), Physician's Global Evaluation ( $P=0.015$ ), and in producing seizure-free days ( $P=0.0024$ ). Vigabatrin alleviated all seizures in five patients (Patient Numbers: 055-003, 057-003, 061-006, 062-004, and 067-012). There were no placebo patients who achieved complete control of seizures at Endstudy.

### **Sponsor's Conclusion**

The sponsor concluded that the results of this study supported vigabatrin 3 g/day as safe and effective add-on treatment in patients with focal epilepsy with difficult to control complex partial seizures.

## Protocol 71754-3-C-025

### Study Objective

The objective of this study was to evaluate the therapeutic efficacy and tolerance of vigabatrin in doses 1, 3, and 6g/day when added to currently prescribed antiepilepsy therapy in patients with focal epilepsy whose complex partial seizures were difficult to control.

### Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel study in patients with focal epilepsy whose complex partial seizures were difficult to control with currently available therapy. The study was conducted in the following segments:

- **Initial Evaluation:**  
Patients were evaluated to determine eligibility for participation in the study.
- **Segment I:**  
Patients meeting entrance criteria for participation in the study were evaluated during a 12 week Baseline Period. Patients were to be seen at three clinic visits during Segment I; Visit 1 (Week 4), Visit 2 (Week 8) and Visit 3 (Week 12).
- **Segment II:**  
Patients who met entry criteria at the end of Segment I were randomized to receive 1, 3 or 6g/day vigabatrin or placebo. Segment II was a 6 week Titration Period during which all patients received six tablets twice a day of either a combination of vigabatrin and placebo tablets or only placebo tablets.  
  
Patients were to be seen at three clinic visits during Segment II; Visit 1 (Week 2), Visit 2 (Week 4), and Visit 3 (Week 6).
- **Segment III:**  
Patients entered a 12 week Treatment Period at a maintenance dose of study medication (vigabatrin 1, 3 or 6g or placebo) throughout the segment.

Patients were to be seen at four clinic visits during Segment III; Visit 1 (Week 2), Visit 2 (Week 4), Visit 3 (Week 8) and Visit 4 (Week 12).

Upon study completion, patients were allowed to enroll in a long-term, open-label study, Protocol No. 71754-3-C-026.

- **Taper Segment:**

Patients discontinuing the study during Segment II or III, or patients not entering the long-term (1 year) study (Protocol No. 71754-3-C-026) were to have study medication tapered downward by decreasing the daily dose 1 tablet BID (1g/day) each week until drug was discontinued.

The study design is depicted in Figure 2 (see Appendix IV).

### **Primary Assessment of Efficacy**

The primary assessment of efficacy was the patients' mean monthly (28 day) 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).

### **Secondary Assessments of Efficacy**

Secondary efficacy assessments were performed using each of the following:

- Therapeutic success: A patient who experienced a >50% decrease in the frequency of complex partial seizures plus partial seizures secondarily generalized was considered a therapeutic success.
- Frequency of complex partial seizures (IB).
- Frequency of partial seizures secondarily generalized (IC).
- Frequency of simple partial seizures (IA).
- Frequency of seizure-free days (number per 28 days).
- Physician's global evaluation (completed at the final visit).
- Physician's evaluation of therapeutic effect (completed at the final visit).
- Physician's overall assessment of tolerability (completed at the final visit).

### **Sponsor's Efficacy Results**

#### **Subject Disposition**

A total of 203 patients were entered into the Baseline Period (Segment I) of the study. There were 29 patients who discontinued during the Baseline Period. Of the remaining 174 patients, 45 were randomized to receive placebo, 45 were randomized to receive 1g VGB, 43 were randomized to receive 3g VGB, and 41 were randomized to receive 6g VGB. The distribution of randomized patients by investigative sites and treatment groups is summarized below.

Investigative Site	Number of Randomized Patients				Total
	Placebo	1g 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
<b>Total</b>	<b>45</b>	<b>45</b>	<b>43</b>	<b>41</b>	<b>174</b>

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 and safety analyses using the treatment assignment they actually received. The treatment pertinent information for these eleven patients is contained in Sponsor's Table 8-12 on page 8-8413, vol 1.114.

Of the 174 patients who were randomized and consumed study medication, 14 were considered to have major protocol violations and therefore were classified as Not Protocol Correct. The following table presents disposition assignment by treatment group.

Treatment	Protocol Correct	Not Protocol Correct	Total
	N (%)	N (%)	
Placebo	43 (96%)	2 (4%)	45
1g VGB	42 (93%)	3 (7%)	45
3g VGB	40 (93%)	3 (7%)	43
6g VGB	35 (85%)	6 (15%)	41
<b>Total</b>	<b>160 (92%)</b>	<b>14 (8%)</b>	<b>174</b>

A listing of patients classified as Not Protocol Correct with major protocol violations is presented in Sponsor's Table 8-17 on page 8-8419, vol 1.114.

## Analysis Datasets

Efficacy analyses used the Intent-to-Treat dataset composed of 174 patients who were exposed to double-blind study medication. Supportive efficacy analyses included the following datasets (all of these datasets were subsets of the Intent-to-Treat dataset.):

- Protocol Correct Completers: All patients who completed the 12-week Maintenance Period and had no major protocol violations.
- Protocol Correct: All patients with no major protocol violations.
- Study Completers: All patients who completed the 12-week Maintenance Period.
- 8-Week Completers: All patients with at least 8 weeks of post-randomization seizure data.

The following table gives a summary of the number of patients in each of these datasets across treatment groups.

Analysis Dataset	Number of Patients				Total
	Placebo	1g VGB	3g VGB	6g VGB	
Intent-to-Treat	45	45	43	41	174
Protocol Correct Completers	40	38	33	27	138
Protocol Correct	43	42	40	35	160
Study Completers	42	40	36	31	149
8-Week Completers	42	41	39	35	157

## Baseline Comparisons

The Table 3 in Appendix V gives a summary of the 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, concomitant antiepilepsy drugs (AEDs), age at onset of epilepsy, and duration of epilepsy. Antiepilepsy drug (AED) use was similar in all treatment groups.

## Efficacy Results

### 1. Analysis of Primary Efficacy Parameters

#### a. Primary Analysis of Complex Partial Seizures Plus Partial Seizures Secondarily Generalized (Intent-to-Treat Dataset)

The primary assessment of efficacy used an *Intent-to-treat analysis* of patient's mean monthly frequency of complex partial seizures plus partial seizures secondarily

generalized (IB + IC). This analysis included all patients who were randomized and ingested study medication.

The Endstudy seizure frequencies were analyzed using analysis of covariance. A rank transformation was applied to the data prior to statistical analysis. A model adjusting for investigative site, Baseline seizure frequency, and investigative site by treatment interaction was used to compare patient response across treatments.

The test for a linear trend across doses was highly statistically significant ( $P=.0001$ ), indicating the effect of vigabatrin increases as the dose increases from 0 to 6g per day. The 1g vigabatrin dose was not statistically different from placebo ( $P=.1263$ ). The 3g vigabatrin and 6g vigabatrin doses were significantly superior to placebo in reducing seizure frequency ( $P=.0001$  for each). The 6g vigabatrin dose was not superior to the 3g vigabatrin dose ( $P=.8140$ ).

The median monthly frequency of seizures was reduced by 0.2 seizures per 28 days in the placebo group, 0.8 seizures per 28 days in the 1g vigabatrin group, 4.3 seizures per 28 days in the 3g vigabatrin group, and 4.5 seizures per 28 days in the 6g vigabatrin group. The following table (which is a portion of Sponsor's Table 8-29 on page 8-8438, v1.114) gives the median Baseline and Endstudy seizure frequencies (IB + IC) together with the 95% confidence intervals for the medians for each treatment group.

<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	9.0 ( 7.0, 10.5)	8.8 ( 6.0, 12.1)
1 g VGB	45	8.5 ( 6.0, 12.3)	7.7 ( 4.1, 11.5)
3 g VGB	43	8.0 ( 7.0, 10.5)	3.7 ( 2.5, 6.0)
6 g VGB	41	9.0 ( 7.0, 14.5)	4.5 ( 3.3, 6.0)

The test for treatment by investigative site interaction was statistically significant ( $P=.0112$ ), and was therefore included in the model for all analyses of complex partial seizures plus partial seizures secondarily generalized. The significance of this interaction indicates that the relative effect of the vigabatrin doses was not consistent across the different sites.

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.

*b. Supportive Analyses of Complex Partial Seizures Plus Partial Seizures  
Secondarily Generalized*

Supportive analyses used the Protocol Correct Completer, Protocol Correct, Study Completer, and 8 week Completer datasets. These analyses used the same model as the Intent-to-treat analysis.

The results of the Intent-to-Treat analysis and the supportive analyses are summarized in the following table (which is a portion of Sponsor’s Table 8-31 on page 8-8441, v1.114). The results of the four supportive analyses were consistent with the primary Intent-to-Treat analysis.

Population	N	Treatment Comparison p-Values*					
		Linear Trend	Placebo versus 1g VGB	Placebo versus 3g VGB	Placebo versus 6g VGB	3g VGB versus 6g VGB	Placebo + 1g VGB versus 3g VGB + 6g VGB
Intent-to-Treat	174	0.0001	0.1263	0.0001	0.0001	0.8140	0.0001
Protocol Correct Completers	138	0.0002	0.4886	0.0004	0.0008	0.9276	0.0001
Protocol Correct	160	0.0001	0.2043	0.0009	0.0001	0.4404	0.0001
Study Completers	149	0.0001	0.2254	0.0001	0.0001	0.4863	0.0001
Eight-Week Completers	157	0.0002	0.2151	0.0001	0.0007	0.5682	0.0001

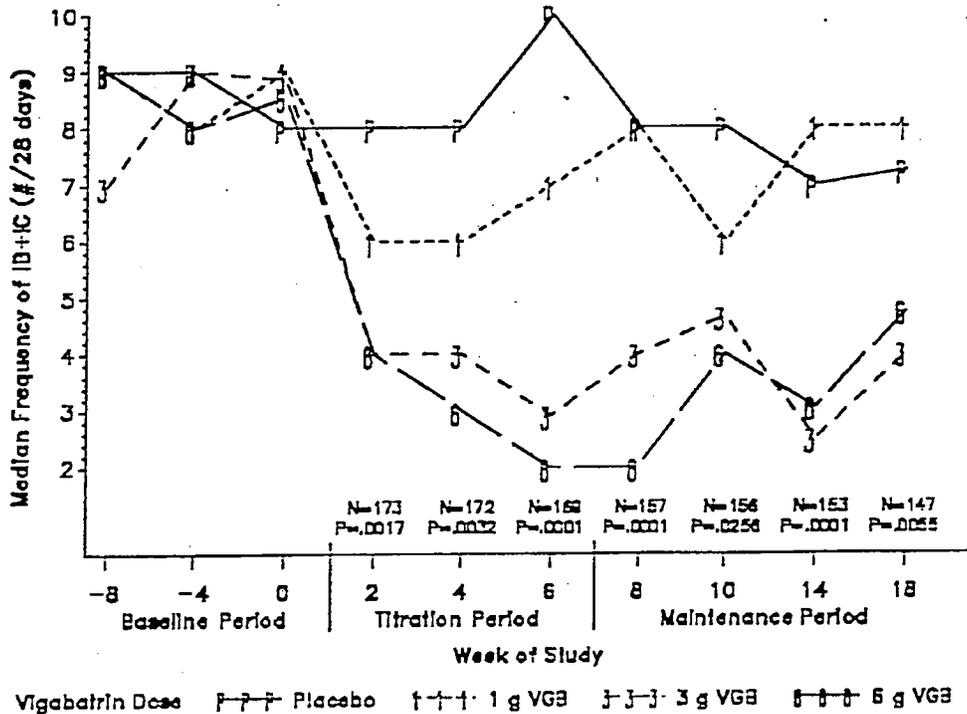
\*: P-values from ANCOVA of the ranked endstudy seizure frequencies using model which adjusted for treatment, investigative site, ranked baseline seizure frequency, and site-by-treatment interaction.

*c. By-Visit Analysis of Seizure Frequencies*

A separate analysis of complex partial seizures secondarily generalized was performed for each visit following the start of study medication. The analysis of each study visit included only patients who had data in that visit window, as defined in

IV.B.2."1. Dataset Definitions" on page 8-8403, v1.114. Two patients (012-113, 089-008) had missing Study Dose Records for Segment III Visit 4, but were Study Completers. Since it was uncertain whether study medication was consumed during the Segment III Visit 4 window, seizure frequencies were not computed. Each analysis used the rank transformed data and the same statistical model as the Endstudy Intent-to-treat analysis.

Figure 8-3 on page 8-8442, v1.114, displayed below, presents a graphical display of the median frequency of IB + IC seizures at each study visit. Also included are the P values for the linear trend test at each visit. A significant dose response relationship in reduction of seizure frequency was observed following 2 weeks of treatment and at each subsequent visit.



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

Figure 8-3. Median Frequency of Complex Partial Seizures Plus Partial Seizures Secondarily Generalized, By Study Visit.

## 2. Analysis of Secondary Efficacy Parameters

### a. Analysis of Therapeutic Success

#### 1.) Intent-to-treat Patients

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. The following table (which is a portion of Sponsor's Table 8-32 on page 8-8444, v 1.114) gives the results of the Intent-to-treat patients analysis. Twenty-four percent (24%) of the patients achieved therapeutic success on 1g vigabatrin versus 7% on placebo. Therapeutic success was achieved in 51% of the patients receiving 3g and 54% receiving 6g vigabatrin. A statistically significant linear dose response ( $P < .0001$ ) was observed in the percentage of therapeutic success patients. All three vigabatrin dose groups were statistically significantly different from placebo, with 6g not statistically different from 3g.

Therapeutic Success				Treatment Comparison p-Values*					
Placebo (N=45) % N	1g VGB (N=45) % N	3g VGB (N=43) % N	6g VGB (N=41) % N	Linear Trend	Placebo versus 1g VGB	Placebo versus 3g VGB	Placebo versus 6g VGB	3g VGB versus 6g VGB	Placebo + 1g VGB versus 3g VGB + 6g VGB
7% (3)	24% (11)	51% (22)	54% (22)	<.0001	0.0248	<.0001	<.0001	0.9655	<.0001

\*: P values from the comparison of the therapeutic success rates for each contrast, using a logistic regression model which adjusted for ranked baseline seizure frequency and investigative site.

#### 2.) Protocol Correct Completer Patients

Results for the Protocol Correct Completer patient population, the most restrictive subset of the Intent-to-treat population, are given in the following table (which is a

Therapeutic Success				Treatment Comparison p-Values*					
Placebo (N=40) % N	1g VGB (N=38) % N	3g VGB (N=33) % N	6g VGB (N=27) % N	Linear Trend	Placebo versus 1g VGB	Placebo versus 3g VGB	Placebo versus 6g VGB	3g VGB versus 6g VGB	Placebo + 1g VGB versus 3g VGB + 6g VGB
8% (3)	24% (9)	55% (18)	56% (15)	<.0001	0.0538	<.0001	0.0001	0.6126	<.0001

\*: P values from the comparison of the therapeutic success rates for each contrast, using a logistic regression model which adjusted for ranked baseline seizure frequency and investigative site.

portion of Sponsor's Table 8-33 on page 8-8445, v 1.114). The results were very similar to the Intent-to-treat patient population.

*b. Analysis of Each Partial Seizure Type*

Separate analyses were performed for the three types of partial seizures: simple partial (IA), complex partial (IB), and partial seizures secondarily generalized (IC). Analyses for each seizure type were first performed using all Intent-to-treat patients. Results of these analyses are not given here. Then, each analysis was repeated using Intent-to-Treat patients after excluding patients who had zero Baseline frequency of that seizure type. Results of these analyses are given here.

The analysis of complex partial seizures (IB) was performed using the 171 Intent-to-treat patients who had a nonzero Baseline frequency of complex partial seizures. The following table (which is a portion of Sponsor's Table 8-34 on page 8-8447, v1.114) gives the results of the analysis of complex partial seizures.

<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)

The following table (which is a portion of Sponsor's Table 8-34 on page 8-8447, v1.114) gives treatment comparison p-values for complex partial seizures (IB).

<i>Population</i>	<i>N</i>	<i>Treatment Comparison p-Values*</i>					
		<i>Linear Trend</i>	<i>Placebo versus 1g VGB</i>	<i>Placebo versus 3g VGB</i>	<i>Placebo versus 6g VGB</i>	<i>3g VGB versus 6g VGB</i>	<i>Placebo + 1g VGB versus 3g VGB + 6g VGB</i>
ITT Patients with Baseline Seizure Frequency > 0.	171	0.0001	0.1662	0.0014	0.0001	0.0557	0.0001

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

The results were consistent with the primary analysis which combined complex partial seizures and partial seizures secondarily generalized.

The analysis of partial seizures secondarily generalized (IC) using the 53 Intent-to-treat patients who had a nonzero Baseline frequency of partial seizures secondarily generalized is presented in the following table (which is a portion of Sponsor's Table 8-35 on page 8-8448, v1.114).

<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	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)

The reduction in median frequency of IC seizures increased as the dose of vigabatrin increased (0.7 for placebo, 1.0 for 1g VGB, 1.0 for 3g VGB, and 1.6 for 6g VGB). However, there was not statistically significant difference between the treatment groups in the Endstudy frequency of partial seizures secondarily generalized ( $P=0.4796$ ), and none of the treatment comparison contrasts were statistically significant ( $P\geq 0.1828$ ) as can be seen from the following table (which is a portion of Sponsor's Table 8-35 on page 8-8448, v1.114). The lack of statistical significance may be because the Baseline seizure frequencies for this seizure type were very low, thus allowing only small differences between groups at Endstudy.

<i>Population</i>	<i>N</i>	<i>Treatment Comparison p-Values*</i>					
		<i>Linear Trend</i>	<i>Placebo versus 1g VGB</i>	<i>Placebo versus 3g VGB</i>	<i>Placebo versus 6g VGB</i>	<i>3g VGB versus 6g VGB</i>	<i>Placebo + 1g VGB versus 3g VGB + 6g VGB</i>
ITT Patients with Baseline Seizure Frequency > 0.	53	0.8064	0.7527	0.1828	0.8610	0.2184	0.4140

\*: P-values from ANCOVA of the ranked endstudy seizure frequencies using model which adjusted for treatment, investigative site, ranked baseline seizure frequency.

The following table (which is a portion of Sponsor's Table 8-99 on page 8-11262, v1.122) gives the results of the analysis of simple partial seizures (IA). The analysis of simple partial seizures (IA) was performed using the 73 Intent-to-treat patients who had a nonzero Baseline frequency of simple partial seizures.

<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	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)

The median monthly rate of simple partial seizures was increased by 2.0 seizure per 28 days in the placebo group, 3.2 seizures per 28 days in the 1g VGB group, 2.2 seizures per 28 days in the 3g VGB group, and 3.2 seizures per 28 days in the 6g VGB group. However, there was not statistically significant difference between the treatment groups ( $P=.5940$ ). None of the treatment comparison contrasts were statistically significant ( $P \geq .1773$ ) as can be seen from the following table (which is a portion of Sponsor's Table 8-99 on page 8-11262, v1.114).

<i>Population</i>	<i>N</i>	<i>Treatment Comparison p-Values*</i>					
		<i>Linear Trend</i>	<i>Placebo versus 1g VGB</i>	<i>Placebo versus 3g VGB</i>	<i>Placebo versus 6g VGB</i>	<i>3g VGB versus 6g VGB</i>	<i>Placebo + 1g VGB versus 3g VGB + 6g VGB</i>
ITT Patients with Baseline Seizure Frequency > 0.	73	0.2051	0.9088	0.7511	0.1773	0.4035	0.2703

\*: P-values from ANCOVA of the ranked endstudy seizure frequencies using model which adjusted for treatment, investigative site, ranked baseline seizure frequency.

*c. Analysis of Seizure-Free Days*

The mean monthly frequency of seizure-free days was compared for the four treatment groups. The following table (which is a portion of Sponsor's Table 8-36, page 8-8449,

v1.114) gives the results of the Intent-to-treat analysis of seizure-free days.

Treatment	N	Mean Monthly Frequency of Seizure-Free Days		Adjusted* Change From Baseline Mean $\pm$ SE
		Baseline Mean $\pm$ SE	Endstudy Mean $\pm$ SE	
Placebo	45	17.6 $\pm$ 0.9	17.6 $\pm$ 1.0	(-0.1) $\pm$ 0.5
1 g VGB	45	17.4 $\pm$ 1.1	18.7 $\pm$ 1.1	1.3 $\pm$ 0.5
3 g VGB	43	17.4 $\pm$ 1.2	19.6 $\pm$ 1.4	2.0 $\pm$ 0.6
6 g VGB	41	19.3 $\pm$ 0.9	22.6 $\pm$ 0.8	3.2 $\pm$ 0.6

\* : Adjusted means and associated SEs from two-way ANCOVA of change from Baseline to Endstudy in rate of seizure-free days. Model used adjusted for investigative site and Baseline rate of seizure-free days.

There was a highly significant relationship between increased vigabatrin dose and increased number of seizure-free days ( $P=0.0001$ , see Sponsor's Table 8-36, page 8-8449, v1.114).

d. *Analysis 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. Also at the final visit, the investigators performed an overall assessment of the tolerability of study medication.

1.) Physician's Evaluation of Therapeutic Effect

The following table (which is a portion of Sponsor's Table 8-37 on page 8-8450, v1.114) gives the results of the analysis of the Physician's Evaluation of Therapeutic Effect. There was a significant dose response relationship between increased vigabatrin dose and improvement ( $P < 0.001$  from Mantel-Haenszel stratified by investigative site).

Evaluation	Placebo % (N)	1 g VGB % (N)	3 g VGB % (N)	6 g VGB % (N)
Seizure Free	0% (0)	0% (0)	5% (2)	13% (5)
Markedly Improved	4% (2)	9% (4)	14% (6)	11% (4)
Moderately Improved	16% (7)	23% (10)	21% (9)	32% (12)
Minimally Improved	33% (15)	36% (16)	30% (13)	26% (10)
Unchanged	44% (20)	32% (14)	30% (13)	16% (6)
Minimally Worse	2% (1)	0% (0)	0% (0)	3% (1)
Moderately Worse	0% (0)	0% (0)	0% (0)	0% (0)
Markedly Worse	0% (0)	0% (0)	0% (0)	0% (0)
<b>TOTAL</b>	<b>N=45</b>	<b>N=44</b>	<b>N=43</b>	<b>N=38</b>

For purposes of summarization, the eight categories of response in the Physician's Evaluation of Therapeutic Effect, presented in the previous table were collapsed into three: improved, unchange and worsened. There were 53% (24/45) of the placebo patients, 68% (30/44) of the 1g vigabatrin patients, 70% (30/43) of the 3g vigabatrin patients and 82% (31/38) of the 6g vigabatrin patients who exhibited at least some improvement in Physician's Evaluation of Therapeutic Effect, as shown in the following table.

<b>Evaluation*</b>	<b>Placebo % (N)</b>	<b>1 g VGB % (N)</b>	<b>3 g VGB % (N)</b>	<b>6 g VGB % (N)</b>
Improved	53% (24)	68% (30)	70% (30)	82% (31)
Unchanged	44% (20)	32% (14)	30% (13)	16% (6)
Worsened	2% (1)	0% (0)	0% (0)	3% (1)
<b>TOTAL</b>	<b>N=45</b>	<b>N=44</b>	<b>N=43</b>	<b>N=38</b>

\*: Improved=seizure-free, markedly improved, moderately improved, and minimally improved

Unchanged=unchanged

Worsened=minimally worse, moderately worse, and markedly worse.

## 2.) Physician's Global Evaluation

This evaluation is a combination of efficacy and tolerability. The following table (which is a portion of Sponsor's Table 8-39 on page 8-8452, v1.114) gives the analysis of the Physician's Global Evaluation. There are nine categories of response: marked improvement, moderate improvement, mild improvement, minimal improvement, unchanged, minimal deterioration, mild deterioration, moderate deterioration, and severe deterioration.

<b>Evaluation</b>	<b>Placebo % (N)</b>	<b>1 g VGB % (N)</b>	<b>3 g VGB % (N)</b>	<b>6 g VGB % (N)</b>
Marked Improvement	7% (3)	2% (1)	14% (6)	5% (2)
Moderate Improvement	11% (5)	18% (8)	21% (9)	21% (8)
Mild Improvement	7% (3)	14% (6)	2% (1)	16% (6)
Minimal Improvement	13% (6)	14% (6)	9% (4)	18% (7)
Unchanged	58% (26)	48% (21)	47% (20)	24% (9)
Minimal Deterioration	0% (0)	0% (0)	0% (0)	5% (2)
Mild Deterioration	2% (1)	0% (0)	2% (1)	3% (1)
Moderate Deterioration	2% (1)	5% (2)	5% (2)	5% (2)
Severe Deterioration	0% (0)	0% (0)	0% (0)	3% (1)
<b>TOTAL</b>	<b>N=45</b>	<b>N=44</b>	<b>N=43</b>	<b>N=38</b>

Improvement in physician's global evaluation was not significantly increased with vigabatrin dose ( $P=.215$ ), as shown in Sponsor's Table 8-39 on page 8-8452, v1.114. The lack of statistical significance is in part driven by the 16% (6/38) of the patients receiving 6g vigabatrin who experienced at least minimal deterioration.

For purposes of summarization, the nine categories of response in the Physician's Global Evaluation, presented in the previous table were collapsed into three: improved, unchanged and worsened. In the following table (which is a portion of Sponsor's Table 8-40 on page 8-8453, v1.114), 38% (17/45) of the placebo patients, 48% (21/44) of the 1g vigabatrin patients, 47% (20/43) of the 3g vigabatrin patients and 61% (23/38) of the 6g vigabatrin patients showed at least some improvement.

<b>Evaluation*</b>	<b>Placebo % (N)</b>	<b>1 g VGB % (N)</b>	<b>3 g VGB % (N)</b>	<b>6 g VGB % (N)</b>
Improved	38% (17)	48% (21)	47% (20)	61% (23)
Unchanged	58% (26)	48% (21)	47% (20)	24% (9)
Worsened	4% (2)	5% (2)	7% (3)	16% (6)
<b>TOTAL</b>	<b>N=45</b>	<b>N=44</b>	<b>N=43</b>	<b>N=38</b>

\*: Improved=marked improvement, moderate improvement, mild improvement, and minimal improvement

Unchanged=unchanged

Worsened=minimal deterioration, mild deterioration, moderate deterioration, and severe deterioration.

### 3.) Physician's Overall Assessment of Tolerability

The investigators also performed an Endstudy Physician's Overall Assessment of Tolerability of study drug, which is summarized in the following table (which is a portion of Sponsor's Table 8-41 on page 8-8454, v1.114). There was a statistically significant decrease in tolerability with increased vigabatrin dose ( $P < .001$ ).

<b>Evaluation</b>	<b>Placebo % (N)</b>	<b>1 g VGB % (N)</b>	<b>3 g VGB % (N)</b>	<b>6 g VGB % (N)</b>
Extremely Well Tolerated	36% (16)	32% (14)	33% (14)	13% (5)
Well Tolerated	49% (22)	52% (23)	42% (18)	34% (13)
Fairly Well Tolerated	11% (5)	7% (3)	12% (5)	34% (13)
Poorly Tolerated	4% (2)	5% (2)	9% (4)	11% (4)
Very Poorly Tolerated	0% (0)	5% (2)	5% (2)	8% (3)
<b>TOTAL</b>	<b>N=45</b>	<b>N=44</b>	<b>N=43</b>	<b>N=38</b>

For purposes of summarization, the five categories in the Physician's Overall Assessment of Tolerability were collapsed into two: tolerated and not tolerated.

<b>Evaluation*</b>	<b>Placebo % (N)</b>	<b>1 g VGB % (N)</b>	<b>3 g VGB % (N)</b>	<b>6 g VGB % (N)</b>
Tolerated	96% (43)	91% (40)	86% (37)	82% (31)
Not Tolerated	4% (2)	9% (4)	14% (6)	18% (7)
<b>TOTAL</b>	<b>N=45</b>	<b>N=44</b>	<b>N=43</b>	<b>N=38</b>

\*: Tolerated=Extremely Well Tolerated, Well Tolerated, Fairly Well Tolerated.

Not Tolerated=Poorly Tolerated, Very Poorly Tolerated.

There were 96% (43/45) of the placebo patients, 91% (40/44) of the 1g vigabatrin patients, 86% (37/43) of the 3g vigabatrin patients and 82% (31/38) of the 6g vigabatrin patients that had a tolerability assessment of "fairly well tolerated" or better, as shown in the following table (which is a portion of Sponsor's Table 8-42 on page 8-8455, v1.114).

### **Sponsor's Discussion of Efficacy**

The sponsor stated that the primary assessment of efficacy was an Intent-to-Treat (ITT) Analysis of the frequency of complex partial seizures plus partial seizures secondarily generalized. There was a highly statistical significant linear dose response across the four doses ( $P=0.0001$ ) indicating that seizure frequency is reduced with increased dose. The 1g/day dose was not statistically different from placebo ( $P=0.1263$ ), whereas 3g and 6g vigabatrin doses were ( $P=0.0001$  for each dose). The median monthly frequency of seizures was reduced by 4.3 seizures per 28 days in the 3g vigabatrin group and 4.5 seizures per 28 days in the 6g vigabatrin group versus 0.2 seizures per 28 days in the placebo group. Efficacy for reduction of seizure frequency was evident within two weeks of starting therapy and at each subsequent visit throughout the 18-week study period.

The sponsor also stated that vigabatrin was also effective when considering the secondary efficacy assessment of therapeutic success, defined as  $\geq 50\%$  reduction in seizures. A statistically significant linear dose response ( $P < 0.0001$ ) was observed across the four treatment groups. Nearly one-fourth of the patients achieved therapeutic success on 1g vigabatrin compared to 7% on placebo ( $P=0.0248$ ). Therapeutic success was achieved in over half of the patients treated with either 3g or 6g vigabatrin ( $P < 0.0001$  versus placebo for each). In this analysis, 6g/day was not statistically better than 3g vigabatrin.

The sponsor further stated that there was also a statistically significant dose response relationship observed in the Physician's Evaluation of Therapeutic Effect ( $P < 0.001$ ), and in producing seizure-free days ( $P=0.0001$ ). Vigabatrin alleviated all seizures in four 3g vigabatrin patients (Patient Numbers: 069-004, 071-012, 072-006, 089-008), five 6g vigabatrin patients (Patient Numbers: 006-101, 011-101, 012-113, 070-008, 093-010), while no 1g vigabatrin or placebo patients achieved complete control of seizures at Endstudy. No significant response was seen in the analysis of Physician's Global Evaluation ( $P=0.215$ ).

### **Sponsor's Conclusion**

The sponsor concluded that the results of this study demonstrated that vigabatrin is safe and effective as add-on treatment in patients with focal epilepsy with difficult to control complex partial seizures. The optimal dose of vigabatrin based on response and tolerability was 3g/day.

### III. STATISTICAL REVIEWER'S INDEPENDENT ANALYSES

The statistical reviewer evaluated the following efficacy variables for the two studies utilizing Intent-to-Treat dataset:

1. Patients' mean monthly (28 day) 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).
2. Therapeutic Success: A patient who experienced a >50% decrease in the frequency of complex partial seizures plus partial seizures secondarily generalized was considered a therapeutic success.

#### Protocol 71754-3-C-024

#### Baseline Comparison and Efficacy Evaluation

The following table gives a summary of patients' mean monthly frequency of (IB + IC) seizures for the Intent-to-Treat dataset at Baseline and at endstudy.

	Treatment Group	N	Median	Mean	Std. Error	Minimum	Maximum
<i>Baseline</i>	Placebo	90	8.3	14.9	1.8	1.0	78.5
	VGB 3g/day	92	8.3	35.3	11.1	3.0	663.0
<i>Endstudy</i>	Placebo	90	7.5	13.5	1.9	0.0	100.0
	VGB 3g/day	92	5.3	21.4	6.6	0.0	465.0

Note that the means are not appropriate statistics for this positively skewed data. The medians are appropriate here.

There is 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 a difference in response to vigabatrin versus placebo was statistically significant ( $P=0.0002$ ).

Also, an analysis of untransformed frequency of (IB + IC) seizures using the CMH test yielded a p-value of 0.608 for baseline comparison and 0.001 for endpoint comparison. That is, there is no statistically significant difference at baseline, but there is a statistically significant difference at endpoint, between the treatment groups in terms of raw (IB+IC) seizure frequencies.

A careful look at the above table indicates a presence of outliers in the VGB group. This reviewer reanalyzed the data by removing 6 patients from VGB group that had an (IB+IC) seizure frequency of 150 or more at baseline and at endpoint. The following table contains the results of the reanalysis.

	Treatment Group	N	Median	Mean	Std. Error	Minimum	Maximum
<i>Baseline</i>	Placebo	90	8.3	14.9	1.8	1.0	78.5
	VGB 3g/day	86	7.8	10.5	1.1	3.0	60.0
<i>Endstudy</i>	Placebo	90	7.5	13.5	1.9	0.0	100.0
	VGB 3g/day	86	4.5	8.2	1.6	0.0	108.0

Note that the means are not appropriate statistics for this positively skewed data. The medians are appropriate here.

There is no statistically significant difference between the treatment groups at baseline ( $P=0.1884$ , 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 a difference in response to vigabatrin versus placebo was statistically significant ( $P=0.0001$ ).

Also, an analysis of untransformed frequency of (IB + IC) seizures using the CMH test yielded a p-value of 0.197 for baseline comparison and  $p < 0.001$  for endpoint comparison. That is, there is no statistically significant difference at baseline, but there is a statistically significant difference at endpoint, between the treatment groups in terms of raw (IB+IC) seizure frequencies.

The following table gives a summary of patients' therapeutic success for the two treatment groups.

Treatment	N	Therapeutic Success	Treatment Comp. p-Value
		% (N)	
Placebo	90	19% (17)	<0.001
3 g VGB	92	43% (40)	

A significantly greater percentage of patients in the VGB group achieved therapeutic success than in the placebo group ( $P < 0.001$ , CMH test stratified by sites).

In the opinion of this reviewer, for the protocol 71754-3-C-024, the sponsor has provided sufficient statistical evidence of the effect of VIGABATRIN 3g/day as an add-on treatment in patients with focal epilepsy with difficult to control complex partial seizures.

**Protocol 71754-3-C-025**

**Baseline Comparison and Efficacy Evaluation**

The following table gives a summary of patients' mean monthly frequency of (IB + IC) seizures for the Intent-to-Treat dataset at Baseline and at endstudy.

	Treatment Group	N	Median	Mean	Std. Error	Minimum	Maximum
<i>Baseline</i>	Placebo	45	9.0	13.2	2.0	3.0	70.5
	VGB 1g/day	45	8.5	44.1	18.6	2.5	786.0
	VGB 3g/day	43	8.0	20.2	6.4	1.0	228.0
	VGB 6g/day	41	9.0	11.6	1.3	2.0	44.5
<i>Endstudy</i>	Placebo	45	8.8	13.1	1.9	2.0	54.0
	VGB 1g/day	45	7.7	28.7	10.4	0.0	437.8
	VGB 3g/day	43	3.7	15.9	6.0	0.0	211.5
	VGB 6g/day	41	4.5	6.6	1.2	0.0	42.9

Note that the means are not appropriate statistics for this positively skewed data. The medians are appropriate here.

There is no statistically significant difference between the treatment groups at baseline ( $P=0.9265$ , 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 a linear trend across doses was highly statistically significant ( $P=.0001$ ), indicating the effect of vigabatrin increases as the dose increases from 0 to 6g per day. The 1g vigabatrin dose was not statistically different from placebo ( $P=.1263$ ). The 3g vigabatrin and 6g vigabatrin doses were significantly superior to placebo in reducing seizure frequency ( $P=.0001$  for each). The 6g vigabatrin dose was not superior to the 3g vigabatrin dose ( $P=.8140$ ). Also, an analysis of untransformed endstudy (IB + IC) seizure frequencies using the CMH test (stratified for sites) yielded a p-value of  $< 0.001$ .

The following table gives a summary of patients' therapeutic success for the four treatment groups.

Therapeutic Success				Treatment Comparison p-Values*					
Placebo (N=45) % N	1g VGB (N=45) % N	3g VGB (N=43) % N	6g VGB (N=41) % N	Linear Trend	Placebo versus 1g VGB	Placebo versus 3g VGB	Placebo versus 6g VGB	3g VGB versus 6g VGB	Placebo + 1g VGB versus 3g VGB + 6g VGB
7% (3)	24% (11)	51% (22)	54% (22)	<.0001	0.0248	<.0001	<.0001	0.9655	<.0001

\*: P values from the comparison of the therapeutic success rates for each contrast, using a logistic regression model which adjusted for ranked baseline seizure frequency and investigative site.

Twenty-four percent (24%) of the patients achieved therapeutic success on 1g vigabatrin versus 7% on placebo. Therapeutic success was achieved in 51% of the patients receiving 3g and 54% receiving 6g vigabatrin. A statistically significant linear dose response ( $P < .0001$ ) was observed in the percentage of therapeutic success patients. All three vigabatrin dose groups were statistically significantly different from placebo, with 6g not statistically different from 3g.

#### **IV. FDA-REQUESTED ANALYSES**

##### **Protocol 71754-3-C-024**

The protocol stated that any patient experiencing a two-fold increase in the frequency of complex partial seizures or an episode of status epilepticus would be dropped from the study. The FDA requested the sponsor to identify the patients who meet the criteria for withdrawal due to lack of efficacy as set out in the protocol, as well as patients who experienced seizure flurries which could not be accurately counted by the patient or investigator, and for whom the MMD monitor assigned a seizure count at a later date. The FDA further requested the sponsor to perform additional analyses on the primary efficacy variable adjusting for all seizure data for such patients.

The sponsor recomputed seizure frequencies for these patients ( $N=8$ ) and all patients were then analyzed using the same statistical model used in the primary Intent-to-Treat analysis. Table 1 (Amendment dated September 21, 1994) gives a listing of the patients whose data was recomputed, the reason, and their seizure frequency before and after recomputing. The sponsor stated that the results of the Intent-to-Treat analysis, after recomputing the seizure frequencies of those patients identified, of (IB + IC) seizures were consistent with the original analysis presented in the Clinical Study Report for protocol 71754-3-C-024, page 8-1391, v1.94. The test for a difference in response to vigabatrin versus placebo was statistically significant ( $P=0.0003$ , ANCOVA on the ranked seizure frequencies adjusting for treatment, site, and ranked baseline seizure frequency).

For therapeutic success, the requested analysis was to assign all patients identified as non-responders. The sponsor stated that the results of the reanalysis were consistent with the original Intent-to-Treat analysis given in the Clinical Study Report 71754-3-C-024, page 8-1395, v1.94. A significantly greater percentage of patients in the vigabatrin group achieved therapeutic success than in the placebo group ( $P=0.001$ , CMH test stratified by site).

The FDA further requested the sponsor to identify the patients who meet the criteria for a two-fold increase in complex partial seizures OR partial seizures secondarily generalized, and to reanalyze as before. The sponsor recomputed seizure frequencies for these additional patients who experienced a two-fold increase in partial seizures secondarily generalized, and all patients were then analyzed using

the same statistical model used in the primary Intent-to-Treat analysis. All recomputed seizure data for the reanalysis performed in the Amendment dated September 21, 1994 was also used here, so that this new analysis recomputed data for all patients identified before plus patients with a two-fold increase in partial seizures secondarily generalized. Table 1 (Amendment dated February 15, 1995) gives a listing of the patients whose data was recomputed, the reason, and their seizure frequency before and after recomputing. The sponsor stated that the results of the Intent-to-Treat analysis, after recomputing the seizure frequencies of those patients identified, of (IB + IC) seizures were consistent with the original analysis presented in the Clinical Study Report for protocol 71754-3-C-024, page 8-1391, v1.94. The test for a difference in response to vigabatrin versus placebo was statistically significant ( $P=0.0001$ , ANCOVA on the ranked seizure frequencies adjusting for treatment, site, and ranked baseline seizure frequency).

For therapeutic success, the FDA-requested analysis was to assign all patients identified in Table 1 (Amendment dated February 15, 1995) and Table 1 (Amendment dated September 21, 1994) as non-responders. The sponsor stated that the results of the reanalysis were consistent with the original Intent-to-Treat analysis given in the Clinical Study Report 71754-3-C-024, page 8-1395, v1.94. A significantly greater percentage of patients in the vigabatrin group achieved therapeutic success than in the placebo group ( $P<0.001$ , CMH test stratified by site).

#### **Protocol 71754-3-C-025**

The FDA again requested, as in Study 71754-3-C-024, a reanalysis of this study in keeping with the protocol that stated that any patient experiencing a two-fold increase in the frequency of complex partial seizures plus partial seizures secondarily generalized or an episode of status epilepticus would be dropped from the study. The protocol further stated that in patients who were randomized, but who did not complete Segment III, seizure rates available at the time of dropout would 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, or medication to control the seizures, or loading dose of another AED would be included in the reanalysis and considered dropouts at the time of the episode in question. The FDA requested the sponsor to 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 sponsor.

The sponsor recomputed seizure frequencies for these patients (N=35) and all patients were then analyzed using the same statistical model used in the primary Intent-to-Treat analysis. The sponsor stated that the results of the Intent-to-Treat analysis, after recomputing the seizure frequencies of those patients identified, of (IB + IC) seizures were consistent with the original analysis presented in the Clinical Study Report for protocol 71754-3-C-025, page 8-8437, v1.114. The following table gives the median Baseline and Endstudy seizure frequencies (IB + IC) together with the 95% confidence intervals for the medians for each treatment group.

<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	9.0 ( 7.0, 11.0)	9.0 ( 6.0, 13.0)
1 g VGB	39	7.5 ( 6.0, 11.0)	7.5 ( 4.0, 10.0)
3 g VGB	39	8.0 ( 7.0, 12.5)	4.5 ( 3.0, 9.0)
6 g VGB	38	8.3 ( 6.5, 14.0)	4.3 ( 2.5, 6.0)

The test for a linear trend across doses was statistically significant (P=0.0001, ANCOVA on the ranked seizure frequencies adjusting for treatment, site, site by treatment interaction, and ranked baseline seizure frequency), indicating the effect of vigabatrin increases as the dose increases from 0 to 6g per day. The 1g vigabatrin dose was not statistically different from placebo (P=.0786). The 3g vigabatrin and 6g vigabatrin doses were significantly superior to placebo in reducing seizure frequency (P=.0012 for Placebo versus 3g VGB, P=.0001 for Placebo versus 6g VGB ). The 6g vigabatrin dose was not superior to the 3g vigabatrin dose (P=.5051).

For therapeutic success, the requested analysis was to assign all patients identified as non-responders. The following table gives the results of the Intent-to-treat patients reanalysis according to paradigm suggested by the FDA.

Therapeutic Success				Treatment Comparison p-Values*					
Placebo (N=45) % N	1g VGB (N=39) % N	3g VGB (N=39) % N	6g VGB (N=38) % N	Linear Trend	Placebo versus 1g VGB	Placebo versus 3g VGB	Placebo versus 6g VGB	3g VGB versus 6g VGB	Placebo + 1g VGB versus 3g VGB + 6g VGB
8% (4)	26% (10)	44% (17)	53% (20)	<.0001	0.0379	0.0007	< 0.0001	0.3264	<.0001

\*: P values from the comparison of the therapeutic success rates for each contrast, using a logistic regression model which adjusted for ranked baseline seizure frequency and investigative site.

The sponsor stated that the results of the reanalysis were consistent with the original Intent-to-Treat analysis presented in the Clinical Study Report for protocol 71754-3-C-025, page 8-8444, v1.114. A statistically significant linear dose response ( $P < .0001$ ) was observed in the percentage of therapeutic success patients. All three vigabatrin dose groups were statistically significantly different from placebo, with 6g not statistically different from 3g.

There were 11 patients in a drug replacement error in this study. The FDA further requested the sponsor to reanalyze assigning these patients the treatment group they were actually randomized to, rather than the treatment they actually received. Of the 11 patients involved in the drug replacement error, 5 continued into Segment III where they received the correct drug. These patients were originally assigned the treatment they were randomized to for statistical analysis. The other 6 patients discontinued the study prior to Segment III, and were assigned the treatment they received in Segment II. Two analyses of the data were performed, assigning these 6 patients the treatment they were randomized to, rather than the treatment they received. The first reanalysis used the original data, the second used the recomputed data from the Amendment of January 25, 1995. Results of both the reanalyses were consistent with the original Intent-to-Treat analysis presented in the Clinical Study Report for protocol 71754-3-C-025, page 8-8444, v1.114.

In the opinion of this reviewer, the sponsor has provided sufficient statistical evidence in the sense of robust results of the effect of VIGABATRIN as an add-on treatment in patients with focal epilepsy with difficult to control complex partial seizures. The optimal dose of vigabatrin based on response appears to be 3g/day.

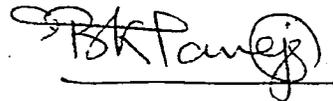
V. REVIEWER'S CONCLUSIONS (That may be conveyed to the Sponsor)

**Protocol 71754-3-C-024**

In the opinion of this reviewer, the sponsor has provided sufficient statistical evidence in the sense of robust results of the effect of VIGABATRIN 3g/day as an add-on treatment in patients with focal epilepsy with difficult to control complex partial seizures. The p-values were  $\leq 0.0002$  for various analyses of patients' mean monthly (28 days) frequency of complex partial seizures plus partial seizures secondarily generalized at endstudy compared to baseline. The p-values were  $\leq 0.001$  for various analyses of therapeutic success.

**Protocol 71754-3-C-025**

In the opinion of this reviewer, the sponsor has provided sufficient statistical evidence in the sense of robust results of the effect of VIGABATRIN as an add-on treatment in patients with focal epilepsy with difficult to control complex partial seizures. The optimal dose of vigabatrin based on response appears to be 3g/day. The p-values were  $\leq 0.0001$  for the test for a linear trend across doses and p-values were  $\leq 0.0012$  for the comparison of 3g VGB versus placebo for patients' mean monthly (28 days) frequency of complex partial seizures plus partial seizures secondarily generalized at endstudy compared to baseline. The p-values were  $\leq 0.001$  for various analyses of therapeutic success.



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Mathematical Statistician (Biomed)

Concur: Dr. Nevius *SN 3-7-95*

Dr. Dubey *6 3-7-95*

cc:

Orig. NDA 20-427

HFD-120

HFD-120/Dr. Leber/Dr. Katz/Dr. McCormick/Ms. Pitts

HFD-713/Dr. Dubey [File: DRU 1.3.2]/Group 2 File/Dr. Taneja

HFD-344/Dr. Lisook

Chron.

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This review contains 41 pages: 36 pages of text and 5 pages of Appendices.

## APPENDIX I

**Table 1: 1981 Revision of the International Classification of Epileptic Seizures.**

- I. Partial Seizures (seizures beginning locally)**
  - A. Simple Partial Seizures (consciousness not impaired) (IA)
    - 1. With motor symptoms
    - 2. With somatosensory or special sensory symptoms
    - 3. With autonomic symptoms
    - 4. With psychic symptoms
  - B. Complex Partial Seizures (with impairment of consciousness) (IB)
    - 1. Beginning as simple partial seizures and progressing to impairment of consciousness
      - a. With no other features
      - b. With features as in A. 1 through A. 4
      - c. With automatisms
    - 2. With impairment of consciousness at onset
      - a. With no other features
      - b. With features in A. 1 through A. 4
      - c. With automatisms
  - C. Partial Seizures Secondarily Generalized (IC)
- II. Generalized Seizures (bilaterally symmetrical and without local onset)**
  - A. 1. Absence seizures
  - A. 2. Atypical seizures
  - B. Myoclonic seizures
  - C. Clonic seizures
  - D. Tonic seizures
  - E. Tonic-clonic seizures
  - F. Atonic seizures

## APPENDIX II

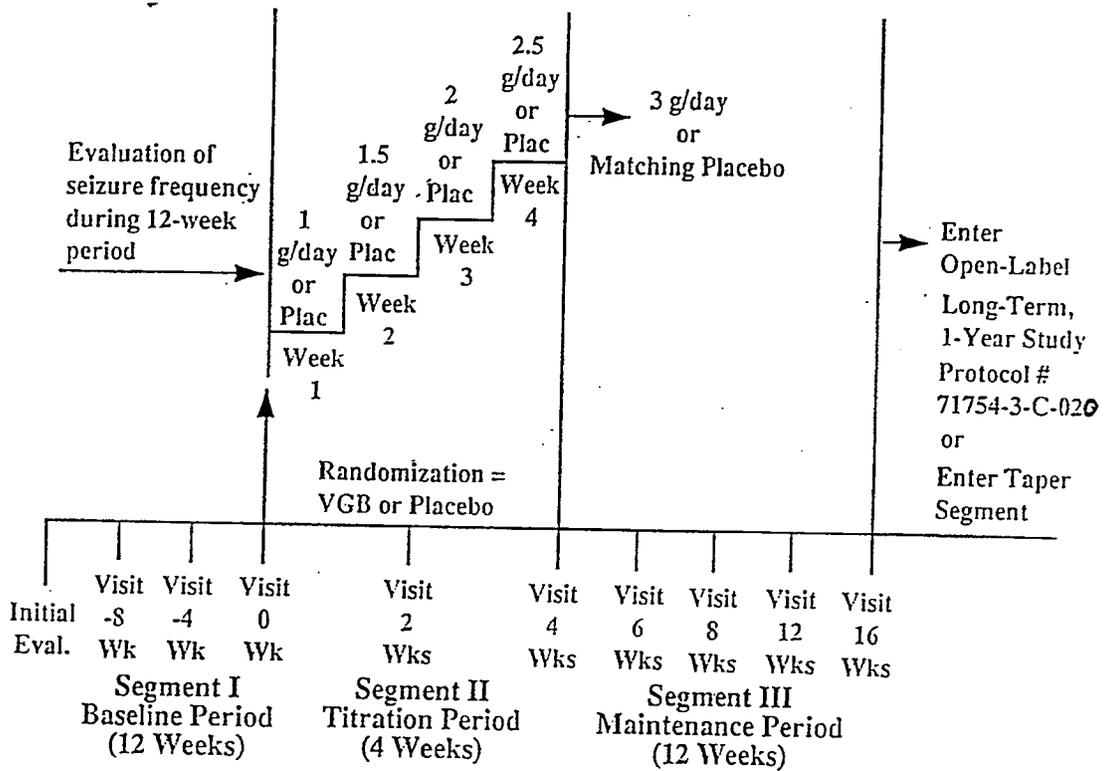


Figure 1: Study Design Schematic (Protocol 024) - Segments I, II, III

### APPENDIX III

**Table 2: Baseline Characteristics for the Intent-to-Treat Dataset  
Protocol 024**

Baseline Characteristic	Treatment		Total N=182	P-Value*
	Placebo (N=90)	3 g VGB (N=92)		
Sex				0.304
Male % (N)	48% (43)	40% (37)	44% (80)	
Female % (N)	52% (47)	60% (55)	56% (102)	
Age (years)				0.9944
Median	33	34	33.5	
Mean ± Std Dev	34 ± 8	34 ± 9	34 ± 9	
Range	19 - 57	18 - 60	18 - 60	
Weight (kg)				0.6394
Median	70.2	72.3	71.1	
Mean ± Std Dev	74.0 ± 18.7	75.8 ± 20.2	74.9 ± 19.4	
Range	41.3 - 125.6	42.2 - 137.9	41.3 - 137.9	
Race				0.912
Caucasian % (N)	91% (82)	90% (83)	91% (165)	
Negroid % (N)	7% (6)	7% (6)	7% (12)	
Other % (N)	2% (2)	3% (3)	3% (5)	
Concurrent Use of AEDs				0.136
One AED % (N)	43% (39)	33% (30)	38% (69)	
Two AEDs % (N)	57% (51)	67% (62)	62% (113)	
Barbiturates	22% (20)	21% (19)	21% (39)	0.796
Benzodiazepines	7% (6)	5% (5)	6% (11)	0.727
Carbamazepine	70% (63)	66% (61)	68% (124)	0.593
Hydantoins	34% (31)	39% (36)	37% (67)	0.512
Valproic Acid	19% (17)	30% (28)	25% (45)	0.071
Other AEDs	4% (4)	3% (3)	4% (7)	0.678
Age at onset of Epilepsy (yrs)				0.516
Median	9	12	10	
Mean ± Std Dev	12 ± 10	13 ± 9	12 ± 10	
Range	0.3 - 44	0 - 42	0 - 44	
Duration of Epilepsy (years)				0.6574
Median	23	22	22	
Mean ± Std Dev	22 ± 10	22 ± 9	22 ± 9	
Range	4.0 - 44	2.0 - 42	2.0 - 44	

\* P-values for baseline comparability of categorical variables from chisquare tests, for continuous variables from Kruskal-Wallis tests.

# APPENDIX IV

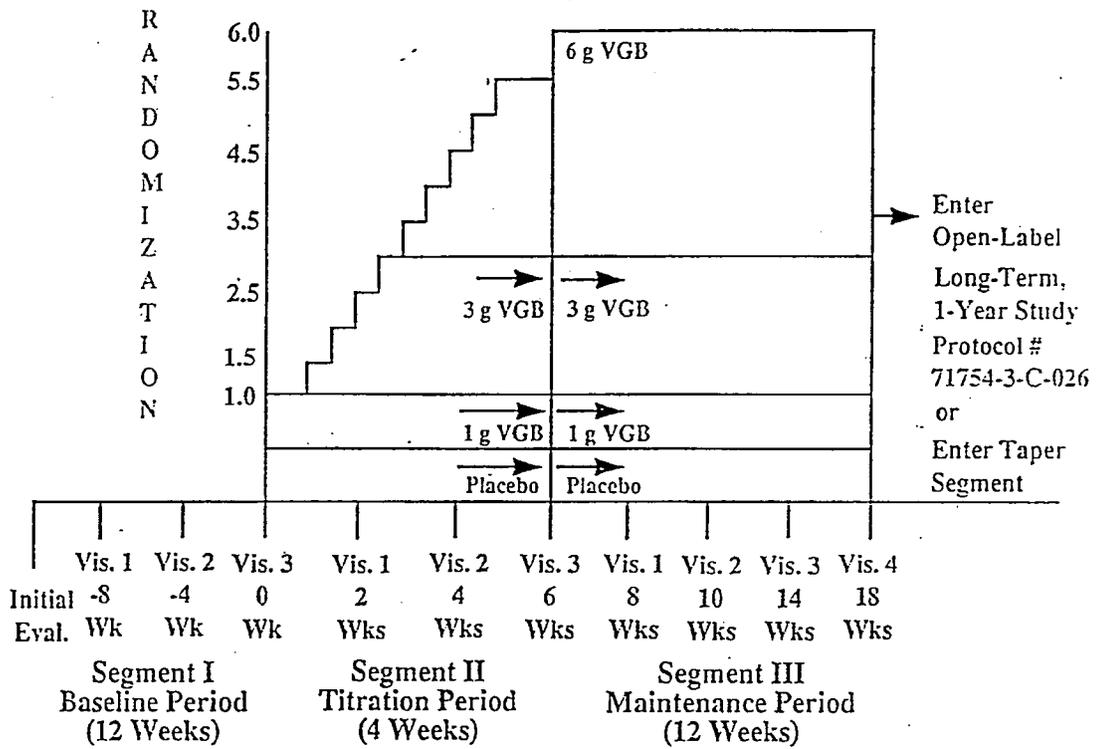


Figure 2: Study Design Schematic (Protocol 025) - Segments I, II, III

## APPENDIX V

**Table 3: Baseline Characteristics for the Intent-to-Treat Dataset  
Protocol 025**

Baseline Characteristic	Treatment				Total N=182	P-Value*
	Placebo N=45	1g VGB N=45	3g VGB N=43	6g VGB N=41		
Sex						0.203
Male % (N)	38% (17)	42% (19)	56% (24)	56% (23)	48% (83)	
Female % (N)	62% (28)	58% (26)	44% (19)	44% (18)	52% (91)	
Age (years)						0.9908
Median	33	33	35	33	33	
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)						0.3477
Median	68	71	70	72	70	
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						0.838
Caucasian % (N)	93% (42)	98% (44)	95% (41)	93% (38)	95% (165)	
Negroid % (N)	2% (1)	2% (1)	2% (1)	5% (2)	3% (5)	
Other % (N)	4% (2)	0% (0)	2% (1)	2% (1)	2% (4)	
Concurrent Use of AEDs						0.339
One AED % (N)	42% (19)	53% (24)	53% (23)	37% (15)	47% (81)	
Two AEDs % (N)	58% (26)	44% (20)	47% (20)	63% (26)	53% (92)	
Three AEDs % (N)	0% (0)	2% (1)	0% (0)	0% (0)	1% (1)	
Barbiturates	22% (10)	18% (8)	7% (3)	10% (4)	14% (25)	0.151
Benzodiazepines	7% (3)	4% (2)	12% (5)	15% (6)	9% (16)	0.345
Carbamazepine	69% (31)	62% (28)	74% (32)	71% (29)	69% (120)	0.656
Hydantoins	33% (15)	42% (19)	28% (12)	44% (18)	37% (64)	0.369
Valproic Acid	16% (7)	16% (7)	21% (9)	20% (8)	18% (31)	0.878
Other AEDs	11% (5)	7% (3)	5% (2)	5% (2)	7% (12)	0.605
Age at onset of Epilepsy (yrs)						0.1428
Median	11	8	14	13	12	
Mean ± Std Dev	13 ± 10	10 ± 8	14 ± 10	15 ± 10	13 ± 10	
Range	0.6 - 40	0.6 - 40	0.4 - 41	0 - 40	0 - 41	
Duration of Epilepsy (years)						0.2536
Median	20	24	21	21	21	
Mean ± Std Dev	22 ± 11	24 ± 9	20 ± 9	21 ± 11	22 ± 10	
Range	4 thru 43	1 thru 46	3 thru 45	3 thru 51	1 thru 51	

\* P-values for baseline comparability of categorical variables from chisquare tests, for continuous variables from Kruskal-Wallis tests.