NDAs 20-427 & 22-006: Sabril AC Backgrounder

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DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought NDA 20-427, vigabatrin for adjunctive therapy for the treatment of refractory complex partial seizures in adults, and NDA 22-006, vigabatrin for treatment of infantile spasms, to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

MEMORANDUM

DATE: December 8, 2008

FROM: Director
Division of Neurology Products/HFD-120

TO: Members of the Peripheral and Central Nervous Systems Drugs Advisory Committee (PCNS AC)

SUBJECT: Overview Memo for NDAs 20-427 & 22-006, for the use of Sabril (vigabatrin) as adjunctive therapy for Complex Partial Seizures (CPS) in adults and Infantile Spasms (IS) in children, respectively, to be discussed at a meeting of the PCNS AC on January 7 & 8, 2009

As you know, NDAs 20-427 & 22-006, for the use of Sabril (vigabatrin; a GABA transaminase inhibitor that increases CNS GABA levels), as adjunctive therapy for Complex Partial Seizures (CPS) in adults and Infantile Spasms (IS) in children, respectively, will be discussed at a meeting of the PCNS AC on January 7 & 8, 2009. NDA 20-427 has had a very long and complex regulatory history, briefly described below, and NDA 22-006 has only relatively recently been submitted. This briefing package consists of this cover memo, copies of the previously issued action letters for NDA 20-247, the statistical review of the controlled trials in that NDA, performed by Dr. Baldeo Taneja, my earlier memos of 3/31/95, 11/9/97, and 10/14/98 which supported these three previous actions, safety reviews of the current submissions performed by Dr. Gerard Boehm of the division's safety group, a statistical review of NDA 22-006 (IS) performed by Dr. Julia Luan, statistician, a medical review of the efficacy and safety data for NDA 22-006 (IS) performed by Dr. Philip Sheridan of the division, a review of the ophthalmologic toxicity data, performed by Dr. Ron Farkas of the division, reviews of juvenile rat toxicity studies by Dr. Ed Fisher, pharmacologist, and Dr. Larry Schmued, neurotoxicologist of the Agency's National Center for Toxicological Research, a review of the sponsor's proposed plans for risk management (a Risk Evaluation and Mitigation Strategy [REMS]), by the Sabril Risk Evaluation and Mitigation Strategy Review Team of the Office of Surveillance and Epidemiology, the agenda for the meetings, and the questions we would like you to vote on and discuss. In this memo, I will very briefly describe the regulatory history of these applications, as well as the effectiveness and safety data for both.

NDA 20-247, for the use of Sabril (vigabatrin), as adjunctive therapy for Complex Partial Seizures (CPS) in adults

History

The IND for vigabatrin was submitted in 1980. In 1983, the Agency became aware of the occurrence of a unique histopathologic finding in animals (rats, dog, mice, and to a lesser extent, monkey) given vigabatrin. Specifically, at doses approximating those to be given to humans, vacuoles between the myelin lamellae (so-called intramyelinic edema; IME) was seen. The division placed the IND on clinical hold until the sponsor was able to develop a non-invasive method that could detect the occurrence of the lesion in a sufficiently early stage to ensure that it would be reversible if the drug was discontinued. After several years, the sponsor was able to validate visual evoked potentials and MRI (in the dog) as a sensitive test, and clinical testing was permitted to resume in 1989.

The NDA was submitted in April, 1994 and contained the results of two adequate and well-controlled trials in patients with CPS. The Agency issued a Not Approvable letter on 4/28/95. The basis for the action was largely deficiencies in the structure of the submission, primarily related to the safety data. A provisional judgment was made at that time, however, that effectiveness had been shown. The sponsor submitted a response to the Not Approvable letter in May, 1997. In response, the Agency issued an Approvable letter on 11/26/97. That letter conveyed the Agency's conclusion that the sponsor had submitted substantial evidence of effectiveness for vigabatrin as adjunctive therapy for CPS, but that it should be indicated as second line adjunctive treatment because of concerns related to IME. The letter also requested additional safety analyses.

The sponsor responded to the Approvable letter in April, 1998. By that time, the Agency had become aware of a unique visual field defect associated with the use of vigabatrin, and, as a result, the sponsor had proposed that vigabatrin be approved as a last resort treatment under very restrictive conditions. The Agency had concluded that the risk had not been sufficiently characterized to permit marketing at that point, so a third action letter, a Not Approvable action, was issued on 10/26/98.

After numerous discussions between the Agency and the previous and current sponsors, Ovation Pharmaceuticals submitted an acceptable response to the 1998 Not Approvable letter on 12/28/07. It is this submission that serves as the basis for the up-coming August 2008 AC meeting.

Effectiveness

As noted above, the sponsor previously submitted the results of two parallel group trials in which patients were randomized to one of several doses of drug or placebo. The trials were multi-center trials performed in the United States. Also

as noted, the Agency has previously determined that these trials establish substantial evidence of effectiveness for vigabatrin as adjunctive treatment for CPS in adults.

Study 24

A total of 183 patients treated with 1 or 2 AEDs were randomized to vigabatrin (N=93) or placebo (N=90) at 15 US centers. Patients were observed for 12 weeks, titrated up to 3 gms/day of vigabatrin or placebo over the next 4 weeks, then maintained on their dose for 12 weeks. The following charts display the results of the outcome measures:

Median Monthly Seizure Frequency

	N	Baseline	Final	P-value
Vigabatrin	92	8.3	5.3	
Placebo	90	8.3	7.5	.001-.0002

Proportion of Patients Achieving At Least 50% Reduction

	N	%	P-Value
Vigabatrin	92	43%	
Placebo	90	19%	<.001

Median Monthly CPS Seizure Frequency

	N	Baseline	Final	P-Value
Vigabatrin	84	8.5	5.0	
Placebo	89	8.0	7.0	<.0006

Study 25

A total of 174 patients were randomized in this multi-center parallel group study to either vigabatrin 1, 3, or 6 gms/day or placebo (the design was similar to Study 24, except the titration phase was 6 weeks long). The following table represents the results:

Median Monthly Seizure Frequency

	N	Baseline	Final	P-value
Vigabatrin 1 gm	45	8.5	7.7	NS
Vigabatrin 3 gm	43	8.0	3.7	.0001
Vigabatrin 6 gm	41	9.0	4.5	.0001
Placebo	45	9.0	8.8	

Proportion of Patients Achieving At Least 50% Reduction

	N	%	P-Value
Vigabatrin 1 gm	45	24%	.02
Vigabatrin 3 gm	43	51%	<.0001
Vigabatrin 6 gm	41	54%	<.0001
Placebo	45	7%	

Median Monthly CPS Seizure Frequency

	N	Baseline	Final	P-Value
Vigabatrin 1 gm	45	7.5	7.0	NS
Vigabatrin 3 gm	43	7.0	3.5	.001
Vigabatrin 6 gm	39	8.5	3.5	.0001
Placebo	44	8.8	8.3	

Safety

As noted by Dr. Boehm, the sponsor has submitted some safety data from over 4800 subject/patients exposed to at least one dose of vigabatrin. These data have been gathered over many years of development, under various conditions that were more or less well documented. According to the sponsor, 4,077 patients have been exposed in epilepsy trials for whom sufficient evidence to evaluate adverse events (AEs) is/was available. Of these, 3,456 subjects were exposed for at least 6 months, 2,753 were exposed for at least one year, and 403 patients were exposed for at least 5 years. A total of 1,112 patients were exposed to a daily dose of between 3 and 4 gms for at least 6 months, and 587 patients were exposed to the same dose for at least one year.

Treatment with vigabatrin is associated with typical CNS toxicities (somnolence, dizziness, ataxia, diplopia), but also several other changes. Besides the special ophthalmologic toxicities to be described below, the following other AEs were noted:

Anemia; Changes in Hemoglobin, Hematocrit

Very slight mean decreases in hemoglobin and hematocrit were seen in controlled trials of vigabatrin, which appeared to be dose related. The following results were seen in Studies 24 and 25:

Mean Change From Baseline

	Pla	1 GM	3 GM	6 GM
Hemoglobin	0.53	0.58	-0.24	-1.39
Hematocrit	0.02	-0.12	-0.44	-0.91

There were 3 SAEs (.06%) and 3 (.06%) discontinuations due to related changes, and no cases of aplastic anemia.

Liver Function Abnormalities

Treatment with vigabatrin results in dose-related decreases in LFTs. The following results were seen in Studies 24 and 25:

Mean Change From Baseline

	Pla	1 GM	3 GM	6 GM
AST	-0.18	-1.51	-3.65	-3.88
ALT	-0.07	-11.82	-16.23	-19.12

In these trials, the majority of patients had a decrease in LFTs. There were no patients who had an increase in LFTs of 3 XULN with an increase in bilirubin of 2 X ULN. There were 4 patients in the development program who died with liver failure, but there were other factors more likely to be the cause. In post-marketing experience (all foreign), there were 3 cases of death or transplant without an obvious other cause, although all were taking other AEDs. The reporting rate exceeds the background rate (although, again, these were all foreign cases), but these other AEDs may have been the cause, or may have contributed.

Weight gain

Vigabatrin use causes weight gain. Combined data from 9 controlled trials revealed 17% of vigabatrin-treated patients gained at least 7% of their baseline body weight compared to 8.5% of placebo-treated patients (a mean gain of about 3-4 kg compared to about 1.5-2 kg for placebo patients). Including open-label, uncontrolled data, a total of about 26% (484/1843) of treated patients gained at least 7% of their body weight. It was impossible to perform adequate dose-response analyses.

Edema

In 12 controlled trials there was a slight increase in the rate of peripheral edema in vigabatrin-treated patients compared to placebo-treated patients (4.3/100 PYs vs 3/100 PYs, respectively); there was a clear dose response based on an analysis of 5 fixed dose controlled trials (maximum rate of .23/100 PYs for >5 gms/day compared to .06/100Pys for placebo). Edema did not seem to be associated with other cardiovascular, renal, hepatic, or pulmonary signs or symptoms. A total of 215 patients in the database had an edema-related AE; 50 also had weight gain.

Depression

There was no important difference in the incidence of depression as an AE between drug and placebo-treated patients in a pool of Phase 2/3 trials (446 PYs of vigabatrin compared to 101 PYs of placebo), but there was an increase in the rate of SAEs of depression (2.2/100 PYs vs 0) and discontinuations due to depression (3.4/100 PYs vs 1/100 PYs); there was one suicide attempt. There was only one completed suicide in the epilepsy experience (N=4,855).

Ophthalmologic Toxicity

As noted earlier, in 1997 the Agency became aware that vigabatrin use was associated with a stereotypical concentric visual field defect, worse in the nasal visual field. As a result, the sponsor has performed numerous analyses of multiple data sources in an attempt to characterize the incidence of this lesion, as well as to characterize important other aspects, including the time of onset, whether the lesion increases with treatment discontinuation or continuation, and, importantly, whether or not the lesion can be detected early enough so that it might be reversible. These data have been reviewed in great detail by Dr. Ron Farkas, ophthalmologist in the division. I will here very briefly review the most important findings and conclusions.

Adults

Several major data sources were used to evaluate these issues.

Study 4020

This was a multi-center study in 46 centers in France, South Korea, Italy, Spain, and Australia. Investigators enrolled only those patients with visual field defects they felt not likely due to another cause (e.g., glaucoma). Patients in this study were either taking vigabatrin for variable durations, or had discontinued its use. Patients were assessed with various methods of perimetry (methods use varied between patients, and sometimes within patients over time).

The sponsor divided the patients into 3 groups:

Group 1-Currently receiving vigabatrin
Average 4.2 years of treatment. 38 children, 149 adults

Group 2-Previously treated, not on current vigabatrin treatment
Average treatment duration-2.4 years. 47 children, 152 adults

Group 3-Never treated with vigabatrin

The first test occurred about 5 years after treatment initiation, on average. A total of 524 patients had at least one useable test.

According to the sponsor, 25% of adults and 15% of children had a confirmed VFD characteristic of vigabatrin. As noted by Dr. Farkas, in patients with 5 tests, 35% (12/33) adults continuing treatment had a progressive lesion, compared to 13% who were never treated with vigabatrin. The earliest time of onset of a VFD was 12 months in adults and 16 month in pediatric patients.

As described in great detail by Dr. Farkas, this study suffered from many and profound methodological deficiencies; many of these were noted by members of the study steering committee. In Dr. Farkas's view, these deficiencies make the results of the study unreliable.

Pooled Cohort Study

The sponsor presented results of a pool of 367 of the total of 403 vigabatrin-treated patients in multiple studies from Finland, Japan, US, UK, Canada, Spain, Germany, and Australia. The studies were of many different designs (e.g., monotherapy, adjunctive, varying durations, controlled or uncontrolled) and included 112 non-vigabatrin treated patients. Of the 367 vigabatrin patients, 335 had usable visual fields. Various testing methodology was used, and patients were tested only once, unless an abnormality was suspected.

Of the 335 vigabatrin patients tested, 105 had a VFD (31%). According to Dr. Farkas's review, about 1/3 of these VFDs were "profound". There were no VFDs in non-vigabatrin treated patients. According to Dr. Farkas, it appeared that a VFD had to be relatively severe (given the grading system used) for a test to be considered "positive". An amendment to the original study report added 119 patients, with only 7 additional patients noted with a VFD. The average duration of treatment with vigabatrin was about 3 years. There was no real relationship between severity of VFD with increasing duration of exposure or with cumulative dose. Interestingly, the report states that 8% of patients tested complained of symptoms that could be referable to the VFD.

Based on these data, the sponsor estimated the time of onset of the lesion. According to these analyses, the maximum incidence of VFD occurred before 1 year, then declined slowly over 8 years (although there were still some new events out in time). The prevalence of VFDs continued to increase over 8 years (with increasing variability in the estimate), but appeared to approach a plateau at about 4-5 years.

The incidence also seemed to peak at a cumulative dose of about 1 kg, and the prevalence reached a plateau at a cumulative dose of about 2 kg.

Study R003

This was a prospective study of 25 patients treated at 4 Canadian centers. Perimetry and ERG were performed every 3 months. The median duration of treatment was 500 days (range 2-988 days).

A total of 7 patients (28%) developed VFDs. In 3, the severity was Moderate at diagnosis. The median cumulative dose was about 1 kg. Dr. Farkas describes one patient, a 44 year old woman, who was treated for 63 days (cumulative dose about 82 gms), who was determined to have a moderately severe VFD 2 months after vigabatrin was discontinued (ERG was negative). This case clearly suggests that the lesion can occur before 2 months of treatment.

Study 4021

This was an observational study performed in Finland of 29 patients (currently receiving vigabatrin or who had previously discontinued treatment due to a VFD). Nine patients were noted to have a vigabatrin-induced VFD.

Pediatric Patients

Toronto Study

A total of 246 infants, mostly with IS, were examined at a tertiary care center that treats most of the IS patients in the Toronto region. A total of 117 patients had a baseline and at least one on-treatment exam, and 85 patients did not have a baseline exam. A total of 179 patients were treated with vigabatrin, and 117 of these discontinued treatment during the study. Patients were examined initially (including with ERG) every 6 months, and more recently every 3 months. The median age at the most recent ERG was about 2 years old.

The incidence of a "sustained" ERG abnormality (defined as an abnormality on the last 2 consecutive exams) was about 25%, with at least one abnormality seen in 63% of subjects. The sponsor concluded that no abnormality occurred earlier than 3 months, but, of course, testing was not performed before 3 months. In patients with a sustained abnormality, the average time to abnormality was 27-36 months (depending on the test performed), However, as Dr. Farkas notes, sustained abnormality was defined by the last 2 exams, so the time to this endpoint is confounded with the definition. The sponsor reports a frequency of visual field defects of 8%, but, as Dr. Farkas notes, the test used (confrontation) is likely not sensitive in this population.

Several cases described by Dr. Farkas are worth recounting. A 13 year old boy with autism had been treated for about 6 years prior to his first test, which was reported as "mildly" abnormal; he had no visual difficulties (parent report) at that time. Eighteen months later the parent noted that he was bumping into things; the ERG was markedly abnormal. This case implies that a significant abnormality can occur, in Dr. Farkas's words, "precipitously".

Additionally, a 13 month old boy with Trisomy 21 had a normal ERG after 5 months of treatment with vigabatrin. Six months later, the ERG was still within normal limits. Five months later (a total of 16 months of treatment), the ERG was "dramatically" reduced. Although the dose was reduced, 8 months later there was clinical evidence of a profound field defect. At that time, the drug was discontinued, but 3 months later the ERG was even more abnormal.

Study 4102

This was another cross-sectional observational study in 39 pediatric patients in 3 centers. Twelve patients were tested with perimetry, H-stimulus was used in 35, and ERG in 26. VFD was detected in about 1/3 of the patients.

Study 0201

This was a 1 year follow-up study in 210 pediatric patients who were studied with ERG, field exams, and VEPs.

On average, ERG flicker amplitude decreased from 83 mcV to 69 mcV in 88 patients followed for one year. A total of 23/51 patients with normal visual fields had ERG progression.

ERG/Visual Field Correlation

Dr. Farkas has reviewed numerous articles submitted by the sponsor in support of their contention that ERGs are an acceptably sensitive test of VFDs in patients who cannot cooperate with formal visual field testing. Some of the articles simply demonstrate that ERG can detect already existing significant VFDs, and other articles demonstrate a relatively poor correlation between ERG abnormalities and VFDs (see, for example, the article by McDonagh et al, which demonstrates that most patients with abnormal visual fields had normal ERGs; of 19 patients with a VFD, at least 13 had a normal ERG). No adequately reported and documented article adequately established the ability of ERG to detect a VFD very early in its evolution.

Post-Marketing reports

Although there have been post-marketing reports of VFDs, it is difficult to interpret these reports, and, of course, it is difficult to assess the incidence/prevalence of VFDs from this sort of data. What is of note, however, as Dr. Farkas points out, is that these data are consistent with the reasonable conclusion that VFDs are not likely to occur in the first few days of treatment with vigabatrin, and that treatment with vigabatrin is only very rarely likely to cause severe central acuity loss.

NDA 22-006, for the use of Sabril (vigabatrin) as a treatment for Infantile Spasms (IS)

As noted earlier, the sponsor submitted this NDA for the use of vigabatrin in IS in December, 2007. The application consists of reports of two randomized controlled trials, neither of which was performed by the sponsor. These studies have been reviewed in great detail by Drs. Sheridan and Luan. Here, I will very briefly review the pertinent findings.

Study 1A

This was a multi-center study in which patients were randomized to receive either low dose (18-36 mg/kg/day) or high dose (100-148 mg/kg/day) vigabatrin. The

treating physician was unblinded to treatment assignment, but the parents and the readers of the EEGs were blinded (parents were blinded to dose). Patients were titrated for the first 7 days, and then left on constant treatment for another 7 days. If the patient became spasm-free within the first 14 days, an additional 7 days of constant dose was given.|

The primary outcome was the proportion of patients spasm-free for 7 days beginning within the first 14 days of treatment. This was to be confirmed by the caregiver and a CCTV EEG performed within 3 days of the seventh day of spasm-freedom.

The study was originally submitted as a "compassionate" IND, but was changed to be a controlled trial, in which 44 patients were to be enrolled. Subsequently, however, the sample size was increased on two occasions, first to allow up to 150 patients, then to allow up to 250 patients. According to the sponsor, an interim analysis was requested by the FDA in order to put language about pediatric use in the product labeling (presumably, this was at the time that the Agency was considering the approval of the CPS application). This first analysis included data from 62 patients out of 89 randomized patients. Then, a second analysis was performed with 142 patients out of 179 randomized patients, again apparently, according to the sponsor, at the request of the Agency. The results of this analysis were published in Neurology in 2001. Finally, the analysis presented as primary in this NDA submission included 221 patients out of 227 randomized patients. These analyses were not prospectively designated in the original protocol.

The following results for these various analyses are presented below for the primary outcome measure as defined above:

	First 44	First Interim	Second Interim	Final
Responders, High Dose	14%	28%	15%	16%
Responder, Low Dose	0%	15%	5%	7%
P-value	.23	.35	.09	.0375

It should be noted that the second interim analysis that was published in Neurology described a Responder Rate in the High Dose group of 36% and in the Low Dose Group of 11% (P<.001). However, this was a result of a difference in the application of the definition of a Responder.

In this study, it was difficult for the EEG to always be obtained within the protocol-specified 3 day window. The sponsor performed additional analyses that examined the outcome when the window for performing the EEG was widened. As can be seen in Table 22 of Dr. Sheridan's review (page 49), analyses become increasingly positive with increasing widening of this EEG window. Further, the a

comparison between the two treatment groups on the Time to Spasm Cessation for 7 days, with or without EEG confirmation, the second secondary outcome to be tested, was highly significant in favor of the high dose group (p=0.0016).

The first secondary outcome to be tested, the Proportion of Patients Spasm-Free for 7 days and who remained spasm-free for the duration of the study, revealed 68% and 52% in the high and low dose groups, respectively.

Study W019

This was a double blind parallel group study of vigabatrin as monotherapy in pediatric patients with IS. In this study, patients underwent a 2-3 day prospective baseline, during which caregivers were to determine the time of day during which the patient's spasms were most frequent. Then, patients entered a 5 day double-blind period, in which they were initially randomized to vigabatrin 50 mg/kg/day or placebo. If spasms continued, the dose was increased to a maximum of 150 mg/kg/day.

The primary outcome measure was the percent change in spasm frequency evaluated during a pre-determined 2 hour/day window from baseline to the final 2 days of the double-blind period. The outcome on this measure is described below. In addition, although entirely post hoc, the outcome on this measure, but measured over 24 hours, is also given:

Percent Change in Mean Spasm Frequency

	2 Hours	24 Hours
Vigabatrin	46%	31%
Placebo	59.5%	83%
P-value	0.56	0.030

A total of 35% of the vigabatrin-treated and 10% of the placebo-treated patients were spasm-free on the final day of the double-blind phase (NS).

Study FR03 in Patients with IS and Tuberous Sclerosis

Because there was some evidence from Study 1A that patients with Tuberous Sclerosis might be particularly sensitive to the beneficial effects of vigabatrin, this study was designed to examine the drug's effects in this specific sub-group.

This study was designed to compare the effectiveness of vigabatrin (150 mg/kg/day) and hydrocortisone (15 mg/kg/day) in previously untreated patients with IS. Patients were randomized to one of the treatments for one month

(evaluated every 2 weeks). If spasms did not completely cease, patients were crossed over to the other treatment after 4 weeks of treatment. This study was open-label, and there was no prospective statistical plan.

A total of 11 patients were randomized to receive vigabatrin first, compared with 12 randomized to receive hydrocortisone. None of the patients treated with vigabatrin first crossed-over; that is, all 11 were spasm-free. A total of 7 patients treated first with hydrocortisone were crossed over to vigabatrin; that is, only 4/12 of these patients were spasm-free (p=0.001). When these 7 patients were treated with vigabatrin, they became spasm-free.

MRI

Previous evaluation of MRI studies in patients revealed no lesions that could reasonably associated with vigabatrin treatment. However, recently, the literature has contained reports of MRI changes in pediatric patients that have raised concerns. These lesions were considered to possibly represent a different lesion from IME (although, again, even if they represented IME, they would have been more or less the first detection of IME in humans) because they were located in the deep grey matter (IME in animals was a white matter lesion). For this reason, the sponsor undertook a retrospective analysis of MRI data from 5 studies. In addition, after we met with the sponsor in June, 2007 to discuss this issue, the sponsor undertook to retrospectively examine data from an additional 10 centers in which infants were studied, as well as a re-examination of previously reviewed MRI studies in older children and adults (this latter study was considered appropriate because it was possible that previous examinations of these studies might have missed deep grey matter lesions, given that this was not the area expected to become abnormal with vigabatrin treatment).

Retrospective Study of 5 centers

In this study, MRI studies of 204 patients treated with vigabatrin in Canada, US, and France were examined. Of these, 42 patients were noted to have T2 abnormalities. Of these, 23 were considered likely due to vigabatrin (only 2 had baseline studies), 13 were considered of questionable relationship, and 10 were considered unrelated to treatment.

Of the 23 considered to have lesions likely related to treatment, 12 had complete or partial resolution of the abnormalities (7 continued on treatment, 5 had discontinued). The remaining 11 patients did not have repeat studies.

Retrospective Epidemiologic Studies

In this study, MRIs of 205 infants treated for IS (with vigabatrin or other treatments) were blindly examined by 2 pediatric neuroradiologists.

The prevalence of vigabatrin-like MRI lesions in this study was 21.5% in vigabatrin treated patients and 4% in patients treated with other drugs. The incidence was 36% and 6%, respectively. It appeared that the lesion was transient in many patients, but in most of these patients the drug was discontinued when the lesion was detected, and there was a suggestion of a dose response (of course, patients were not randomized to dose). There seemed to be no characteristic clinical signs or symptoms that routinely accompany the lesions.

Retrospective re-examination of previously reviewed MRIs

In this study, in over 400 adults and 200 children, the prevalence of vigabatrin-like MRI lesions was 14% in vigabatrin treated patients and 13% in those treated with other drugs. The incidence was 11% and 8%, respectively.

Juvenile Toxicity

The sponsor asserts that the MRI lesion seen in pediatric patients represents the well-known IME seen in multiple animal species, but in a location not previously noted before. Dr. Schmued concludes that the lesion seen in the juvenile rat (seen in the same anatomic locations as the MRI lesions in pediatric patients) are different from IME, in that the juvenile lesions are seen in deep grey matter, and appear to not be intra-myelinic edema, but may represent neuronal degeneration (though he notes significant limitations in the studies performed).

REMS

The sponsor has proposed to market Sabril under specific conditions, including product labeling that would mandate a specific schedule of ophthalmologic monitoring (for patients with IS, every 3 months for the first 18 months, then every 6 months; for patients with partial seizures, every 6 months). Further, they propose to require that prescribers must receive education about Sabril's risks, and that the product would be distributed through specialty pharmacies only when prescribers have attested to understanding the risks and the monitoring protocol. In addition, patients will receive educational materials, and physicians and patients will agree to re-assess the appropriateness of continued treatment with Sabril after 12 weeks on therapy. Presumably, the sponsor believes that the proposed ophthalmological monitoring in both adults and pediatric patients is adequate to detect visual loss at a relatively early stage.

SUMMARY

The sponsor has submitted what they believe is substantial evidence of effectiveness for Sabril as adjunctive therapy for adults with partial seizures, and as a treatment for infantile spasms in infants. We have previously concluded that there is substantial evidence of effectiveness for the former indication, but have not reached a conclusion about Sabril's effectiveness as a treatment of infantile spasms. In the latter case, the results and design of the controlled trials pose numerous interpretive challenges.

Further, the sponsor believes that the safety data presented are adequate to support approval of Sabril for both indications, under appropriate conditions of use, as proposed in their REMS.

We are bringing these applications to the Committee because the issues raised are extremely complex. The questions we are asking the Committee to discuss are included with this package, and, as you can see, are themselves complex and quite numerous.

The first day of the meeting will be devoted to discussing NDA 20-427, for the use of Sabril in patients with partial seizures. As I noted above, the Agency has previously determined that Sabril is effective as an adjunctive treatment for adults with partial seizures, and we are not specifically asking the Committee's view on this question. We will, however, be asking the Committee to consider if there are any circumstances under which Sabril could be approved for this indication (specific population, monitoring, specific conditions of use), and, if so, the specifics. If the Committee does not believe Sabril can be approved at this time for this indication, we are interested to know what additional information, if any, the sponsor could obtain to support approval in the future.

The second day will be devoted to discussing NDA 22-006, for the use of Sabril in the treatment of patients with infantile spasms. Here, we are asking the Committee's opinion about whether or not the sponsor has provided substantial evidence of effectiveness for this indication. As I noted above, the issues raised related to efficacy are complex; by our usual standards, we might conclude that the sponsor has not submitted substantial evidence of effectiveness for this indication. However, there are several findings across the studies submitted that could be interpreted to provide such data.

Here, too, we are asking the Committee to address the question of whether or not there is any combination of patient population and conditions of use that could support approval for this indication at this time, and, if there are, what those are, and, if there are not, what additional data could the sponsor obtain in order to support approval in the future. For this population, we are also very eager to know whether or not the sponsor has identified a reliable, sensitive test of visual fields and visual function.

As I noted above, the question list for the meeting is unusually long and complex. However, it has been designed to ensure that all of the relevant issues are discussed, so that the Committee will be in a position to ultimately consider the questions of whether or not Sabril should be approved for either of the proposed indications. Of course, as the meetings progress, we may determine that it might not be necessary to take a formal vote on all of the (sub-parts of the) questions posed.

I want to thank you for your work in advance of, and during, the meetings, especially given the amount of material we are sending you, and the complexity of the issues raised, and I look forward to seeing you in January.

Russell Katz, M.D.

FOOD AND DRUG ADMINISTRATION (FDA)

Center for Drug Evaluation and Research (CDER)

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

HILTON WASHINGTON DC/ROCKVILLE
1750 ROCKVILLE PIKE, ROCKVILLE, MARYLAND

QUESTIONS TO THE ADVISORY COMMITTEE

JANUARY 7 & 8, 2009

For January 7, 2009: For treatment of refractory complex partial seizures in adults

1. Vigabatrin has been shown to cause irreversible visual loss (central and/or peripheral).
    a. Does the committee believe that continued treatment results in a clinically meaningful loss of vision in some patients?
    b. Has the sponsor shown that this visual loss can be detected before it becomes clinically meaningful?
    c. Has the sponsor adequately shown that discontinuation of treatment halts the progression of the visual loss?
    d. The sponsor asserts that vigabatrin does not cause central visual loss. Does the committee think that the sponsor has adequately shown this?

2. Can the committee envision any combination of patient population and conditions of use that would support approval?

3. If yes to question 2, then:
    a. What is the appropriate population (e.g., standard population of patients with epilepsy or some subset [e.g., candidates for surgery or intractable patients who are not surgical patients])?
    b. If Sabril is to be approved for use in a refractory population, should additional effectiveness (comparative) data be obtained specifically in this population?

4. If yes to question 2, under what circumstances could Sabril be approved? For example, should it be available only under a Risk Evaluations and Mitigation Strategy (REMS)?

    Following is a partial list of potential components of a REMS:
    -Should it be made available only under restricted conditions (e.g., certain practitioners, restricted distribution, an educational campaign, special training program for practitioners, registry, etc.)?
    -Should continued access to the drug be linked to results of ophthalmologic monitoring?

DRAFT

-Other?

5. Is there sufficient evidence to support specific recommendations on the schedule of ophthalmologic monitoring?
    a. Should there be a requirement for periodic ophthalmologic monitoring?
    b. If so, is the sponsor's plan for monitoring adequate?
    c. If the sponsor's plan is not adequate, does the committee have any proposal?

6. Is there additional data related to the visual loss that should be obtained prior to approval of Sabril? If yes, what data?

7. Does the Committee believe that the intramyelinic edema seen in animals has any clinical consequences in adults?

8. If yes to number 7, should there be additional clinical requirements (e.g., additional monitoring, additional analyses, additional data)?

9. Given the data in hand, does the committee recommend that Sabril should be approved for the treatment of partial seizures?

For January 8, 2009: For treatment of infantile spasms

1. Has the sponsor provided substantial evidence for vigabatrin as a treatment of infantile spasms?

2. Do the studies indicate efficacy in: 1) cessation of spasms, 2) amelioration of the EEG, 3) prevention of other seizures types later in life, or 4) improvement in long-term developmental outcome?

3. There is a view that current unapproved treatments (ACTH or steroids) can provide long-term protection against infantile spasms with a short duration course of treatment (e.g., about two weeks). The sponsor has proposed that vigabatrin be given chronically but has not provided evidence from controlled trials that treatment with vigabatrin chronically provides an additional benefit beyond a brief treatment course. Should the sponsor be required to adequately study this question?

4. Vigabatrin has been shown to cause irreversible visual damage, and the sponsor has proposed that monitoring with ERG can adequately detect this damage at an acceptably early stage.

    a. Has the sponsor provided evidence that ERG is a reliable way to detect lesions in the pediatric population before they become clinically meaningful?

DRAFT

b. Has the sponsor presented any other methods to detect lesions sufficiently early?
c. If the committee concludes that the sponsor has identified an adequate method to detect visual damage sufficiently early, is there evidence to support a monitoring regimen over time that will detect damage sufficiently early? If there is inadequate evidence to support a monitoring regimen, should the sponsor be required to develop that evidence?
d. If the committee concludes that the sponsor has not identified an adequate method to detect damage sufficiently early, should the sponsor be required to develop one?
e. Has the sponsor adequately shown that the visual loss will not progress if the treatment is discontinued once visual damage has been detected?
f. Has the sponsor provided adequate evidence about the functional consequences of treatment with vigabatrin on the developing visual system and overall function, especially against the background of preexisting neurological abnormalities?

5. Has the sponsor presented adequate evidence that central visual loss does not occur in pediatric patients?

6. Can the committee envision any combination of patient population and conditions of use that would support approval?

7. If yes to question 6, then:
   a. What is the appropriate population (e.g., all patients with infantile spasms, only age-specific subsets, etiologic subsets such as tuberous sclerosis, patients who have failed other treatments)?
   b. If Sabril is to be approved for use in a specific subset of patients, should additional effectiveness data in this subset be obtained?

8. If yes to question 6, under what circumstances could Sabril be approved? For example, should it be available only under a Risk Evaluations and Mitigation Strategy (REMS)?

   Following is a partial list of potential components of a REMS:
   -Should it be made available only under restricted conditions (e.g., certain practitioners, restricted distribution, an educational campaign, special training program for practitioners, registry, etc.)?
   -Should continued access to the drug be linked to results of ophthalmologic monitoring?
   -Other?

9. Given alternative off-label therapy (ACTH, valproic acid etc.), do the safety concerns preclude marketing even if efficacy has been demonstrated?

10. Does the Committee believe that the intramyelinic edema seen in animals has any clinical consequences in pediatric patients?

11. What is the clinical significance, if any, of the observation of neuropil vacuolation in young animals? Are these related to newly appreciated MRI findings in children revealing grey matter lesions? If the committee does not believe that the MRI findings in children are related to the neuropil vacuolation in animals, are they of clinical concern nonetheless?

12. Should additional safety data be obtained prior to approval for Sabril as a treatment for infantile spasms? If so, what data?

13. Given the data in hand, does the committee recommend that Sabril should be approved for infantile spasms?

DRAFT

NDA 20-427: Complex Partial Seizures in Adults

January 7, 2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-427

Food and Drug Administration
Rockville MD 20857

APR 28 1995

Marion Merrell Dow Inc.
Attention: Gregory A. Hileman, Ph.D.
US Regulatory
Marion Park Drive
P.O. Box 9627
Kansas City, Missouri 64134-0627

Dear Dr. Hileman:

Please refer to your pending April 29, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Sabril® (vigabatrin) 500mg tablets.

We acknowledge receipt of your amendments dated:

05-05-95	05-23-94	06-06-94	06-08-94	06-10-94	06-14-94
06-20-94	06-27-94	07-11-94	07-19-94	07-26-94	08-03-94
08-04-94	08-09-94	08-29-94	09-21-94	09-22-94	10-07-94
10-18-94	10-27-94	11-09-94	11-10-94	01-16-95	01-17-95
01-25-95	02-01-95	02-08-95	02-09-95	02-10-95	02-15-95
02-22-95	02-23-95	02-27-95	03-02-95	03-03-95	03-06-95
03-08-95	03-14-95	03-24-95	03-27-95	03-22-95	03-23-95
03-31-95	04-14-95				

Reference is also made to an Agency letter dated January 31, 1995, requesting additional Chemistry and Manufacturing Control information.

We have completed our review of your application, and have determined that it is not approvable under section 505(d) of the Act. Our review reveals that there is insufficient information to determine whether Sabril® is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling [21 CFR 314.125(b)(4)]. We also cannot reach a final conclusion as to the effectiveness of Sabril®.

GENERAL COMMENTS

Deficiencies in the organization, analysis and content of the new drug application have made it impossible to adequately assess the safety and effectiveness of the drug. Some of these deficiencies may be remedied by further analysis on your part, but some may reflect an irreparable lack of critical data.

The deficiencies in the application can be considered to fall into 2 general categories: 1) Inadequate collection and availability of important safety information, and 2) Inadequate analysis and reporting of information collected relative to both effectiveness and safety. Because of these

deficiencies it has been impossible for us to rely upon your reports of the studies you have performed. In the remainder of this letter, we will enumerate specific problems that we have been able to identify in these 2 categories. Because the flaws in the application are so serious, however, we cannot be certain that we have identified all the relevant problems with the application or the drug itself.

Safety concerns are most critical, particularly given the long history of a concern with findings of intramyelinic edema in multiple animal species at doses close to those used clinically. Many of our concerns arise from the unavailability of the primary Case Report Forms (CRFs) for European patients in the CRF database. Without secure knowledge of results in at least a portion of the patients exposed to Sabril® in European trials, the available safety data base that can be fully assessed is the domestic data base of somewhat over 500 patients, not, we believe, an adequate-sized exposure. The unavailability of European CRFs is perplexing to us, given that the studies from which the data in the CRFs was generated were conducted by your European affiliate. Although regulations require that you submit with the initial application only those CRFs for patients who died or discontinued treatment due to adverse events, regulations also require (21 CFR 314.50(f)(3)) that a sponsor submit additional CRFs needed to conduct a proper review as requested by the Agency.

Access to these primary records for our review is particularly critical in this case, because in our review of CRFs that have been submitted we have discovered important data that have not been reported in study reports. Because of these findings (examples of which are detailed below), we cannot be confident that your study reports accurately reflect the data as collected. Without the ability to review these primary records, we are unable to confirm your conclusions about the safety of the drug that derive from studies for which CRFs are not available. Although we also detected similar serious discrepancies between the data recorded in CRFs and reported in study reports for the 2 domestic effectiveness trials (Studies 024 and 025), which contributed to our view that your study reports were potentially unreliable, because we did have access to the CRFs, we were able to re-analyze the studies using all the relevant data.

EFFECTIVENESS

You have submitted the results of two adequate and well-controlled clinical investigations that appear (but note reservations below) to provide evidence to support your claim that Sabril® is effective as adjunctive treatment for patients with partial seizures, with and without generalization. These trials do not provide evidence that doses of Sabril® greater than 3 grams/day provide any greater therapeutic benefit than that obtained at a maximum daily dose of 3 grams.

We were not able to conclude from the evidence submitted, however, that Sabril® is effective as a treatment for complex partial seizures that become generalized. As you know, you have submitted data on the effects of Sabril® on **all** partial seizures that generalize, but have not

submitted data for each individual type of partial seizure (complex partial seizures or simple partial seizures) that can generalize. As a result, we are unable to conclude that complex partial seizures that generalize, specifically, are successfully treated by Sabril®.

Our tentative positive interpretation of the evidence adduced in these two clinical trials has been possible only because of the extraordinary efforts of our medical and statistical review staff. Because their initial audit of the documents in the NDA file bearing on the efficacy of Sabril® revealed numerous troubling, and unexplained, discrepancies between the evidence presented in the summary reports you compiled and the evidence recorded in primary data sources (individual case reports and other primary records), our staff undertook a complete and independent analysis of the evidence using primary data for one of the two trials (Study 025). It is this analysis that persuades us that Study 025 is positive; given time and resource constraints, however, we have not yet conducted an independent audit of Study 024 records. If you intend to resubmit the NDA, you will need to carry out a similar audit/re-review of study 024. We believe it important to illustrate the kind of discrepancies that we found and why we consider them so disconcerting.

Our review of individual CRFs from Study 025, for example, detected a total of 32 patients who were inappropriate recipients of concomitant anti-epileptic treatment for inadequately controlled seizures **(an explicit protocol violation).** Your summary report identified only 24 patients with this protocol violation; a misclassification rate of 25% for so critical a factor unacceptable and difficult to explain if the process of data tabulation, transfer, and auditing that you employed in the construction of your NDA was reliable.

Another troubling finding of our review involved your attempts to quantify the number of seizures that occurred during those episodes originally described in the CRFs as "seizure flurries", "clusters", etc. As you have acknowledged, in these cases, the assignment of a specific number of seizures to these episodes were made by company monitors, on some occasions years after the trial was completed, based on discussions with the patients, families, and/or investigators. On a number of occasions, however, the number of seizures assigned were inconsistent with previously recorded data for a given patient (e.g., the number "4" was assigned as a score for a seizure flurry 1 1/2 years after the trial was completed for a patient whose mother had been able to record up to 11 seizures/day on other occasions.). Admittedly, your summaries described the "assignment" procedure in a generic way, but specific examples of the kind of data re-expression just cited are inconsistent with the generic depiction of the process and require further specific explanation. Your study report summaries, unfortunately, had no detailed discussion of these numerical assignments made retrospectively by the company monitor.

Our review of Study 025 case reports also led to the discovery of individual records in which seizure counts for subjects were not recorded during hospitalizations. This omission has the potential to introduce significant bias, yet it was not noted in your study reports.

In sum, although we are reasonably confident that the NDA provides evidence from more than a single controlled trial to support a claim that Sabril® is an effective treatment for partial complex seizures, the review that supports this judgment also shows serious and pervasive

deficiencies in the reports submitted to the NDA. These will have to be addressed in any resubmission of the NDA; specifically, a full re-review of study 024 will be needed.

SAFETY

The information provided in the NDA fails to show that Sabril® is safe for use.

While you have ostensibly provided safety data for a cohort of greater than 3000 patients who have received Sabril®, close inspection reveals that you have not adequately recorded and/or reported important information required to establish the safety and characterize the toxic potential of Sabril®.

Deficiencies in the safety data base can be characterized as falling into one of 2 types; 1) Inadequate collection of potentially important safety information, and 2) Inadequate reporting of adverse event data collected.

1) **Inadequate collection of potentially important safety information**

In order for the Agency to adequately assess the safety of Sabril®, and characterize the adverse events associated with its use, we must be able to review data from a sufficiently large cohort of patients followed forward in time prospectively. This cohort must be exposed to sufficiently high doses for an appropriate duration, all adverse event data must be collected contemporaneously with the conduct of the studies, and complete, or essentially complete, case ascertainment must be assured. Specifically, the status of all patients (i.e., whether or not they discontinued treatment) must be known at the time their contribution to the safety data base ends. For example, a given patient may contribute 6 months of exposure to the data base because he or she had received six months of treatment at the time of the cut-off date for data collection. In such a case, we can know with confidence the reason for such a patient not having contributed to the data base any data beyond 6 months (despite the fact that he or she might actually have continued on treatment). On the other hand, there must also be assurance that it was not an adverse event that led to discontinuation.

Your application contains data from 3 cohorts; 1)Domestic- we consider this cohort to consist of all patients who were treated with GVG in the United States (N=537), 2)CRF- this cohort consists of all patients who received GVG outside the US, and for whom data was recorded into the NDA database either directly from CRFs or from ICSs (N=1233), 3)ARF- this cohort consists of foreign patients for whom data was entered into the NDA database from secondary sources (N=1550).

We believe that the data from the Domestic cohort is complete and that there are prospective follow-up and disposition data on essentially all 537 patients. In contrast, we consider the ARF database as unreliable because the data in it have not been prospectively recorded and cannot, therefore, be considered to provide complete follow-up and disposition data on this cohort. It is the CRF data base that is critical to providing an adequate safety data base but whose status is

in question. It may be that these data can be made complete and reliable; at present, however, we cannot conclude they are.

For example, although you were very recently (April 14, 1995) able to provide a brief tabular summary of the nominal causes for discontinuations in the CRF database, the lack of primary case records makes it impossible for us to conduct an independent audit of this report. In light of the deficiencies identified in our review of your application, this presents a serious problem. Moreover, if the case reports forms are unavailable, we are perplexed as to the primary source of information used to construct the summary tabulations provided in your April 14th submission, especially in view of your repeated earlier assertions that the information provided was not available.

We are not disputing your belief that CRFs were appropriately designed to collect information on deaths and adverse events, nor your view that they would have captured these events, if they were used as intended. This, however, is irrelevant to the matter of how reliably information recorded on CRFs was transferred to ICSs, summary reports, and tables. This can only be evaluated objectively if we have access to the CRFs.

In sum, the reports provided in the application concerning the CRF database cannot be evaluated for accuracy and reliability because we do not have access to the CRFs.

In addition, you have acknowledged that information about hospitalizations (for any reason) was not systematically collected on the European CRFs. As you know, we regard hospitalizations due to adverse events as a signal of the severity of the event. Without an accurate accounting of the number of hospitalizations, we cannot adequately characterize the severity of any adverse events that may have resulted in hospitalization that might not have been recorded.

2) **Inadequate reporting of adverse event data collected**

As noted above, a detailed review of the CRFs you have submitted reveals many examples of inadequate reporting of data collected on the CRFs.

For example, in the study report for Study 006, a study performed in the US and designed specifically to monitor patients for evidence of ocular toxicity, you describe 12 patients with abnormalities and concluded that VGB had no important ocular toxicity. Review of all 45 CRFs, however, revealed 36 patients with abnormalities that may or may not have been related to treatment. Other examples of inadequate reporting include your assertion that no significant cardiovascular adverse events occurred. This statement cannot be independently confirmed because you have submitted none of the EKG data collected.

A problem that recurs in the application is the lack of complete, detailed, comprehensive reports of specific safety issues. For example, although you have collected a considerable amount of evoked response data, you have not provided a comprehensive summary report of the findings. Similarly, you have not commented upon potentially important findings seen in some of the

autopsy examinations, nor have you submitted an analysis and report of the cases of hepatic failure, even in the face of our explicit request to do so.

A particularly troublesome omission has been the absence of a single locatable report of the serious adverse events that have occurred in association with the use of VGB. Although reports of some serious events have been included in various sections of the application, we have been unable to find a single report that describes and discusses these events in a comprehensive manner. We acknowledge that there is a section titled Serious Adverse Events in the application, but this is, in reality, a list of hospitalizations (As discussed earlier in this letter, records of hospitalizations were not systematically kept, so that this categorization cannot be relied upon to include all serious adverse events that might have occurred).

Finally, once you have reliable data on all deaths that have occurred in association with treatment with Sabril®, it will be important for you to present data on Sudden Unexplained Deaths (SUDs) in the form of SUDs/per patient-years of exposure. In this way, we will be able to compare the incidence of these events with similar estimates for recently approved anti-epilepsy drugs.

In summary, the series of deficiencies described above have made it impossible for us to independently confirm or refute your conclusions that VGB is safe for the conditions of use proposed in your draft labeling. Although it is probable that data from the Domestic database may be re-analyzed and reported adequately, it appears that repairing the deficiencies in the CRF database may be more problematic, not only because you currently do not have access to them, but also because some important information may not have been collected. In the absence of reliable data from this cohort, even if the Domestic database can be repaired, the NDA would not contain data from a sufficiently large cohort to permit the conclusion that Sabril® is safe under the conditions of use.

We encourage you to pursue approval of this application; it appears probable that Sabril® will prove to be effective therapy of partial seizures. We also recommend that you consider submitting a Treatment protocol to your IND. The Treatment protocol would provide a mechanism for making the drug available to patients who could benefit from it, while serving the critical function of allowing you to accrue the patient experience necessary to establish the safety of Sabril®. The Division of Neuropharmacological Drug Products will be happy to discuss this option with you.

In addition, we have the following comments and requests for information that should be addressed:

BIOPHARMACEUTICS

1) While you have provided the results of a population based analysis of the interactions between Sabril® and other commonly administered AEDs, we suggest that you perform more formal interaction studies to examine the effects of Sabril® on plasma levels

of these drugs, as well as studies to examine the effects of these other drugs on Sabril® plasma levels.

2) We request that you study the effect of pH changes in urine and its influence on the urinary excretion of vigabatrin.

3) Please adopt the following dissolution methodology and specification for vigabatrin 500 mg film-coated tablet:

Medium:	900mL 0.1 N HCl at 37 ± 0.5 C
Apparatus:	USP Apparatus II (paddle) at 50 rpm
Specification:	Not less than 80% in 30 minutes

ENVIRONMENTAL ASSESSMENT

Please refer to an Agency letter dated January 31, 1995, providing for deficiencies in your environmental assessment. We requested that the exact address for the site of disposal of drug substance and drug product be included in the Freedom of Information (FOI) releasable environmental assessment document. The exact addresses for the backup locations for disposal at Dow Chemical in Plaquemine, Louisiana, and Freeport, Texas, are not given.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

Should you have any questions concerning this NDA, please contact Ms. Robin M. Pitts, Consumer Safety Officer, at (301) 594-2777.

Sincerely yours,

Robert Temple 4/28/95

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
NDA Orig.
HFD-120/DIV File
HFA-100
HFC-130/Allen\
HFD-5/THassall
HFD-80
HFD-100/RTemple 4/14/95
HFD-120/PLeber 4/13/95
/RKatz/CMcCormick 4/20/95
/Fitzgerald/BRosloff 4/14/95
/Blum/Guzewska 4.14.95 4/14/95
/RPitts
HFD 426/Baweja/Tammara
HFD 713/Nevius/Taneja
draft:March 20, 1995
draft2:April 10, 1995
draft/ with revision/leber/4/13/95
draft/with spellcheck/pitts/4/13/95
M:/dos/wpfiles/sabril/gvgna6.ltr
Not Approvable

MEMORANDUM

DATE: March 31, 1995

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-427, Sabril

SUBJECT: Supervisory Review of NDA 20-427, Sabril for Adjunctive Treatment of Patients with Refractory Partial Seizures

BACKGROUND

NDA 20-427, for the Use of Sabril as adjunctive treatment for patients with refractory partial seizures, was submitted by Marion Merrel Dow on April 29, 1994. The complete NDA was reviewed by Dr. Cynthia McCormick, Medical Officer, and the definitive effectiveness trials were also reviewed by Dr. Baldeo Taneja of the Division of Biometrics. In this memo I will briefly review the relevant effectiveness trials, as well as describe in some detail what I believe to be flaws in the collection and reporting of the safety data of sufficient severity to preclude approval of the NDA at this time.

Initially, though, it seems important to provide a summary of the regulatory history of the development of this product.

REGULATORY HISTORY

The IND for Sabril was submitted on February 15, 1980. Chemically known as gamma vinyl Gamma amino butyric acid (Gamma vinyl GABA, or GVG), it is an irreversible inhibitor of GABA-transaminase, the enzyme responsible for the metabolism of GABA, the most important inhibitory neurotransmitter in the CNS. As a consequence of this pharmacological property, and the resulting elevation of CNS GABA levels, it appeared promising as a treatment for any number of conditions characterized by

neuronal hyperactivity, including, for example, Huntington's Disease, tardive dyskinesia, and epilepsy. The initial submission, however, documented the occurrence of intra-myelinic edema in a 3 month rat study, at the highest dose, and in the cerebellum only. The IND was permitted to proceed, but the sponsor was urged to further evaluate the lesion.

Several protocols had been submitted and were proceeding as of February, 1983, when we were informed by the sponsor that the intra-myelinic edema, previously seen in one species at the high dose, was now seen in 3 species (rat, mouse, and dog) at doses overlapping with the clinical dose, and in many other areas of the brain in addition to the cerebellum. After the Division's review of the studies, the sponsor was informed on April 7, 1983, that no new patients were to be enrolled in any on-going trials, but that patients currently enrolled and judged to have been receiving benefit (approximately 50 with refractory epilepsy at the time) could continue to receive drug. All new trials were placed on Hold, and the issue was discussed at a meeting of the PCNS Advisory Committee on May 18, 1984.

At this meeting, the Committee recommended that adequate and well-controlled trials should be permitted, in an effort to establish the utility of the treatment as rapidly as possible. Further, they recommended that additional animal work to further characterize the lesion, and, importantly, to validate a method to monitor the onset, progress, and potential reversibility of the lesion be conducted simultaneously with the clinical trials.

Subsequent to this meeting, the sponsor submitted protocols for definitive effectiveness trials, but these submissions essentially coincided with the completion of a 1 year monkey toxicity study. Because this study demonstrated the occurrence of the same lesion in the high dose monkey group, as well as evidence of irreversible neuronal injury, the issue was presented again to the PCNS Advisory Committee at a meeting held on October 18, 1985.

At this meeting, the Committee recommended that no new patients be

permitted to receive GVG until an adequate non-invasive method of monitoring for the lesion be developed and validated in an animal model. In particular, serial evoked potential and MRI monitoring in dogs, linked temporally to histologic verification of lesion onset and regression, was recommended to be performed.

A third meeting of the PCNS Advisory Committee was held on November 20, 1989, at which the results of evoked potential monitoring in the dog were presented, as were additional human data that was continuing to accrue in European trials. The Committee was convinced, based on the dog data, that evoked potential monitoring could be relied upon to detect the onset, and follow the course, of the lesion, should it occur, in humans, and that, coupled with the additional human data, adequately designed clinical trials could be permitted to proceed. As a result, the IND was taken off hold, and subsequent clinical trials employed evoked response monitoring. There have been no additional problems identified, and trials have continued without interruption.

EFFECTIVENESS

The sponsor has submitted the results of 2 controlled trials in patients with refractory partial epilepsy conducted in the United States. In addition, they have presented 13 small, often uncontrolled trials performed in Europe that presumably support the conclusion that Sabril is effective in this population. Because of the size and design of these trials, they have not been reviewed in detail by either Drs. McCormick or Taneja. I, too, will not discuss them any further, since they contribute no useful information beyond that contained in the 2 domestic trials.

STUDY 024

This was a multi-center, double blind, placebo controlled, parallel group, add-on trial comparing the effects of GVG 3 gms/day to placebo, in patients with refractory complex partial epilepsy being treated with one or two available AEDs. The study consisted of 3 Segments; Segment I was a prospective 12 week evaluation period, the last 8 weeks of which were considered the baseline period, and after which randomization occurred; Segment II represented a 4 week titration period in which patients were to be titrated from 1.0 g/day to 3.0 g/day, in weekly increments of 0.5 g/day; Segment III, which was a 12 week maintenance, the last 8 weeks of which were considered the maintenance phase. Seizure counts were collected in patient diaries. The primary outcome measure was designated to be the frequency of all complex partial plus all partial onset generalized seizures. Simple partial seizures that did **not** generalize were not included. Other, secondary measures, included 50% Reduction in the 2 seizure types, individual frequencies of simple partial, complex partial, and partial seizures that generalized, frequency of seizure free days, and various global evaluations.

RESULTS

Fifteen (15) centers entered a total of 203 patients into Segment I. Of this 203, 183 were randomized to treatment (90 placebo, 93 GVG). One GVG patient withdrew prior to receiving treatment.

PRIMARY OUTCOME MEASURE

Of the 182 patients receiving treatment, 170 completed the entire trial. Of the 12 who discontinued, 8 GVG and 2 placebo patients discontinued due to adverse events. The following table describes the baseline and final median data for the combined seizure types of interest for the Intent-to-Treat data set:

MEDIAN MONTHLY SEIZURE FREQUENCY

	N	Baseline	Final
Placebo	90	8.3	7.5
GVG	92	8.3	5.3

Various analyses of rank-transformed and untransformed frequency yielded p-values of between 0.001 and 0.0002 for the drug-placebo comparison.

SECONDARY OUTCOME MEASURES

The following Table describes the proportion of patients achieving a 50% or greater reduction in frequency of the combined seizure types (Therapeutic Success):

PROPORTION OF PATIENTS ACHIEVING THERAPEUTIC SUCCESS

	N	% With 50% Reduction (N)
Placebo	90	19% (17)
GVG	92	43% (40)

The p-value associated with this difference is <0.001.

(Results presented for the following Secondary Measures are those of the sponsor, and have not been independently confirmed by Dr. Taneja).

The following Table describes the effect of GVG on the Frequency of Complex Partial Seizures Alone (patients were included in this intent-to-treat cohort who had this seizure type at baseline) :

MEDIAN MONTHLY SEIZURE FREQUENCY (COMPLEX PARTIAL SZS)

	N	Baseline	Endstudy
Placebo	89	8.0	7.0
GVG	84	8.5	5.0

The drug-placebo difference was highly significant, with $p<0.0006$.

While there was a numerical difference in the Median Monthly Frequency of Partial Seizures with Secondary Generalization (Decrease of 1.5 on GVG vs 0 on Placebo), this difference did not reach statistical significance. There were insufficient patients with Simple Partial Seizures Alone to perform an analysis.

The following Table describes the changes seen in the number of Seizure-Free Days per Month:

MEAN MONTHLY FREQUENCY OF SEIZURE-FREE DAYS

	N	Baseline	Endstudy
Placebo	90	18.4	19.1
GVG	92	18.6	20.8

This difference was significant, with $p=0.0024$.

STUDY 025

This was a multi-center, randomized, double-blind, add-on, placebo controlled, parallel group, fixed dose ranging trial comparing the effects of 1, 3, and 6 gms of GVG and placebo. It was similar to Study 024 in most aspects, including patient population, general outline, and outcome measures. Segment II in this study, however, represented a 6 week titration in which patients were randomized to receive placebo, 1 gm GVG throughout, 3 gms GVG (reached by Week 3), or 6 gms GVG (reached by Week 5).

RESULTS

A total of 203 patients entered Segment I. A total of 174 patients were randomized to drug in Segment II (45 Placebo, 45 1 gm, 43, 3 gm, and 41, 6 gm), and a total of 149 patients (42 Placebo, 40, 1 gm, 36, 3 gm, and 31, 6 gm) completed the trial. There was a dose dependent increase in the number of dropouts due to ADRs.

The primary analysis was performed on the Intent-to-treat population. The following Table displays the results on the primary outcome measure, which represents the combination of complex partial seizures and all partial seizures that secondarily generalized:

MEDIAN MONTHLY FREQUENCY OF SEIZURES

	N	Baseline	Endstudy
PLACEBO	45	9.0	8.8
1 GM	45	8.5	7.7
3GM	43	8.0	3.7
6 GM	41	9.0	4.5

The results of a linear trend test across doses were highly statistically significant, with p=0.0001. While 1 gm was not statistically significantly different from placebo, both 3 and 6 gms were, with p=0.0001 for each comparison. The difference between the effects of 3 and 6 gms were not significant, with p=0.81.

SECONDARY MEASURES

The following Table displays the results by dose for the variable Therapeutic Success (again, defined as the proportion of patients with a 50% or greater decrease in frequency compared to baseline):

PROPORTION OF PATIENTS WITH THERAPEUTIC SUCCESS

PLACEBO (N)	1 GM (N)	3 GM (N)	6 GM (N)
7% (3/45)	24% (11/45)	51% (22/43)	54% (22/41)

Again, a linear trend test was highly significant, with p<0.0001. All comparisons between individual doses and placebo were significant (p=0.02, <0.0001, and <0.001 for 1, 3, and 6 Gm respectively), and no difference was detected between 3 and 6 Gm (p=0.97).

(The following analyses of other secondary outcome measures have not been independently confirmed by the Division of Biometrics).

The following Table presents the results of analyses of the effect of GVG on Complex Partial Seizures:

MEDIAN MONTHLY FREQUENCY OF COMPLEX-PARTIAL SEIZURES

	N	Baseline	Endstudy
Placebo	44	8.8	8.3
1 GM	45	7.5	7.0
3 GM	43	7.0	3.5
6 GM	39	8.5	3.5

According to the sponsor's analysis, a linear trend test was highly significant ($p<0.0001$). Individual comparisons of 3 and 6 Gm with placebo were both significant ($p=0.001$, and 0.0001, respectively).

Analyses of the effect of GVG on the treatment of simple partial seizures only in the subset of patients who had simple partial seizures at baseline yielded no statistically significant comparisons (Total N=73). Similarly, analyses of all partial seizures that secondarily generalized did not detect significant differences (total N=53).

According to the sponsor, there also was a highly significant dose trend ($p=0.0001$) for the variable Seizure-Free Days, although the actual results are unavailable to me at this time.

The sponsor has proposed that the drug be indicated for complex partial seizures with and without generalization. Since the data were not presented for this particular seizure type specifically (**all** partial seizures that generalized was the categorization presented by the sponsor), we asked the firm to analyze this specific seizure type. They responded that they could not perform this analysis, since the data were collected as all partial seizures, not broken down into simple and complex partial seizures. Presumably, this primary data could be retrieved from the patient diaries, but this was not done. For this reason, we cannot perform this analysis for either study 024 or 025.

Analyses of both controlled trials demonstrates that levels of concomitant AEDs are not systematically increased (indeed, they may be decreased, particularly levels of phenytoin) in patients on GVG compared to patients treated with placebo. For this reason, effects on seizure frequency are not considered to be due to pharmacokinetic interactions with other AEDs.

In each study, the protocol stated that certain patients would be excluded from the primary analysis. Specifically, patients who experienced a 2-fold or greater increase in seizures while on treatment, or who developed status epilepticus would be excluded. This was not done. We asked the

sponsor to perform this analysis, and in addition to exclude data from patients who required treatment with additional AEDs (in the spirit of the philosophy of the protocol, which was to exclude patients with seizure worsening), as well as patients for whom seizure counts could not be recorded for a given episode (flurry, cluster), and for whom the sponsor assigned a seizure count. For purposes of this re-analysis, patients were considered to have withdrawn at the time of their event, and their subsequent data was not utilized. In addition, they were considered failures for the analysis of Therapeutic Success.

In this re-analysis, data from 8 patients in Study 024 and data from 35 patients in Study 025 were excluded. There were no substantive changes in any of the analyses of the primary outcome measure or Therapeutic Success.

SAFETY

Although the NDA ostensibly contains reports of a sufficient number of patients (upwards of 3000) on which to base an adequate decision about the safety of the product, a detailed review has revealed that there are deficiencies in two critical areas: 1) Primary documentation of exposure and adverse event occurrence, and 2) accurate transcription and reporting of adverse event data from primary sources. In the following section, I will detail what I believe to be serious inadequacies in the safety section as submitted. These inadequacies, in my view, make it impossible to assess the safety of GVG according to the usual standards for an NDA for a new chemical entity. Accordingly, I have not reviewed any specific safety concerns raised by the data, incidences of ADRs, etc. (although Dr. McCormick, in her review, has made a heroic effort to do so).

ISSUES RELATED TO EXPOSURE AND INADEQUATE DOCUMENTATION OF ADVERSE EVENTS

A total of approximately 3320 patients exposed to vigabatrin in a non-post marketing setting are reported on in the NDA. This represents domestic and European experience. A total of 443 patients with epilepsy and 94 patients with other diagnoses have received vigabatrin in the US, for a total of 537 domestic patients contributing data to the safety data base.

The remaining 2783 patients have been divided into 2 separate cohorts by the sponsor. These are the CRF cohort and the ARF cohort.

The CRF (Case Report Form) cohort consists of 1233 patients who received vigabatrin in various controlled and open studies in Europe. According to the sponsor (based on a telephone conversation of 3/14/95) essentially all patients in this cohort had adverse reaction data recorded contemporaneously on Case Report Forms. For 594/1233 (48%) of these patients, data from the CRFs was directly keyed into the sponsor's NDA database by MMD's European affiliate, and this data is the data presented in the NDA. For the remaining 639/1233 (52%), data from the CRFs was first transcribed onto a shorter form, called the Individual Case Study (ICS) Form, from which the data were then keyed into the NDA database. For this cohort, the data from the ICS represents the data presented in the NDA. According to the sponsor, the ICS, a relatively short form, was primarily designed to abstract Adverse Event data from the CRF, and was filled out for an individual patient when the sponsor felt that the original CRF did not contain sufficient data. In order to adequately fill out the ICS, information on the CRF was supplemented with adverse event data from original patient records, study reports, summaries, manuscripts, etc. In this same telephone conversation, the sponsor acknowledged that they did not have the original CRFs for any of this cohort of 1233, and that some percentage of them presumably might be available, but could offer no estimate of how many could be retrievable.

According to the sponsor, after the ICSs were created from the CRFs, they

(the ICSs) were shown to the investigator for his/her concurrence and signature. Also according to the sponsor, these ICSs could have been completed up to several years after the patient's participation in the study.

According to the sponsor, the CRFs from the European studies (both those from which data were directly entered into the NDA database and those transcribed onto the ICSs) were designed primarily to record Adverse Events, but important information ordinarily included in current CRFs was not necessarily captured. This was also presumably true for the data in the ICSs, despite the fact that these were supplemented with additional patient data. For example, by the sponsor's admission, whether or not patients were hospitalized as a result of an adverse event (or for any other reason) was not systematically or reliably recorded on the European CRFs.

The second data base, the ARF (Abbreviated Report Form) database, consists of data from the remaining 1550 patients. While the sponsor asserts that some proportion of these patients also had contemporaneous CRFs filled out, the data in the NDA database for this cohort was collected from sources **other than** the CRFs. That is, the data included in the NDA for this cohort was collected from study reports, published articles, and other secondary sources, not from primary data collected at the time of the patients' exposure to drug. As with the CRF database, original data, when it exists, is not available to the sponsor, and certainly not to us.

With regard to the ARF database, due to the nature of the collection and reporting of events, and the unavailability of primary data sources, we have no assurance that all events of interest have been reliably captured and reported, nor does the sponsor. For these reasons, we cannot accept data from this database as contributing to the safety data base.

Given the unreliability of the ARF database, any attempt to assess the toxicity profile of GVG must focus on data from the remaining 2 cohorts, the US domestic experience, and the CRF database. If data from both cohorts can be considered reliable, this would yield a combined safety

database of 1770, ordinarily a number of exposures quite sufficient on which to assess the safety of the drug. However, if the US cohort of 537 is the only cohort in the NDA for which reliable safety data is available, we would not be able to adequately assess the safety profile of the drug.

With regard to the US experience in 537 patients, we have confidence that all relevant safety information has been recorded and is available for our review. However, we have serious reservations about the presentation of this data, on which more later.

Whether or not the NDA can even be considered Approvable, then, depends on the assessment of the reliability of the data contained in the CRF cohort.

It has been extraordinarily challenging to figure out how the data in this cohort was collected, recorded, and presented. Our current view is based both on the submission itself, as well as multiple telephone conversations with the sponsor. On many occasions, the sponsor has acknowledged the shortcomings in this database, and has not been able to give completely satisfying answers to a number of questions.

Problems in the database are first encountered when examining dose and duration of exposure data. While the sponsor has presented tables of dose information, duration of exposure information, and dose and duration of exposure information combined, they have done so for the entire database of 3320. In these presentations, they have acknowledged that they do not have combined dose and duration data for approximately half of this cohort, **but we do not know to which patients the known dose and duration data apply**. Consequently, it is impossible to tell which, and what proportion, of the 1233 patients in the CRF database have reliable dose and duration of exposure data, so that we cannot say with certainty with what dose, and for how long, this cohort was treated.

Another serious deficiency in the database relates to the number of dropouts reported. The sponsor has presented the number of patients who left treatment as a result of death or adverse events. However, they

acknowledge that there may have been additional dropouts for whom they have not accounted (a number which they acknowledge may be large or small). That is, the sponsor does not know (and hence cannot, of course, report), the reasons why individual patients stopped contributing exposure data when they did. (For example, an individual patient's contribution to the NDA may have been 6 months of exposure because they had been on drug for 6 months at the time of the NDA cut-off date, or because the protocol in which they were enrolled ended at 6 months. However, the sponsor acknowledges that they do not know why some [unknown number of] patients stopped their contribution to the data base when they did.)

The sponsor is "confident" that they have reported all dropouts due to adverse events (and deaths), because they assert that the CRFs from which they abstracted the data were designed primarily to record adverse events and actions related to adverse events, so that if a patient discontinued treatment secondary to an adverse event, this action would have been recorded. However, they agree that, since they cannot be certain of how many patients actually may have discontinued treatment at the time they contributed data to the NDA or why, they cannot reliably conclude that none of these additional patients did not leave as a result of adverse events (or death). One reason to suspect that all relevant ADR related information was not collected, for example, is that, as noted earlier, information about hospitalizations, (for any reason), was not systematically collected on many of the CRFs.

Documentation about the number of deaths and in which cohort deaths occurred has also been a difficult problem. Dr. McCormick has, for example, identified reports in the Neuropathology section of the application of patients who died for whom no corresponding information is contained in the section on deaths. Multiple telephone conversations intended to get the sponsor to collate all deaths and identify in which cohort they occurred have still not, as of this writing, been entirely successful.

There are additional shortcomings in the safety data base as reported. For example, Serious Adverse Events have not been collected in one section of

the NDA. Although there is a Section of the NDA called Serious Events, inspection of that section reveals that this is, in fact, a list of hospitalizations. Since we have already seen that hospitalizations were not systematically collected for patients in the CRF database, this list is unreliable. Dr. McCormick has made every effort to accumulate and report those adverse events located throughout the NDA which appear to be serious; as of this date, because of the inadequacy of the submission, she cannot be confident that she has identified all such events.

ISSUES RELATED TO INADEQUATE DESCRIPTION OF COLLECTED ADVERSE EVENTS

In addition to those problems related to questionable primary data acquisition and documentation of exposure, there are many problems relating to the inadequate presentation of data that we know has been collected, including serious flaws in the reporting of data from the US database.

For example, the sponsor warrants that no significant cardiovascular adverse events were seen, but did not present **any** of the routine EKG data that was collected.

Because of the concerns raised about the potential for GVG to cause intra-myelinic edema (IME) in animals, considerable attention was to be paid to evaluating any brain tissue that was obtained. As discussed by Dr. McCormick, tissue was derived from 2 sources; brain biopsy and autopsy. Since biopsy material was limited to areas of brain that were not necessarily expected to be involved with the neuropathology (based on the animal studies), attention was largely focused on the autopsy material. Beside the fact that very few of the 17 autopsy specimens had examinations of the areas of interest (e.g., only 2/17-12%- of autopsied brains had an examination of the fornix, an area with extensive IME involvement in animals), of more concern here is that the sponsor made no attempt to report or discuss findings that were seen in some patients that were at least consistent with the animal data. For example, Dr.

McCormick notes 4 patients in whom findings consistent with the animal lesions (axonal ballooning, spheroids in the cerebellum) were seen, but the sponsor made no comment of the findings (Dr. McCormick discovered the findings upon reading the primary pathology reports). It is also important to point out that there was no description of the methodology employed (e.g., how controls were chosen, maintenance of blinding), as well as any protocol for obtaining material and performing the pathology examinations.

Another critical example of the sponsor's inadequate reporting of potentially important drug related findings involves Study 97-006. This study was performed in the US and was undertaken specifically to examine any ocular effects of GVG, since studies in albino rats demonstrated retinal pathology, and because of theoretical concerns about the effects of GABA on pathways involved in visual function. The study involved 45 patients who underwent extensive ophthalmologic testing every 6 months. The sponsor reported that the results demonstrated that GVG was not associated with any ocular pathology, although they did list 12 patients with abnormalities. Dr. McCormick undertook a review of the CRFs of these patients, and uncovered multiple changes in a total of 36 patients (the description of the changes in the CRFs caused Dr. McCormick to request the primary ophthalmologic records-data from which was used to create the descriptions in the CRFs-and review of which revealed additional findings). Some findings included vessel narrowing (12 reports), retinal drusen (15 reports), retinal pigment epithelial loss and/or changes, and cataracts and other lenticular changes (7 reports). Much of this pathology was neither discussed, described, nor reported by the sponsor, other than in the CRFs. An ophthalmology consultant obtained by the Division felt that there was compelling evidence suggestive of possible ocular toxicity requiring further study. A similar "trial" was performed in Europe, and was described also as demonstrating the absence of any effects of GVG on the eye or visual system. However, no primary records are available to us that would allow us to independently confirm or refute the sponsor's conclusions.

Further, in the course of review, Dr. McCormick became aware of several

cases of liver failure (some had been reported to the IND, but not the NDA). The firm was requested to submit a tabulation of the cases and discuss and analyze the findings in their safety update. They submitted a tabulation, but no analysis or discussion. Dr. McCormick has described 12 cases of hepatic failure, with 7 deaths. Half of the cases of hepatic failure occurred in children below the age of 10.

As noted earlier, as a result of the concerns raised by the animal findings, evoked potential monitoring was incorporated into Studies 024 and 025, as well as into several other trials. In Studies 024 and 024, patients were monitored with Visual Evoked Responses (VER) at baseline and at 4 months of treatment. Dr. John Feeney has reviewed the sponsor's report of the electrophysiologic monitoring, as well as the individual tracings for Study 25 (no other actual tracings were submitted). His detailed inspection of the data for Study 25 reveals deficiencies strikingly similar to those found in the rest of the NDA. For example, data for latencies of wave forms (the primary outcome of interest) are presented for certain patients that review of the primary tracings cannot confirm. Also, in certain cases, the individual investigator performing the studies concluded that the tracings were inadequate and that the data generated should not be utilized, yet latencies for these patients are reported without comment by the sponsor. As with the larger safety data base, close inspection again reveals the disturbing disparities between the primary data and the sponsor's summary and reports of that data. While no consistent important findings are reported to have emerged in the entire evoked response experience (total N is difficult to calculate, but may be in the range of several hundred patients worldwide), we have the same concerns about the reliability and accuracy of the sponsor's reports, although, in fact, there is **no** comprehensive report of the total evoked response experience, an example of another generic flaw in the application.

Another important example of inadequate reporting is the sponsor's report of Study 025, the second controlled trial described in the first part of this memo.

In this trial a number of protocol violations not disclosed by the sponsor were discovered only upon review of the CRFs. For example, while 34 patients with violations relating to use of inappropriate concomitant anti-epileptic medication were reported, a total of 42 were discovered on review of the CRFs. The sponsor alleged that none of the additional 8 patients received sufficient doses of the additional medication to effect the outcome, but review of the CRFs revealed that investigators had prescribed these drugs specifically for the purpose of achieving increased seizure control, and in some cases documented (what they believed to be) a response. Other problems with reporting include the fact that the number of seizures during a seizure flurry were sometimes assigned by a company monitor, sometimes years after the trial had been performed. While this practice was described by the sponsor, according to Dr. McCormick, review of the CRFs demonstrated that the number of seizures assigned by the sponsor did not make sense in the context of the other seizure data for a given patient. The sponsor never made mention of these discrepancies, which Dr. McCormick describes as having occurred frequently. For example, in one case, the original seizure count during several flurries was listed as being uncountable (the code used was the letter "Z") for each flurry. The number of seizures assigned by the sponsor 1 1/2 years later to each flurry was "4", despite the fact that the CRF reveals that at other times in the study, the mother of the patient was quite capable of counting up to 11 seizures/day.

An additional difficulty related to the fact that seizure counts were sometimes not recorded during hospitalizations, a fact that was not highlighted by the sponsor, and, once again, only emerged after review of the individual case records. While deficiencies in the reporting of this trial do not impinge upon the assessment of the safety of the compound, they clearly are consistent with the serious reporting deficiencies in the other parts of the application.

COMMENTS

Review of the controlled trials reveals that GVG is effective as adjunctive treatment for adult patients with partial seizures. Data has not been submitted to answer the question of whether the drug can effectively treat complex partial seizures that generalize (an indication the sponsor proposes). There is little, if any, evidence to suggest that doses greater than 3 grams/day offer any benefit beyond that seen with 3 gms/day.

Review of the safety data base reveals, however, that much of the data from the cohorts described has not been adequately recorded and/or reported. In the first instance, we have no confidence that adverse event data has been adequately collected in the ARF database, since it has been derived retrospectively from manuscripts, articles, summaries (in other words, secondary sources).

While the CRF database appears on the surface to be adequate, closer inspection reveals it, too, to be seriously flawed. The primary concerns are that we do not know the dose and duration of treatment for this cohort, and we do not reliably know how many deaths and dropouts there actually were in this cohort (nor, of course, do we know the reasons for any additional deaths and/or dropouts not reported). Further, other important information (e.g., hospitalizations), was not systematically recorded. In addition, the organization of the NDA has made a complete review difficult, if not impossible. As an example, as noted earlier, Serious Adverse Events were not described or analyzed in one section, making it extremely difficult to gather and review this important information.

In addition, we have found many examples of inadequate reporting of information that has been collected. Serious deficiencies in the reporting of all adverse events seen in Study 006 (the ophthalmology study), as well as similar serious omissions in the reporting of protocol violators in efficacy study 025 make all the data in the NDA as reported by the sponsor suspect with regard to its completeness and accuracy.

The question of the accuracy of the sponsor's reports takes on particular importance in light of the fact that **almost no primary data sources are now available to the sponsor.** Given our experience with finding additional important information in CRFs (in Studies 006 and 025, for example,) not reported by the sponsor, I think it is critical that we have the ability to retrieve and review (should we find it necessary) the CRFs for all patients included in the safety data base before we can conclude that the data are as the sponsor claims they are.

Given the deficiencies in the data in the CRF database, it would seem that the only cohort for which we currently have reliable data is the US cohort (although, as stated, even this cohort is inadequately reported). It is my view that a cohort of 537 patients is not sufficiently large on which to base an assessment of the safety of a new chemical entity. This is particularly true in this case, where there is concern about the occurrence of potentially serious neurotoxicity. I should hasten to add that, at the moment, I am not aware of any toxicity identified that would preclude approval of this compound. However, I believe that we have not adequately characterized the toxic potential of the drug, and certainly, we cannot rule out the occurrence of any serious adverse events (that <u>could</u> theoretically preclude approval) that may occur at small, but potentially important, rates.

As of January, 1994, GVG was approved in 31 countries, including the UK, France, Spain, Germany, and Canada. The sponsor states that at the time of submission of the NDA 200,000 patient years of exposure had accrued. While the sponsor alleges that this experience supports the safe use of GVG, it should be noted for the record that post-marketing data of this sort cannot substitute for detailed data obtained in a sufficiently large cohort of patients treated with an appropriate dose for a clinically meaningful duration, and followed prospectively with essentially complete follow-up.

RECOMMENDATIONS

Although the sponsor has submitted substantial evidence of effectiveness, they have not provided sufficient safety information on which to adequately assess the safety of the drug, and, therefore, I recommend that a Not Approvable letter should be issued.

In order to make the application Approvable, they must submit data on a sufficiently large cohort of patients followed prospectively for sufficient duration and for whom essentially complete and accurate adverse event information has been collected and appropriately reported. This particularly applies to all deaths and discontinuations, and the reasons for all of these events, but it certainly also applies to the collection and reporting of all serious and other adverse events, as well as all laboratory data. Further, of course, accurate and complete information about the doses given and the duration of treatment for each patient included in such a cohort must be available and reported. Whether the current body of information available to the sponsor can be rehabilitated to conform to this standard is very questionable.

Should it become necessary for the sponsor to enroll new patients in order to accrue a sufficient number of adequately evaluated patients, a reasonable mechanism that might be employed would be a Treatment protocol. It appears that all of the criteria for granting a Treatment protocol would be met in this case (the criterion that there be no other alternative therapy available could be met by restricting the use of GVG to those patients shown to be inadequately controlled on available AEDs), and I believe that our willingness to entertain this as an option should be included in any Not Approvable letter that issues.

Russell Katz, M.D.

cc:
NDA 20-427
HFD-120
HFD-120/Katz/Leber/McCormick/Pitts
rk 3/31/95

STATISTICAL REVIEW AND EVALUATION

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

MAR 7 1995

Applicant: Marion Merrell Dow Inc.

Name of Drug: Sabril®(vigabatrin)

DETION

Indication: Treatment of Epilepsy

MAR 0 / 1995

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 table 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
Total	**90**	**93 #**	**183 #**

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.

Treatment	N	Seizure Frequency (Number/28 Days)	
		Baseline Median (95 % CI)	Endstudy Median (95 % CI)
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).

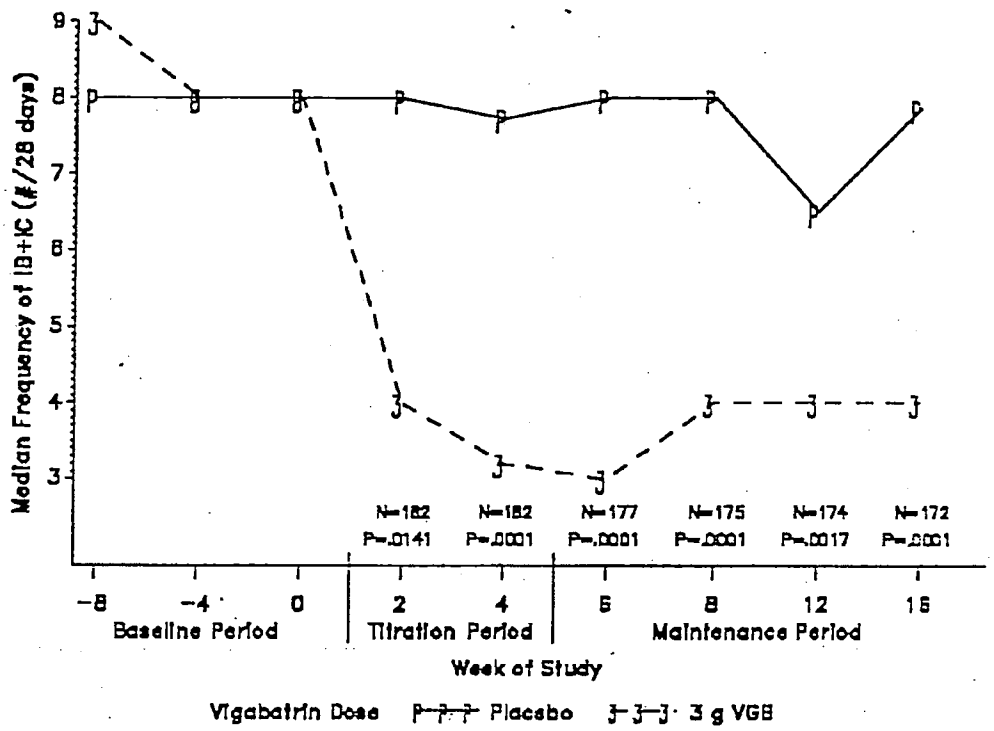
Analysis Datasets	Total N	Treatment Comparison p-Value*
Intent-to-Treat	182	0.0002
Protocol Correct Completers	160	0.0006
Protocol Correct	169	0.0002
Study Completers	170	0.0002
8-Week Completers	174	0.0003

* : 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 % (N)	Treatment Comp. p-Value
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 % (N)	Treatment Comp. p-Value
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.

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.

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

*: 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 ≥ 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.

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.

		Seizure Frequency (Number/28 Days)	
Treatment	*N*	*Baseline Median (95 % CI)*	*Endstudy Median (95 % CI)*
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 statistically significance may be because the Baseline frequencies of partial seizures secondarily generalized was low, thus allowing only small differences between groups at Endstudy.

		Seizure Frequency (Number/28 Days)	
Treatment	*N*	*Baseline Median (95 % CI)*	*Endstudy Median (95 % CI)*
Placebo	29	1.5 (1.0, 2.0)	1.5 (1.0, 2.5)
3 g VGB	31	4.0 (1.0, 5.0)	2.5 (1.0, 3.0)

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).

Treatment	N	Seizure Frequency (Number/28 Days)	
		Baseline Median (95 % CI)	Endstudy Median (95 % CI)
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.

Treatment	N	Mean Monthly Frequency of Seizure-Free Days		Adjusted Change From Baseline	Treatment Comparison p-Value*
		Baseline Mean ± SE	Endstudy Mean ± SE	Mean ± SE	
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).

Evaluation	Placebo % (N)	3 g VGB % (N)
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)
TOTAL	N=90	N=92

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.

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

*: 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).

Evaluation	Placebo % (N)	3 g VGB % (N)
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)
TOTAL	N=90	N=92

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.

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

*: 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

Evaluation	Placebo % (N)	3 g VGB % (N)
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)
TOTAL	N=90	N=92

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

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
Total	**45**	**45**	**43**	**41**	**174**

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 N (%)	Not Protocol Correct N (%)	Total
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
Total	**160 (92%)**	**14 (8%)**	**174**

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.

		Seizure Frequency (Number/28 Days)	
Treatment	*N*	*Baseline Median (95 % CI)*	*Endstudy Median (95 % CI)*
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.

		Treatment Comparison p-Values*					
Population	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
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

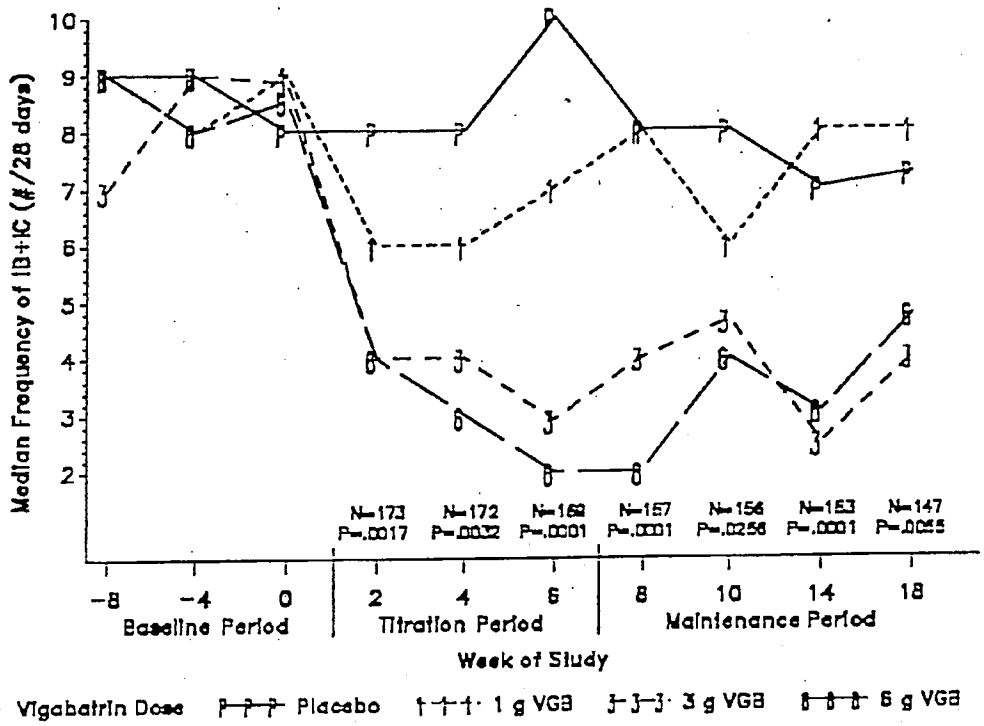
*: P-values from ANCOVA of the ranked endstudy seizure frequencies using model which adjusted for treatment, investigative site, ranked baseline seizure frequency, and site-by-treatment interaction.

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 ar 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.

		Seizure Frequency (Number/28 Days)	
Treatment	*N*	*Baseline Median (95 % CI)*	*Endstudy Median (95 % CI)*
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).

		Treatment Comparison p-Values*					
Population	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
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).

		Seizure Frequency (Number/28 Days)	
Treatment	*N*	*Baseline Median (95 % CI)*	*Endstudy Median (95 % CI)*
Placebo	10	2.0 (0.5, 6.0)	1.3 (0.0, 3.1)
1 g VGB	13	1.5 (0.5, 6.0)	0.5 (0.0, 6.5)
3 g VGB	17	1.5 (0.5, 4.5)	0.5 (0.0, 2.5)
6 g VGB	13	3.5 (0.5, 5.2)	1.9 (0.5, 6.0)

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=.4796), and none of the treatment comparison contrasts were statistically significant (P≥.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.

		Treatment Comparison p-Values*					
Population	**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**
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.

		Seizure Frequency (Number/28 Days)	
Treatment	***N***	***Baseline Median (95 % CI)***	***Endstudy Median (95 % CI)***
Placebo	21	6.5 (3.5, 41.0)	4.5 (2.0, 12.6)
1 g VGB	22	6.8 (4.0, 10.5)	3.6 (2.0, 7.5)
3 g VGB	16	11.0 (4.0, 20.5)	8.8 (3.5, 23.0)
6 g VGB	14	4.5 (2.0, 7.0)	1.3 (0.0, 7.3)

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≥.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).

		Treatment Comparison p-Values*					
Population	**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**
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
		Baseline Mean ± SE	Endstudy Mean ± SE	Mean ± SE
Placebo	45	17.6 ± 0.9	17.6 ± 1.0	(-0.1) ± 0.5
1 g VGB	45	17.4 ± 1.1	18.7 ± 1.1	1.3 ± 0.5
3 g VGB	43	17.4 ± 1.2	19.6 ± 1.4	2.0 ± 0.6
6 g VGB	41	19.3 ± 0.9	22.6 ± 0.8	3.2 ± 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=.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)
TOTAL	N=45	N=44	N=43	N=38

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.

Evaluation*	Placebo % (N)	1 g VGB % (N)	3 g VGB % (N)	6 g VGB % (N)
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)
TOTAL	N=45	N=44	N=43	N=38

*: 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.

Evaluation	Placebo % (N)	1 g VGB % (N)	3 g VGB % (N)	6 g VGB % (N)
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)
TOTAL	N=45	N=44	N=43	N=38

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.

Evaluation*	Placebo % (N)	1 g VGB % (N)	3 g VGB % (N)	6 g VGB % (N)
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)
TOTAL	N=45	N=44	N=43	N=38

*: 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).

Evaluation	Placebo % (N)	1 g VGB % (N)	3 g VGB % (N)	6 g VGB % (N)
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)
TOTAL	N=45	N=44	N=43	N=38

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

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

*: 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 ≥ 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
Baseline	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
Endstudy	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
Baseline	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
Endstudy	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 % (N)	Treatment Comp. p-Value
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
Baseline	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
Endstudy	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 <u>OR</u> 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.

		Seizure Frequency (Number/28 Days)	
Treatment	*N*	*Baseline Median (95 % CI)*	*Endstudy Median (95 % CI)*
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 ≤ 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 ≤ 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 ≤ 0.0001 for the test for a linear trend across doses and p-values were ≤ 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 ≤ 0.001 for various analyses of therapeutic success.

BKTaneja

Baldeo K. Taneja, Ph.D.
Mathematical Statistician (Biomed)

Concur: Dr. Nevius 3-7-95

Dr. Dubey 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.
BKT/NDA20-427/WordPerfect/01-31-95/03-01-95

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
   2. Atypical seizures
B. Myoclonic seizures
C. Clonic seizures
D. Tonic seizures
E. Tonic-clonic seizures
F. Atonic seizures

APPENDIX II

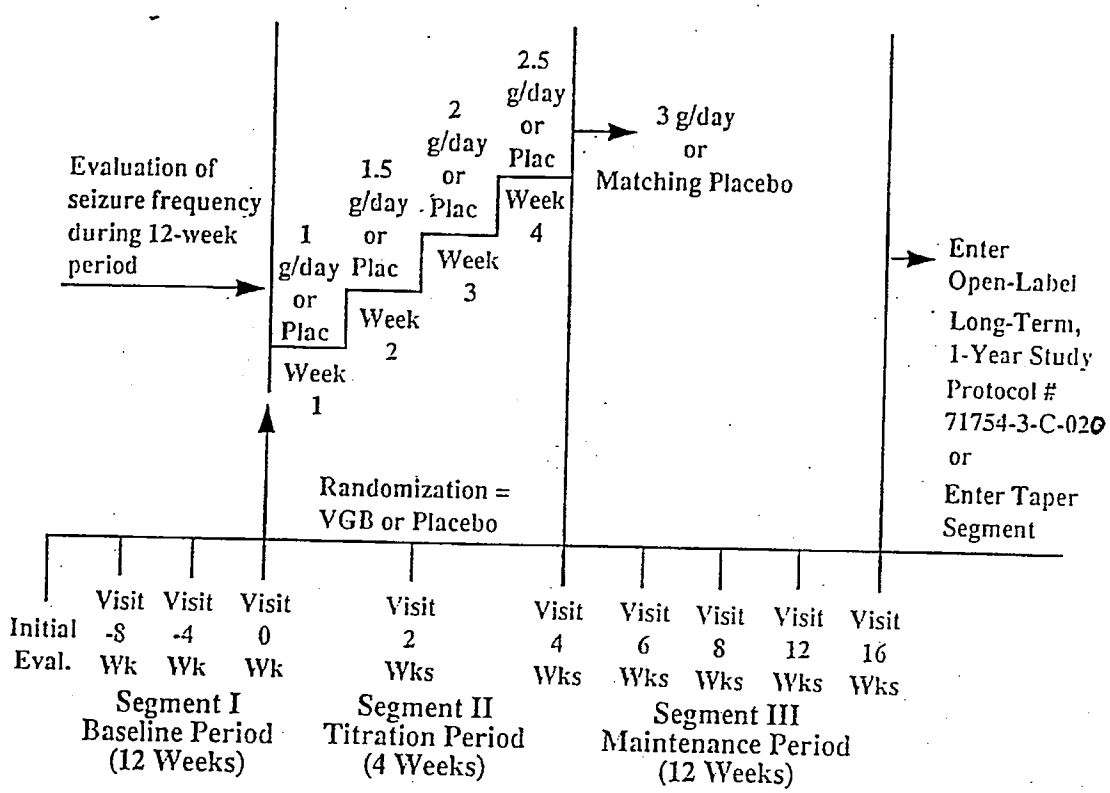


Figure 1: Study Design Schematic (Protocol 024) - Segments I, II, III

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

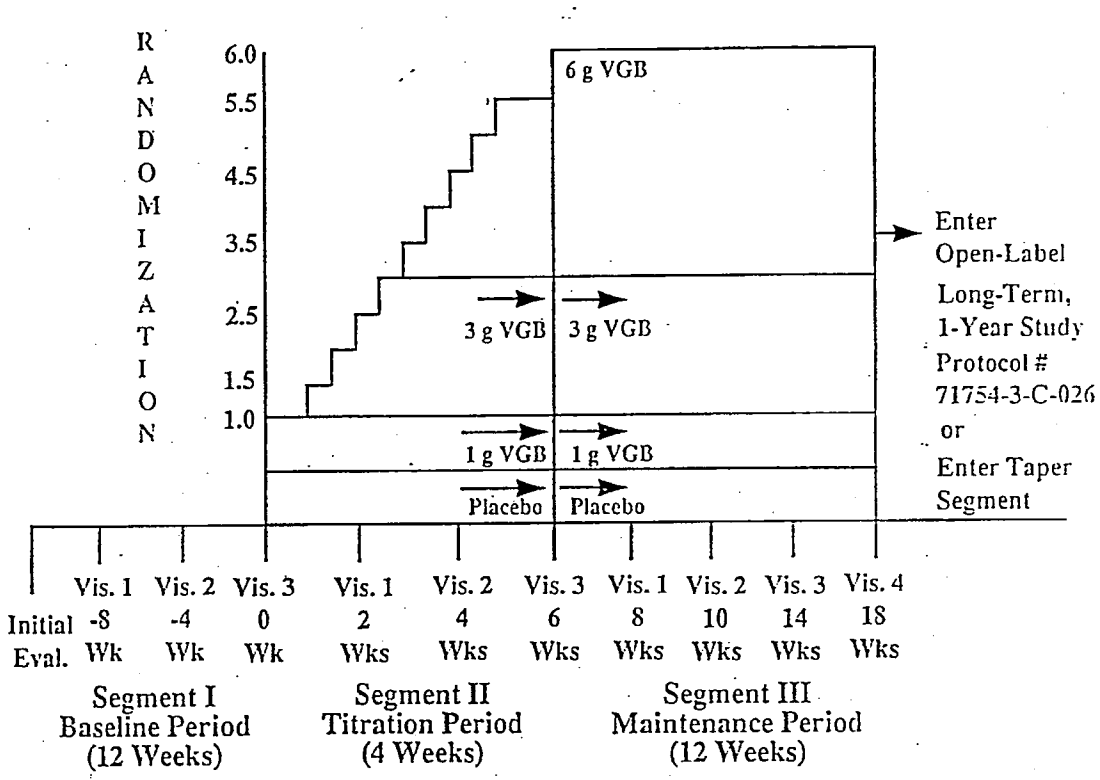


Figure 2: Study Design Schematic (Protocol 025) - Segments I, II, III

APPENDIX V

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

Baseline Characteristic	Treatment				Total	P-Value*
	Placebo N=45	1g VGB N=45	3g VGB N=43	6g VGB N=41	N=182	
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.

NDA 20-427

NOV 26 1997

Hoechst Marion Roussel
Attention: M. Lorie Stewart
Mail Station H4-M2110
P.O. Box 9627
Kansas City, Missouri 64134-0627

Dear Ms. Stewart:

Please refer to your new drug application dated April 29, 1994, received May 2, 1994, and to your amendment dated May 29, 1997, received May 29, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sabril® (vigabatrin) tablets, 500mg.

Reference is also made to the Agency's Not Approvable Letter dated April 28, 1995.

We acknowledge receipt of your additional correspondence and amendments dated:

May 5, 1995	July 17, 1995	September 12, 1996	July 23, 1997
May 15, 1995	August 1, 1995	March 11, 1997	July 28, 1997
June 5, 1995	August 2, 1995	April 1, 1997	July 31, 1997
June 12, 1995	August 9, 1995	April 28, 1997	August 13, 1997
June 13, 1995	September 26, 1995	May 22, 1997	September 16, 1997
June 30, 1995	January 3, 1996	May 29, 1997	September 26, 1997
July 10, 1995	January 4, 1996	May 30, 1997	September 29, 1997

The User Fee goal date for this application is November 29, 1997.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to respond to the following requests or comments.

Labeling

The attachment to this letter provides a draft of the labeling that the Agency asks you to adopt for Sabril® tablets upon its approval. Although sections of this proposal are taken verbatim from the labeling proposed by you in the NDA, other sections have been extensively revised and/or expanded to include new subsections. Please note that we have embedded throughout the text of the attached draft labeling, "Notes to Sponsor:", requesting further revisions or clarification of the label, as well as blank spaces requiring a numeric value which you must provide.

We have the following specific comments and requests for the following sections of labeling. Again, this comprises a relatively small subset of the changes in labeling that we are requesting, but we felt that these deserved special attention.

1. Indication Section

a. You have proposed that vigabatrin be indicated as adjunctive treatment for partial seizures in adults with epilepsy. In support of this claim, you have submitted the results of two adequate and well controlled trials that demonstrate the beneficial effects of vigabatrin on the combination of IB seizures (complex partial seizures that do not generalize) and IC seizures (partial seizures secondarily generalized).

Because this combination of seizures does not support a claim in labeling that would be easily understood by prescribers, analyses were undertaken to examine the effects of vigabatrin on the various relevant seizure types. These analyses demonstrate that vigabatrin has a robust effect on IB seizures, but not on other seizure types. In particular, no significant effects were seen between treatments on IA (simple partial seizures) or IC seizure types. While it is true that in general there were likely too few seizures of these types to detect a statistically significant between treatment difference, inspection of the data reveals that at least in one study (Study 25), there were a sufficient number of IA seizures to detect a between treatment difference; indeed, in that study, the median number of IA seizures in both treatment groups at baseline was either essentially equal to or greater than the analogous number of IB seizures. In this study, the p-value for the between treatment difference for IA seizures was 0.75, compared to a p-value for IB seizures of 0.0014. We note that you have not demonstrated an independent effect of the treatment on complex partial seizures that do generalize (a subset of IC seizures that you have not examined). Nonetheless, we believe it is reasonable to extrapolate from the finding in IB seizures and conclude that vigabatrin is effective adjunct therapy in the treatment of complex partial seizures.

b. Because of unresolved concerns about the potential of Sabril to cause intramyelinic vacuolization in humans, we have concluded that it should not be recommended as first line adjunctive therapy.

Intramyelinic vacuolization (IMV) develops in the CNS of dogs, rats, mice, and arguably monkeys exposed for extended periods to vigabatrin. It is of considerable concern, therefore, that these lesions occur in these species at levels of vigabatrin exposure below those that will be recommended for the management of complex partial seizures if vigabatrin is approved for marketing.

Although the Agency is mindful that there is some evidence that IMV developing in dogs exposed to vigabatrin can be detected by following changes in the latency of visual (VEP) and/or somatosensory (SEP) evoked potentials, the kind (type, size) of lesion that must develop before detection is reliably achieved is unknown. Even more important, there is no evidence that speaks to the degree, if at all, that either VEP or SEP would be sensitive to lesions developing in humans. An identical observation can be made about the capacity of MRI to detect lesions in both dogs and humans.

Our assessment of the risk posed to humans is further confounded by the fact that we cannot be certain about the nature of clinical signs and symptoms that would result from intramyelinic vacuolization. This is of some concern because we know, arguing by extension from experience gained in patients with multiple sclerosis, that relatively extensive white matter injury can occur in the absence of obvious clinical defect.

Accordingly, histopathological examination of brain tissue constitutes the only fully reliable and valid means to assess whether or not chronic exposure to vigabatrin causes IMV in humans. Moreover, it is not sufficient to study any area of brain. To the contrary, it is critical that tissue be taken from regions of white matter likely (based on animal study results) to be at risk of vacuolar pathology. Finally, numbers count. As in any situation where the goal is to exclude a risk not seen, the size of the population examined and found to be free of injury is critical to the warrant of safety.

It should not be surprising, therefore, that we find the citation of a lack of lesions in 11 patients treated for over a year who underwent autopsy insufficient to support a conclusion that vigabatrin poses no risk of IMV to humans. While a considerably larger number of samples of brain tissue taken from neurosurgical cases were also examined and found to be free of IMV, the source of these samples as you acknowledge, was primarily from the temporal lobe, a region found to be free of IMV in animals with white matter lesions elsewhere in their brains.

In sum, the absence of reports of IMV in human tissue is not reassuring given the kind of tissue and the number of samples examined. In light of this, especially in the absence of any documented compensating advantage of vigabatrin among the drugs available for the management of CPS, we believe it prudent to require that the product not be the first AED chosen for adjunctive use in the management of patients with CPS.

2. Cognitive/Neuropsychiatric Adverse Events Section

Alterations in mental status, some so severe as to require discontinuation of vigabatrin treatment, have been reported in association with its use. Our efforts to understand and describe the full panoply of untoward mental status and behavioral changes reported in association with the use of vigabatrin has been severely hampered by the terminology employed. Terms such as confusion, thinking abnormal, even psychosis, convey little in the way of clinically useful information. To some degree, the problem is a generic one arising from the general limitations of COSTART as a dictionary for neuropsychiatric untoward events and phenomena.

Beyond the limitations of COSTART, however, are problems that arise because the strategy you employed for grouping and distributing untoward events among the various named categories of adverse events is unclear. In fact, we are concerned that events may have been misclassified. To illustrate, the differential diagnosis of altered mental status includes absences and absence status. This distinction is important because the treatment of the latter involves withdrawal, not increment, of vigabatrin treatment.

Accordingly, a new analysis must be performed, and any review and analysis of events characterized by complex changes in behavior or mental status must make clear why one particular diagnostic assignment was made in preference to another including an enumeration of the empirical findings supporting that choice (e.g., that an EEG done while the behavior was manifest showed a classic spike and wave configuration, etc.),

Clearly, extensive guidance regarding this effort cannot be provided in this letter. Staff of the Division of Neuropharmacological Drug Products , however, will be happy to meet with your staff to develop an appropriate strategy for the requested analysis.

3. Adverse Reactions Section

In your analyses of the effects of age and gender, you have only included rates for vigabatrin. Please reanalyze your controlled trial data including placebo experience. Please also compare frequency of adverse events for vigabatrin (1g, 3g, 6g) with placebo in the controlled trial data. Additionally, compare the frequency of adverse events by time since treatment initiation. For these analyses, please examine adverse events associated with discontinuation, as well as the more commonly occurring adverse events.

4. Clinical Trials Section

An analysis of the effects of age, gender and race on the estimates of treatment effect obtained in the controlled clinical trials is required. If, upon analysis, these factors are found to have had no effect on these estimates, labeling should make a statement to that effect. Contrawise, if an effect of one or more of these covariates is found, it must be described in labeling.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Safety Issues

1. Although Sabril is not being indicated for use in the pediatric population, it would nonetheless be useful for us to examine the pediatric safety database separately to determine if there are any serious adverse events in this population. Therefore, please submit an analysis of any adverse event resulting in discontinuation or considered serious in this group.

2. Please describe the extent of use for vigabatrin at doses of 4-5g and 5-6g. Please categorize the patients by duration of use (e.g., 1 week, 2 weeks, etc.) for each dose group. Patients can appear in both dose group analyses, if appropriate.

3. We note that in several places in your application, you refer to the use of individual case summaries as a source of safety data, despite your prior assurances that these summaries would not serve as primary source documents. Please summarize the extent to which these case summaries were substituted for primary data.

4. Please provide comprehensive analyses of your urinalysis and coagulation data.

5. Please provide comprehensive clinical descriptions of cases of dyspnea, dependent edema, dysmenorrhea, and urinary tract infections. These events occurred with significantly increased frequency compared to placebo in controlled trials. In your submission, please consider the data from controlled trials and uncontrolled trials separately.

Safety Update

In your May 22, 1997 correspondence, you provided a proposal for the content of the safety update (referred to as final safety update by you) to be submitted in response to an FDA action letter. We find the proposal acceptable with one exception. Your proposal states that you will be presenting U.S. and non-U.S. (i.e. primary and secondary non-U.S.) data combined. We, however, request that you only combine the U.S. and primary non-U.S. databases. For the secondary non-U.S. and non-CRF databases, please submit data only for deaths, discontinuations due to adverse events, and serious adverse events.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Submit U.S. and primary non-U.S. safety data including results of trials that were still ongoing at the time of NDA submission. The presentation of this data can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will facilitate review.

2. Submit U.S. and primary non-U.S. drop-out data with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study. Your request for a waiver of the requirement for submission of CRFs for patients who did not complete a study because of an adverse event is granted, but these CRFs should be available for submission, if requested.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

Nomenclature

Concerns have been raised regarding the potential for medication errors related to similarities between the names Sabril (vigabatrin) and Gabitril (tiagabine). Please address this issue.

Biopharmaceutics

1. Please submit for our review the results of your ongoing phenytoin-vigabatrin interaction study in order that appropriate language regarding this potential interaction may be incorporated into drug product labeling.

2. We ask that the following final dissolution methodology and specification be adopted for Sabril® tablets:

Apparatus:	USP Apparatus II (paddle)
Agitation:	50 rpm
Medium:	**Water**, 900mL, 37± 0.5°C
Specification:	**NLT** — in 30 minutes

b(4)

Chemistry, Manufacturing, and Controls

The expiration dating period for Sabril tablets is extended to 36 months when packaged and stored as per the original NDA submission.

Phase IV Commitments

Because uncertainties remain about vigabatrin's capacity to cause neuronal injury, and because the mechanism of its link to visual field abnormalities and peripheral neuropathy is unclear, future investigations in these areas are warranted. Accordingly, we expect you to commit prior to the approval of vigabatrin to performing appropriately designed studies which will address these concerns. The Division will be happy to discuss the designs of these studies.

Pregnancy Registry

We recognize that you intend to collect information about the use vigabatrin in pregnant women. Please submit your plan to conduct such a registry.

Promotional Material

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Melina Malandrucco, R.Ph., Regulatory Management Officer, at (301) 594-5526.

Sincerely yours,

Robert Temple 11/26/97

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Original NDA 20-427
HFD-120/Div. Files
HFD-002/ORM
HFD-92/DDM-DIAB
HFD-120/M.Malandrucco/Ware
HFD-120/Leber/Katz/Sherry/Burkhart/Boehm/Fitzgerald/Rosloff/Guzewska
HFD-710/Chi/Sahlroot
HFD-860/~~Raweja~~/Tammarra/Chandra Sahajwallah
HFD-101/Office Director
DISTRICT OFFICE
HFD-40/DDMAC (with draft labeling)
HFD-560/OTC (with labeling - for OTC Drug Products Only)

Drafted by: JHW/MNMOctober 21, 1997/20427ae.ltr
Initialed by:
Final:

APPROVABLE (AE)

SABRIL® Tablets
(vigabatrin) 500 mg

DESCRIPTION

SABRIL (vigabatrin) is available as white, film–coated tablets for oral administration. Each tablet contains 500 mg vigabatrin. Tablets also contain as inactive ingredients: hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycols, povidone, sodium starch glycolate, and titanium dioxide. Vigabatrin is an oral antiepilepsy drug with the chemical name (±) 4–amino–5–hexenoic acid. It is a racemate consisting of two enantiomers. The molecular formula is $C_6H_{11}NO_2$ and the molecular weight is 129.16. It has the following chemical structure:

[Insert Structure Here.]

Vigabatrin is a white to off–white powder which is freely soluble in water, slightly soluble in methyl alcohol, very slightly soluble in ethyl alcohol and chloroform, and insoluble in toluene and hexane. The pH of a 1% aqueous solution is about 6.9. The n–octanol/water partition coefficient of vigabatrin is about 0.011 (log P=–1.96) at physiologic pH. Vigabatrin melts with decomposition in a 3–degree range within the temperature interval of 171°C to 176°C. The dissociation constants (pK_a) of vigabatrin are 4.02 and 9.74 at room temperature (25°C).

CLINICAL PHARMACOLOGY

Mechanism of Action

The precise mechanism of vigabatrin's anti-seizure effect is unknown, but it is believed to be the result of its action as a preferential and irreversible inhibitor of γ–aminobutyric acid transaminase (GABA–T), which is the enzyme responsible for the metabolism of the central nervous system (CNS) inhibitory neurotransmitter γ–aminobutyric acid (GABA). This action results in increased levels of GABA in the CNS.

No direct correlation between plasma concentration and efficacy has been established. The duration of drug effect is presumed to be dependent on the rate of enzyme resynthesis rather than on the plasma concentration of drug.

Pharmacokinectics: Following oral administration, vigabatrin is essentially completely absorbed from SABRIL 500 mg film-coated tablets. Food increases Cmax by about 33% and delays Tmax, but the extent of absorption is not affected. The half-life of vigabatrin is about 7 ½ hours.

Vigabatrin is widely distributed throughout the body; mean steady state volume of distribution is 1.1 L/Kg (CV = 20%). Vigabatrin does not bind to plasma proteins. CSF vigabatrin concentrations represent approximately 10% of the corresponding blood concentrations.

Following administration of ^{14}C-vigabatrin to healthy male volunteers, about 95% of total radioactivity was recovered in the urine over 72 hours with the parent drug representing most of this. Vigabatrin is thus excreted essentially unchanged in humans.

Following multiple dosing of vigabatrin 1.5 g bid to epileptic patients, peak plasma concentration occurred in one hour. There was little accumulation on multiple dosing. Vigabatrin displayed linear pharmacokinetics over a single dose range of 0.5 - 4 g, and a repeated dose range of 0.5 to 2.0 g bid, and in a treated population given a 4 -6 g daily dose. Oral administration of vigabatrin resulted in a linear increase in the suboccipital CSF concentration of vigabatrin at 1.5 to 4.5 g doses.

Special Populations

Age Effects: No specific pharmacokinetic study was conducted to investigate the effect of age. Population analysis of patient data indicated that the elderly cleared the drug 25% slower than the young (See Precautions Section).

Gender Effects: No gender differences were observed for the pharmacokinetic parameters of vigabatrin in patients.

Race Effects: No specific pharmacokinetic study was conducted to investigate race effects. A cross study comparison between 23 Caucasians and 7 Japanese subjects who were administered 1, 2, and 4 g of vigabatrin indicated that the AUC, Cmax, and half-life were similar for the two populations, but the mean renal clearance of Caucasians is about 25% higher than that of the Japanese.

Renal Impairment: Mean AUC increased by about 30%, 100%, and 450%, and terminal half-lives rose to 12 hours, 16 hours, and 28 hours in patients with mild (CL_{cr} > 50-70 mL/min), moderate (CL_{cr} > 30-50 mL/min), and severe (CL_{cr} > 10-30 mL/min) renal impairment, respectively.

Accumulation of vigabatrin can occur in patients with moderate or severe renal impairment. Patients with moderate and severe renal impairment should be started with a lower dose of vigabatrin and monitored closely for any side effects considered dose related (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

CLINICAL STUDIES

The effectiveness of SABRIL as adjunctive therapy was established in two multicenter placebo–controlled, double–blind, parallel–group clinical trials in 357 adults with refractory complex partial seizures, with or without generalization, or partial seizures that generalized. The patients (aged 18 to 60 years) had a history of at least six partial seizures per month in spite of receiving one or more antiepilepsy drugs dosed to therapeutic concentrations.

The primary measure of effectiveness was the change from baseline in the frequency ofthe seizures described above. Additional analyses were performed to assess the effect of vigabatrin on individual seizure types. Therapeutic success, a protocol-specified secondary outcome measure, was defined as ≥ 50% reduction in mean monthly combined seizure frequency.

One study (n=174) was a randomized, double–blind, placebo–controlled, dose–response trial consisting of an 8–week baseline period and an 18–week treatment period. After establishing baseline, the patients were randomized to receive placebo or 1, 3, or 6 g/day SABRIL administered as twice a day dose. During the first 6 weeks following randomization, the dose of study medication was titrated upward beginning with 1 g/day and increased by 0.5 g/day on days 1 and 5 of each subsequent week in the 3g/day and 6g/day groups untill the assigned dose was reached. Results are shown in Table 1. The 3g/day and 6g/day doses produced significant reductions in seizure rates. The 6g/day dose was not significantly superior to 3g/day dose.

[Note to Sponsor: In the tables that follow, please fill in the cells with numbers (N's, seizure medians, p-values, etc.), that correspond to the analyses reported in your 6/24 and 6/30 submissions; that is, the results of intent to treat analyses of all patients that incorporate revised (worst case) seizure rates only for patients with revised seizure counts.]

Table 1 **Seizure Frequency (Number/28 Days)**

Treatment	*n*	*Baseline Median*[a]	*End Study Median*	*Change in Median From Baseline to End Study*	*p value for Median Change from Baseline*	*Therapeutic Success Patients at End Study*[b]
Placebo	45	9	9	0		8%
1 g SABRIL®	39	7.5	7.5	0	0.079	26%
3 g SABRIL®	39	8	4.5	–3.5	0.0012	44%
6 g SABRIL®	38	8.3	4.3	–4.0	0.0001	53%

[a] seizure frequency expressed as number / 28 days (median)
[b] defined as achieving as least a 50% reduction from Baseline to Endstudy in the mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized.

In this study, the following results were seen for individual seizure types; most of the seizure reduction seen resulted from the effect on complex partial seizures.

Analysis of Efficacy Results by Seizure Class					
Seizure Class	Study 25				
	Placebo		Vigabatrin 3 g		
	Baseline[a]	Endstudy	Baseline	Endstudy	P-value
IA (partial seizures)	6.5	4.5	11.0	8.8	.7511
IB (complex partial seizures that do not generalize)	8.8	8.3	7.0	3.5	.0014
IC (partial seizures secondarily generalized)	2.0	1.3	1.5	0.5	.1828
IB+IC	9.0	8.8	8.0	3.7	.0001
Therapeutic Success[b] (IB+IC)	7%		51%		<.001

[a] seizure frequency expressed as number / 28 days (median)
[b] defined as achieving as least a 50% reduction from Baseline to Endstudy in the mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized.

The second study (n=183) was a randomized, double–blind, placebo–controlled, parallel trial consisting of an 8–week baseline period and a 16–week treatment period. During the first 4 weeks following randomization, the dose of study medication was titrated upward beginning with 1 g/day and increased by 0.5 g/day on a weekly basis to the maintenance dose of 3 g/day. SABRIL 3 g/day was superior to placebo in reducing the median seizure frequency. The percentage of patients achieving therapeutic success was greater for the SABRIL group compared to placebo.

Table 2 **Seizure Frequency (Number/28 Days)**

Treatment	*n*	*Baseline Median*[a]	*End Study Median*	*Change in Median From Baseline to End Study*	*p value for Median Change from Baseline*	*Therapeutic Success Patients at End Study*[b]
Placebo	90	9	7.5	-1.5		21.1%
3 g SABRIL®	92	8.3	5.5	-2.8	0.0143	39.1%

[a] seizure frequency expressed as number / 28 days (median)
[b] defined as achieving as least a 50% reduction from Baseline to Endstudy in the mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized

In this study, the following results were seen for individual seizure types:

Analysis of Efficacy Results by Seizure Class

Seizure Class	Study 24				
	Placebo		Vigabatrin 3 g		
	Baseline[a]	Endstudy	Baseline	Endstudy	P-value
IA (partial seizures)	*	*	*	*	*
IB (complex partial seizures that do not generalize)	8.0	7.0	8.5	5.0	0.0006
IC (partial seizures secondarily generalized)	1.5	1.5	4.0	2.5	0.3881
IB+IC[b]	9.0	7.5	8.3	5.5	0.0143
Therapeutic Success[b,c] (IB+IC)	21.1%		39.1%		.008

[a] seizure frequency expressed as number / 28 days (median)
[b] utilizes ITT with corrected seizure data
[c] defined as achieving as least a 50% reduction from Baseline to Endstudy in the mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized.
* not enough subjects to analyze

[Note to Sponsor: For these studies, please provide analyses of the effects of age, race, or gender on the realized drug treatment effect, and describe the results of these analyses at this point in the labeling text.]

INDICATIONS AND USAGE

SABRIL is indicated as adjunctive therapy in the treatment of complex partial seizures in adults with epilepsy. Because of its potential to cause intramyelinic vacuolization in mammalian species, SABRIL should not ordinarily be included among the AED treatments first chosen for combination use.

CONTRAINDICATIONS

SABRIL is contraindicated in patients with a known hypersensitivity to vigabatrin or any of the other components of the tablet.

WARNINGS

General

As occurs with other antiepilepsy drugs, abrupt discontinuation may lead to increased seizure frequency, including status epilepticus; therefore, discontinuation of SABRIL should occur by gradual dose reduction over a 2– to 4–week period if possible.

Potential Risk of Irreversible Neural Injury

[Note to Sponsor: The entire following section should be bolded.]

Vacuolization, characterized by a separation of the outer lamellar sheath of myelinated fibers, has been observed in brain white matter tracts in rats, mice, dogs, and possibly monkeys. The lesion, in appearance consistent with what has been called intramyelinic edema (IME) in other settings, was seen in rats given daily oral doses of 30 mg/kg and greater, and in mice and dogs given daily oral doses of 50 mg/kg and greater. Vacuoles were seen at the higher doses as early as 4 weeks and were seen at lower doses with longer duration of treatment. A no-effect dose was not established in these species. The doses at which vacuolization occurred are within the human therapeutic range. On a body surface area basis, these doses are equivalent to 1/10 to ½ of the maximum recommended daily human dose of 3 grams.

In both the rat and dog, vacuolization was not detectable after variable periods following discontinuation of vigabatrin treatment, but changes consisting of swollen or degenerated axons, mineralization, and gliosis have been seen in some of the areas in which vacuolization had been previously observed. The possibility that vigabatrin may

interfere with myelination in the developing brain has not been fully studied (see **PRECAUTIONS, Nursing Mothers** and **PRECAUTIONS, Pediatric Use**).

In the monkey, neither vacuolization nor other changes were seen after 6 years of treatment at 50 and 100 mg/kg/day. In monkeys receiving 300 mg/kg for 16 months, however, minimal vacuolization was noted with equivocal differences between treated and control animals.

In the dog, electrophysiological studies indicated that vacuolization was associated with increased latencies of the somatosensory–evoked potentials (SEP) and visual–evoked potentials (VEP); these changes were reversible when the drug was withdrawn. Vacuolization was also correlated with increased magnetic resonance imaging (MRI) signals in the dog.

Although there has been no clear finding of intramyelinic vacuolization in humans, whether this can occur is unknown, and it is difficult to rule out the possibility. First, it is not clear what clinical manifestations would be associated with intramyelinic vacuolization. Second, although there is a hope that MRI and EP would be able to detect the lesions before they are clinically manifest, there is no evidence in humans that they can do so. This limitation noted, the following sections describe available human data.

Of the 3320 patients exposed to vigabatrin during the development program, __ **[Note to Sponsor: Please state the total number of individual patients who have received at least 1 evaluable MRI or evoked potential test while on treatment with vigabatrin. Do not include in this number those patient who had an MRI or evoked potential, but whose test was not retrievable.]** were evaluated for the occurrence of intramyelinic vacuolation utilizing the techniques shown to be sensitive to this finding in animals. Of these __ patients, __ patients **[Note to Sponsor: Please state the total number of individual patients who meet the criteria described in this sentence.]** received at least 1 evaluation prior to initiation of treatment with vigabatrin and at least 1 evaluation while receiving vigabatrin.

MRI Findings: [Note to Sponsor: Please fill in the blanks contained within this paragraph with the appropriate numbers of patients as described in each sentence.] Of these patients, __ had on-treatment MRIs performed at least 12 months after the initiation of treatment, and __ had on-treatment MRIs done at least 3 years after beginning treatment. An additional __ patients had an evaluation prior to initiation of treatment and a subsequent evaluation after having been off vigabatrin treatment for periods ranging from __ to __ (time period, i.e., days or months). An additional __ patients had an MRI after initiation of treatment but no pre-treatment evaluation; __ of these patients had their MRI while still receiving treatment, while __ patients were evaluated after having discontinued treatment.

In the two controlled clinical trials, 0/181 vigabatrin treated patients and 0/112 placebo treated patients developed any unexplained MRI abnormalities at 4-5 months. In the uncontrolled experience, there were 3 cases which were consistent with intramyelinic vacuolization.

In 1 case, a 53 year old female treated with vigabatrin (2-4g/day) for approximately 6 weeks developed a well defined 1.2 cm non-enhancing are of T2 prolongation and low T1 signal in the splenium of the corpus callosum, a lesion consistent with intramyelinic vacuolization. The lesion was not present on an MRI obtained __ months prior to the administration of vigabatrin. An evaluation for demyelinating diseases, including multiple sclerosis, was negative. There was partial resolution of the lesion following discontinuation of vigabatrin. The relationship of these events to SABRIL cannot be determined.

Evoked Potential Findings: [Note to Sponsor: Please fill in the blanks contained within this paragraph with the appropriate numbers of patients as described in each sentence.] Of these patients, __ had on-treatment EPs performed at least 12 months after the initiation of treatment, and __ had on-treatment EPs done at least 3 years after beginning treatment. An additional __ patients had an evaluation prior to initiation of treatment and a subsequent evaluation after having been off vigabatrin treatment for periods ranging from __ to __ (time period, e.g., days or months). An additional __ patients had an EP after initiation of treatment but no pre-treatment evaluation; __ of these patients had their EP while still receiving treatment, while __ patients were evaluated after having discontinued treatment.

In the two controlled clinical trials, there were no significant changes in VEPs and SEPs seen in either vigabatrin treated or placebo treated patients **[Note to Sponsor: Please confirm and document that this statement is true for both VEPs and SEPs. Further please submit all EP tracings for patients in Study 024.]**. In uncontrolled experience, there were 10 patients who had VEP changes compared to baseline that were unexplained by other pathologies. Of these 10, 6 were being treated with vigabatrin at the time of the abnormality (duration of treatment ranged from __ to __), and 4 had been discontinued from treatment (length of time since last exposure ranged from __ to __). In these 10 patients, MRIs done at approximately the same time as the post-treatment VEPs did not demonstrate findings consistent with vacuolization.
In the uncontrolled experience, there were 11 patients who had SEP changes compared to baseline that were unexplained by other pathologies. Of these 11, 5 were being treated with vigabatrin at the time of the abnormality (duration of treatment ranged from __ to __), and 6 had been discontinued from treatment (length of time since last exposure ranged from __ to __). In these 11 patients, MRIs done at approximately the same time as the post-treatment SEPs did not demonstrate findings consistent with vacuolization.

Human Autopsy Findings: [Note to Sponsor: Please submit detailed information about cases of vacuolization or gliosis seen in human autopsy material. Specifically, we are interested in a more detailed description (i.e., extent and location of lesions) about the 4 cases of vacuolization and 3 cases of gliosis seen in vigabatrin treated patients described in your May 29, 1997 amendment, as well as in the 11 untreated patients with epilepsy described. In addition, we are interested in similar information about any additional cases of which you have become aware since submission of your amendment. You argue that vacuolization without gliosis is an artifact; please submit evidence to support this contention.]

Ophthalmologic Signs and Symptoms: [Note to Sponsor: Please provide a detailed accounting of all cases of visual field defects and retinal abnormalities, as well as all cases of optic neuritis and/or atrophy. Please describe the number of cases of these abnormalities seen in the database.] Whether or not these abnormalities are related to treatment, and if they are related to white matter vacuolization and/or other changes previously described (see WARNINGS: White Matter Neuropathology), is unknown.

Clinical studies in the development program were not designed to systematically identify ocular abnormalities; only 28/537 patients in the U.S. epilepsy trials had pre-treatment ophthalmologic exams. In one study, patients who were previously identified as having MRI and/or EP abnormalities, or visual and/or ocular complaints had confrontational visual field testing and indirect ophthalmoscopy. In this study, __ patients were found to have visual field defects and/or retinal abnormalities. **[Note to Sponsor: Please submit all additional data referable to these cases. Specifically, we are interested in formal visual field and/or retinal tests , follow-up data on these cases, etc...]**

During the routine prescription event monitoring (PEM) performed in the United Kingdom following vigabatrin approval, in cohort of 10,178 patients, there were 3 cases of bilateral, irreversible peripheral field defects. **[Note to Sponsor: Please describe these defects in more detail.]** In similar PEM studies of lamotrigine (11,316 patients) and gabapentin (3,100 patients), no similar cases were reported.

The value of baseline and periodic ophthalmologic examinations has not been systematically evaluated but should be considered.

Peripheral Neuropathy: [Note to Sponsor: There is a clear increase in the incidence of symptoms and signs consistent with peripheral neuropathy [e.g., paresthesia, stocking glove distribution, diminished vibratory sense and reflexes, etc.] with vigabatrin. Please develop a proposed case definition for peripheral neuropathy which should be discussed with us before additional work is done. Once we have agreed on a case definition, please submit comprehensive information about all cases in your database, including nerve conduction studies, if available. Please also provide incidence estimates from your controlled trials,

as well as from open and post-marketing experience. Examine the effects of dose, duration, and vigabatrin discontinuation on the symptoms and signs of peripheral neuropathy.]

Retinal Toxicity

Animal Finding: Disruption of the rod and cone layer of the retina was seen in albino rats (at 3 months) and mice at doses within the human therapeutic range. Reversibility was not examined. The lesion was not seen in dogs or monkeys.

Cognitive/Neuropsychiatric Adverse Events

[Note to the Sponsor: As requested in the FDA approvable letter, we anticipate a full revisitation of these events and an attempt to describe them in clinically meaningful terms. This reanalysis should cover all the relevant terms that now appear in various parts of the adverse events section. Additionally, please examine dose response for the events described in this section and draft appropriate statements, and analyze the time to onset of these events from start of treatment.] Adverse events most often associated with the use of SABRIL were central-nervous system related. The most significant of these can be classified into three general categories: 1) psychiatric symptoms including depression and psychosis, 2) psychomotor slowing, difficulty with concentration, and speech or language problems, in particular, word-finding difficulties, and 3) somnolence or fatigue.

In the studies with the most reliably recorded data, _/_ (_%) of patients discontinued vigabatrin and _/_ (__%) were hospitalized because of reported depression. **[Note to Sponsor: Please calculate these numbers for the combined U.S. and primary non-U.S. studies.]** In North American controlled trials, __ % of patients discontinued vigabatrin and/or were hospitalized and/or received medical treatment due to depression compared to __ % of placebo patients. In North American controlled trials 2/280 (1%) of vigabatrin patients attempted suicide compared to 0/188 of placebo patients.

In the studies with the most reliably recorded data, _/_ (_%) of patients discontinued vigabatrin and _/_ (__%) were hospitalized because of reported psychosis (hallucination, schizophrenic reaction, and/or paranoid reaction) **[Note to Sponsor: Please calculate these numbers for the combined U.S. and primary non-U.S. studies based on those cases conforming to your consultants definition of psychosis.]** In North American controlled trials, __ % of patients discontinued vigabatrin and/or were hospitalized and/or received medical treatment due to psychosis compared to __ % of placebo patients.

Reports of psychomotor slowing, speech and language problems, and difficulty with concentration and attention were common. Although in some cases these events were of mild to moderate severity, they at times led to withdrawal from treatment. **[Note to Sponsor: Please insert statements about dose response and time to onset here.]**

Somnolence and fatigue were the most frequently reported CNS adverse events during clinical trials with SABRIL. Although in some cases these events were of mild to moderate severity, they led to withdrawal from treatment in __ % of the patients enrolled in North American controlled trials. **[Note to Sponsor: Please calculate this proportion from studies 024, 025, and 021. Additionally, insert statements about dose response and time to onset here.]**.

Liver Failure

A total of seven cases of fulminant hepatic failure resulting in six deaths and one transplant have been reported in post-marketing experience from ____ to December 31, 1995. **[Note to Sponsor: Please insert the date range covered by this post-marketing experience.]** Based on an estimated exposure of ____ and an estimated rate of _____ in an untreated population, the estimated rate of fulminant hepatic failure appears to be up to 10 times that of the background rate, without considering under-reporting.

Assuming a 10% reporting rate gives a rate of 3 per 10,000 patient-years. In the development program, there was 1 case of hepatic failure in __ patient-years of vigabatrin use. **[Note to Sponsor: Derive a person-year estimate from the all U.S., primary non-U.S., and ongoing clinical studies that meet the criteria of the primary non-U.S. database.]**

For six of the seven cases, the onset of illness was approximately 270 or more days after initiation of vigabatrin. **[Note to Sponsor: Please describe, to the extent possible, the clinical characteristics of the illness including prodromal symptoms and laboratory findings.]** It is not known whether discontinuing vigabatrin at the first sign of laboratory and/or clinical abnormalities can prevent the occurrence of hepatic failure.

PRECAUTIONS

General

Drowsiness is commonly reported at the start of SABRIL treatment (see WARNINGS: Cognitive/Neuropsychiatric Adverse Events). Patients should be cautioned about this possibility at the start of treatment. Special care should be taken by patients if they drive, operate machinery, or perform any hazardous task.

Vigabatrin is eliminated via the kidneys, and therefore, caution should be exercised when administering SABRIL to patients with a creatinine clearance less than 60 mL/min. These patients should be monitored for adverse events such as drowsiness and confusion (see **DOSAGE AND ADMINISTRATION**).

Anemia

In North American controlled trials, __% of vigabatrin patients experienced an abnormally low hematocrit (females ≤ 32; males ≤ 37) compared to ___% of placebo patients. **[Note to Sponsor: Please describe here the course of these patients; e.g., __% of patients continued on treatment with resolution of the anemia, __% of patients continued on treatment with persistent anemia. Additionally, please submit a description, for our review, of all cases of serious anemia, by the usual definition, occurring in the entire development program. Included in this description should be all relevant information, including time to onset, other hematologic parameters (i.e., RBC indices, Reticulocyte count), other relevant laboratory tests (e.g., Coombs' test, ferritin, etc.), time course of the anemia. Please also provide this information for patients in whom the anemia resulted in treatment discontinuation. Please draft an appropriate description of the relevant findings in this section of labeling.]**

Sudden and Unexplained Deaths in Epilepsy Patients (SUDEP)

[Note to Sponsor: Please revise this section to reflect only the data for the US and non US primary database.] During the course of premarketing development of SABRIL, __sudden and unexplained deaths were recorded among a cohort of__ patients (one patient randomized to SABRIL in a US study never received medication and is not included in the total here) with epilepsy (__ patient–years of exposure). This represents an incidence of __ deaths per patient–year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving SABRIL (ranging from 5/10,000 for the general population of epileptics, to 4/1,000 for recently studied clinical trial populations similar to the population in the clinical development program for SABRIL, to 5/1,000 for patients with refractory epilepsy). The estimated SUDEP rate in patients receiving SABRIL was similar to that observed in patients receiving other antiepilepsy drugs who underwent clinical testing in a similar population at about the same time.

Status Epilepticus

In placebo–controlled studies, the incidence of status epilepticus in epilepsy patients receiving SABRIL was 1.5% (6/406) vs 1.3% in patients receiving placebo (4/311). Across all controlled and uncontrolled epilepsy studies, the overall incidence of status epilepticus in patients receiving SABRIL was 2.6% (51/1942).

[Note to Sponsor: Please include a statement about the risk of absence seizures and absence status and vigabatrin. Please also provide the references in support of such statement.]

SABRIL® Tablets
(vigabatrin) 500 mg

Information for Patients

Patients should be cautioned that SABRIL may cause drowsiness. Special care should be taken by patients if they drive, operate machinery, or perform any hazardous task. Patients should be advised to notify their physician immediately if they develop any worsening of seizures.

Patients should be questioned about pregnancy or lactation before starting SABRIL therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to the fetus.

Patients or their families should be advised to notify the treating physician immediately if they experience any mental or behavioral changes.

Laboratory Tests: Vigabatrin decreases alanine transaminase (ALT) and, to a lesser extent, aspartate transaminase (AST) plasma activity. The magnitude of suppressions for ALT has been reported to vary between 30% and 100% **[Note to Sponsor: Please submit data from the controlled trials examining the extent of LFT decreases. Specifically, please examine the proportion of patients who had LFT decreases in the following ranges; 80%-100%, 60%-80%, etc.. Also please examine the range of time to onset of the first abnormality and the relation to dose]**. Treatment with vigabatrin may be associated with decreases in hematocrit (see **PRECAUTIONS**).

Drug Interactions

Formal interaction studies with vigabatrin and commonly used anti-epilepsy drugs have not been performed Based on population pharmacokinetics, carbamazepine, clorazepate, phenobarbital, phenytoin, primidone, and sodium valproate appear to have had no effect on plasma concentrations of vigabatrin.

SABRIL had no effect on plasma concentrations of carbamazepine, clorazepate, and primidone during controlled clinical trials. During concurrent SABRIL treatment, phenobarbital plasma concentrations were reduced by an average of 8% to 16%, and sodium valproate plasma concentrations were reduced by an average of less than 10% in some multicenter trials but not in others. These reductions did not appear to be clinically relevant.

Phenytoin: A 16% to 33% average reduction in total phenytoin plasma levels has been reported in controlled clinical trials. In a pharmacokinetic study, levels returned to baseline in 7 weeks. The exact nature of this interaction with SABRIL is not understood; in these studies the interaction did not appear to be clinically relevant. Therefore, during concurrent therapy with SABRIL, phenytoin dose adjustment should be considered only in those cases in which both plasma levels of phenytoin decrease and seizures worsen.

SABRIL® Tablets
(vigabatrin) 500 mg

Clonazepam: Clonazepam (0.5 mg) co-administration has no influence on the pharmacokinetics of vigabatrin (1.5 g bid). Vigabatrin increased the mean Cmax of clonazepam by about 30 % and decrease the mean Tmax by 45 %.

Alcohol: Co-administration of ethanol (0.6 g/kg) with vigabatrin (1.5 g bid) indicated that neither drug influences the pharmacokinetics of the other.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Vigabatrin showed no carcinogenic potential when given in the diet to the CD_1 mouse at doses up to 150 mg/kg/day for 18 months or to the Long–Evans rat at doses up to 150 mg/kg/day for 2 years (approximately 1/4 and ½ of the maximum recommended human daily dose of 3 grams on a mg/m^2 basis, respectively).

Vigabatrin was not mutagenic in the *in vitro* Ames assay in Salmonella or the CHO/HGPRT mammalian cell forward gene mutation assay. It was not clastogenic in the *in vitro* chromosomal aberration assay in rat lymphocytes or the *in vivo* mouse bone marrow micronucleus assay.

Reproduction and fertility studies using doses up to 150 mg/kg/day, which corresponds to approximately ½ of the maximum recommended human daily dose on a mg/m^2 basis, have shown no effect on male or female fertility in rats.

Pregnancy

Pregnancy Category C: Administration of vigabatrin to pregnant mice and rabbits was associated with embryolethality and teratogenic effects. When rabbits were dosed orally during the period of organogenesis at 150 and 200 mg/kg/day (approximately equal to or slightly greater than the maximum human daily dose of 3 grams on a mg/m^2 basis) the fetal incidence of cleft palate was 2% and 9%, respectively, and the litter incidence was 12% and 24%, respectively. Cleft palate did not occur in the control group. At 200 mg/kg/day vigabatrin was associated with an increase in resorptions. These doses were maternally toxic as evidenced by decreased food consumption and transient body weight loss. A no-effect dose for these effects was 100 mg/kg/day (2/3 of the human daily dose of 3 grams on a mg/m^2 basis). When mice were dosed by the intraperitoneal route at 300 or 450 mg/kg on a single day during the period of organogenesis (days 7,8,9,10,11 or 12), cranio-facial and skeletal malformations occurred at both doses and exomphalos occurred at 450 mg/kg. There were also increased resorptions and decreased fetal body weights. A no-effect dose for these effects was not determined (Abdulrazzaq Y.M., et al., *Teratology* 55: 165-176 [1997]). Vigabatrin was not teratogenic in rats dosed during the period of organogenesis at oral doses up to 150 mg/kg/day (½ of the human daily dose of 3 grams on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women, and SABRIL should be used during pregnancy only when the potential benefit justifies the potential risk to the fetus.

Pregnancy Exposure Registry: To monitor fetal outcome of pregnant women exposed to SABRIL, Hoechst Marion Roussel supports the Antiepilepsy Drug Pregnancy Registry. Physicians are encouraged to register patients **before fetal outcome (e.g., ultrasound, results of amniocentesis, birth, etc.) is known,** by calling toll–free 1–888–233–2334.

Nursing Mothers

Vigabatrin is excreted in breast milk in low concentrations. Therefore, a decision should be made on whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Because SABRIL causes vacuolization in myelin in rats, mice, and dogs, nursing mothers should be advised that the possibility that it will interfere with myelination in the developing nervous system should be considered.

Pediatric Use

The safety and effectiveness of SABRIL have not been established in the pediatric population.

Because SABRIL causes vacuolization in myelin in rats, mice, and dogs, the possibility of interference with myelination in the developing nervous system should be considered.

Use in Elderly
[Note to Sponsor: Please develop this section of labeling as described in the final rule for the addition of a "geriatric use" subsection. This final rule was recently published in the Federal Register #45313, on August 27, 1997.]

SABRIL tablets should be used with caution in elderly patients due to a decrease in the clearance of vigabatrin.

Use in Renally Impaired Patients

SABRIL tablets should be used with caution in moderately (Cl_{cr} >30-50 mL/min) and severely (Cl_{cr} > 10-30 mL/min) renally impaired patients due to a decrease in the clearance of vigabatrin. These renally impaired patients should be started with a lower dose of vigabatrin and they should be monitored for any side effects (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

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ADVERSE REACTIONS

The most commonly observed adverse events in placebo-controlled epilepsy studies associated with the use of SABRIL in combination with other AEDs, not seen at an equivalent frequency among placebo–treated patients, were nystagmus, amnesia, confusion, paresthesia, depression, weight increase, and peripheral edema.

Approximately 12.9% of the 1942 individuals who received SABRIL in controlled and uncontrolled epilepsy clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with discontinuation were drowsiness (1.5%) and depression (1.4%) **[Note to Sponsor: Please expand this list in decreasing order of frequency of individual events associated with discontinuation, and provide placebo values. The frequency of each event should be included. Please also include a statement about which events are dose related. Make cut at the 1%.].**

In Studies 024 and 025 (U.S. studies), the double-blind, placebo-controlled, parallel-group, add-on studies, the proportion of patients that discontinued treatment because of adverse events was __% for the group treated with SABRIL and __% for the placebo group. The most common adverse events considered the primary reason for discontinuation were [Note to Sponsor: Please create a list in decreasing order of frequency of individual events associated with discontinuation.].

Adverse Event Incidence in Controlled Clinical Trials
Table __ lists treatment-emergent signs and symptoms that occurred in at least 2% of patients treated with SABRIL in placebo-controlled, add-on epilepsy trials and that were numerically more common in the SABRIL group. In these studies, either SABRIL or placebo was added to the patient's current AED therapy.

The prescriber should be aware that these figures, obtained when SABRIL was added to concurrent AED therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis by which to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

[Note to Sponsor: Please switch the order of the placebo and SABRIL columns in the following Table, and within systems, list events in order of decreasing frequency based on SABRIL. Also, please note that comments regarding certain terms are contained within the table and listings, and are located in brackets after the specific term. A response to these comments is necessary.]

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Table __ Treatment-Emergent Adverse Event[1] Incidence in Placebo-Controlled, Add-On Trials (events in at least 2% of patients treated with SABRIL and numerically more frequent than in the placebo group)

Body System/Event	*Placebo (n=311) %*	SABRIL (n=406) %
Neurologic		
Headache	26	28
Drowsiness	15	26
Dizziness	14	19
Nystagmus	5	12
Tremor	8	11
Amnesia	4	9
Ataxia	5	8
Confusion	3	7
Paresthesia	2	6
Coordination Abnormal	3	5
Gait Abnormal	4	5
Concentration Impaired	2	5
Speech Disorder [not clinically meaningful]	1	4
Vertigo	2	4
Hypoesthesia	2	3
Hyporeflexia	0	3
Hyperreflexia	1	2
Tinnitus	1	2
Convulsions Grand Mal	1	2
Twitching	0	2
Psychiatric		
Depression/psychotic depression	4	12
Agitation	8	11
Anxiety	4	7
Emotional Lability	3	5
Thinking Abnormal [not clinically meaningful]	2	4
Aggressive Reaction	2	3
Personality Disorder	1	2
Gastrointestinal System		
Nausea	8	9
Diarrhea	6	7
Abdominal Pain	4	6
Constipation	4	6
Vomiting	5	6
Tooth Disorder [define further]	2	3

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Body as a Whole		
Fatigue	16	26
Fever	3	4
Malaise	1	2
Generalized Edema (including edema) [evaluate & combine with peripheral edema]	1	2
Face Edema	0	2
Respiratory System		
Throat Irritation	6	7
Upper Respiratory Tract Infection	3	5
Dyspnea	0	2
Infectious Disease		
Infection Viral	12	14
Infection Fungal	1	2
Dermatologic		
Pruritus	0	2
Sweating Increased	1	2
Musculoskeletal System		
Arthralgia	4	7
Back Pain	4	6
Arthrosis	2	3
Metabolic & Nutritional		
Weight Increase	4	8
Reproductive, Female		
Dysmenorrhea	1	4
Menstrual Disorder [vague]	1	2
Urinary System		
Urinary Tract Infection	0	3
Cardiovascular		
Peripheral Edema (including dependent and leg) [evaluate & combine with generalized edema]	1	6
Ophthalmologic		
Vision Abnormal [vague]	6	10
Diplopia	6	8
Eye Pain	1	3
Eye Abnormality [vague]	1	2
Hematologic		
Anemia/hypochromic anemia	1	2
Ear, Nose & Throat		
Earache	1	2

[1]Patients in these epilepsy studies were receiving concomitant therapy with other AEDs in addition to SABRIL or placebo. Patients may have experienced multiple adverse events during the study; therefore, patients may be included in more than one category.

Adverse events reported in 1 - <2% and numerically more frequent than in the placebo group were: hearing impaired, myopathy, neuropathy, dreaming abnormal, nightmare, paranoid reaction, euphoria, suicide attempt [vague], hemorrhoids, vaginitis, rigors, urination disorder [vague], urinary retention, lymphadenopathy, and allergy.

Other adverse events reported in ≥1% of patients but equally or more frequent in the placebo group included convulsions (including condition aggravated), aphasia, hypokinesia, hypertonia, insomnia, depersonalization, apathy, dyspepsia, anorexia, abdominal distention, pain, trauma injury, hot flushes, congestion, coughing, rhinorrhea, bronchitis, epistaxis, rhinitis, influenza–like symptoms, infection, herpes simplex, rash, acne, alopecia, eczema, erythema, urticaria, furunculosis, weight decrease, phosphatase alkaline increased, urinary frequency, urinary incontinence, GGT increased, leukopenia, conjunctivitis.

[Note to Sponsor: Please examine dose-response in the safety database. In particular, examine the relationship between dose and discontinuations, serious adverse events, and commonly occurring events. Please describe the results of these analyses at this point in the labeling text. Use a table to display results that show dose response.]

[Note to Sponsor: Current FDA regulations require that you analyze clinical studies to determine whether or not, and if so to what extent, age, race, and/or gender affected the incidence of these events. Please describe the results of these analyses at this point in the labeling text. Reanalyze dysmenorrhea and other menstrual disorders to only include females in the denominator; see FDA approvable letter.]

Other Adverse Events Observed During All Epilepsy Clinical Trials

SABRIL has been administered to 1942 individuals during all phase 2/3 clinical trials, only some of which were placebo controlled. During these studies, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHO dictionary terminology. These categories are used in the listing below. The frequencies presented represent the proportion of the 1942 individuals exposed to SABRIL who experienced an event of the type cited while receiving SABRIL. All reported events are included except those already listed in the previous table, events seen only three times or fewer (unless potentially important), events very

unlikely to be drug-related, and those too general to be informative. Events are included without regard to determination of a causal relationship to vigabatrin.

Events are classified within system organ class categories and enumerated in order of decreasing frequency using the following definitions: *Infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *Rare* events are those occurring in fewer than 1/1000 patients.

Neurologic: *Infrequent:* dyskinesia, EEG abnormal, muscle weakness, sleep disorder, stupor, migraine headache, dysphonia, dystonia, hypotonia, labyrinthine disorder, mental deficiency, upper motor neuron lesion (positive Babinski), dementia, hemiparesis, taste perversion, dryness of mucous membranes, ptosis, cerebellar syndrome, choreoathetosis, delirium, extrapyramidal disorder, paralysis, psychomotor hyperactivity. *Rare:* ataxia vestibular, cerebral infarction, cerebrovascular accident, coma, convulsions petit mal, deafness nerve, encephalopathy, hyperesthesia, opisthotonos, paraplegia, paresis, parosmia, taste loss.

Psychiatric: *Infrequent:* hallucination, libido decreased, crying abnormal, bulimia, delusion, hysteria, lalorrhea, teeth–grinding. *Rare:* cyclothymic reaction, libido increased, schizophrenic reaction.

Gastrointestinal: *Infrequent:* saliva increased, dry mouth, gingivitis, gastroenteritis, stomatitis aphthous, gingival hyperplasia, colitis, gastritis, melena, stomatitis, glossitis, hiccup, stomatitis ulcerative, gastrointestinal hemorrhage, hemorrhage rectum, eructation, gastric ulcer, gingival bleeding. *Rare:* cheilitis, duodenal ulcer, dysphagia, enteritis, esophagitis, fecal incontinence, gastroesophageal reflux, hemorrhoids thrombosed, salivary gland enlargement, tongue edema.

Body as a Whole: *Infrequent:* edema periorbital, pallor, chest pain substernal, abscess, ESR increased, halitosis. *Rare:* perineal pain male.

Respiratory System: *Infrequent:* pneumonia, bronchospasm, apnea, hyperventilation, pulmonary edema, wheezing. *Rare:* hemoptysis, laryngitis, nasal polyp, pleural effusion, pleural fibrosis.

Dermatologic: *Infrequent:* dermatitis, photosensitivity reaction, dry skin, hypertrichosis, rash maculopapular, pruritus genital, hair texture abnormal, seborrhea, chloasma, hair discoloration, psoriasis, skin discoloration, skin hypertrophy, skin ulceration. *Rare:* angioedema, bullous eruption, dermatitis exfoliative, vitiligo.

Musculoskeletal System: *Infrequent:* tendonitis, arthritis. *Rare:* arthritis rheumatoid aggravated, Dupuytren's contracture, hernia, osteoporosis, temporomandibular joint dislocation.

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Metabolic and Nutritional: *Infrequent:* thirst, hyponatremia, amylase increased, hypocalcemia, hypokalemia. *Rare:* acidosis, calcinosis, gout, gamma–globulins increased, hypercholesterolemia, hyperlipemia, hypoglycemia, ketosis.

Urinary System: *Infrequent:* dysuria, cystitis, hematuria, pyelonephritis. *Rare:* albuminuria, nocturia, pyuria, renal calculus.

Cardiovascular: *Infrequent:* hypertension, hypotension, tachycardia, bradycardia, syncope, arrhythmia atrial, AV block, extrasystoles, fibrillation atrial, hypotension orthostatic. *Rare:* arrhythmia nodal, cardiomyopathy, mitral insufficiency, pericardial effusion.

Ophthalmologic: *Infrequent:* cataract, dry eyes, photophobia, retinal pigmentation, visual field defect, corneal deposits, lacrimation abnormal, accommodation abnormal, strabismus, blepharitis, blepharospasm, myopia, photopsia, corneal ulceration, scotoma, vitreous detachment. *Rare:* anisocoria, hemianopia, hemorrhage anterior chamber eye, mydriasis, optic atrophy, optic neuritis, pupillary reflex impaired.

Reproductive, Female: *Infrequent:* menorrhagia, breast pain female, vaginal hemorrhage, leukorrhea, pelvic inflammation, premenstrual symptoms. *Rare:* breast enlargement, cervical uterine polyp, endometriosis, endometritis.

Hematologic: *Infrequent:* granulocytopenia, thrombocytopenia, lymphoma–like disorder, macrocytosis, granulocytosis, leukocytosis. *Rare:* anemia pernicious, bleeding time increased, eosinophilia, hemolysis, lymphadenopathy cervical, lymphocytosis, monocytosis, prothrombin decreased, thrombocytosis.

Ear, Nose and Throat: *Infrequent:* otitis media, otitis externa.

Vascular (extracardiac): *Infrequent:* flushing, peripheral ischemia, vein varicose. *Rare:* aneurysm, hemangioma acquired, thrombophlebitis arm.

Endocrine: *Infrequent:* goiter, hypothyroidism. *Rare:* gynecomastia, inappropriate ADH secretion syndrome, lipidosis.

Reproductive, Male: *Infrequent:* impotence, prostatic disorder, epididymitis. *Rare:* priapism.

Immunologic: *Infrequent:* allergic reaction. *Rare:* lupus erythematosus syndrome, polymyalgia rheumatica, vasculitis.

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Postmarketing Surveillance

In addition to the adverse experiences reported during clinical testing of SABRIL, the following adverse events have been reported in patients receiving SABRIL in an estimated 125,000 patients during worldwide use. Data are insufficient to establish a causal association.

Hypomania and mania have been rarely reported.

Rare instances of marked sedation, stupor, and confusion associated with nonspecific slow wave activity on electroencephalogram have been described soon after the introduction of SABRIL therapy. These events have been reversible following dose reduction or discontinuation of SABRIL.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of SABRIL has not been evaluated in human studies.

OVERDOSAGE

Confirmed and/or suspected SABRIL overdoses have been reported during clinical trials and postmarketing surveillance; many of the cases involved possible suicide attempts. None of the SABRIL overdoses resulted in death. When reported, the SABRIL dose ingested ranged from 3 g to 90 g, but most were between 7.5 and 30 g. Nearly half of the cases involved multiple drug ingestions including carbamazepine, barbiturates, benzodiazepines, lamotrigine, valproic acid, acetaminophen, and/or chlorpheniramine.

Coma, unconsciousness, and/or drowsiness were described in the majority of cases of SABRIL overdose. Other less commonly reported symptoms included vertigo, psychosis, apnea or respiratory depression, bradycardia, agitation, irritability, confusion, and increased seizure activity or status epilepticus. These symptoms resolved with supportive care.

There is no specific antidote for SABRIL overdose. Supportive measures should be employed and standard measures to remove unabsorbed drug should be considered. In an in vitro study, activated charcoal did not significantly adsorb vigabatrin. The effectiveness of hemodialysis in the treatment of SABRIL overdose is unknown. In isolated case reports in renal failure patients receiving therapeutic doses of SABRIL, hemodialysis reduced vigabatrin plasma concentrations by 40% to 60%.

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DOSAGE AND ADMINISTRATION

SABRIL is intended for oral administration twice daily and is given orally with or without food.

The effective dose of SABRIL in adults is 3 g/day given in two divided doses using 500 mg tablets. The starting dose is 1 g given in two divided doses with titration in 500 mg increments at weekly intervals depending on response. Most patients will need 3 g/day for an optimal response and tolerance. Larger doses, up to 6 g/day, are associated with an increased incidence of side effects, and there is no evidence that such doses provide additional benefit.

Patients With Renal Function Impairment

SABRIL is eliminated via the kidney, and therefore, caution should be exercised when administering the drug to patients with decreased creatinine clearance. In moderately renally impaired patients (Cl_{cv} >30-50 mL/min), vigabatrin should be started with a lower dose. As clearance is known to decrease by two-fold in these patients, it is recommended that the starting dose be 500 mg qd and that the maintenance dose be 750 mg bid. In severely renally impaired patients (Cl_{cr} > 10-30 mL/min), vigabatrin should also be started with a lower dose. As clearance is known to decrease by 4.5-fold in these patients, it is recommended that the starting dose be 250 mg qd and maintenance be 750 mg qd.

General Dosing Considerations

It is not necessary to monitor SABRIL plasma concentrations to optimize therapy. If a decision is made to discontinue SABRIL, the dose should be gradually reduced over a 2– to 4–week period.

HOW SUPPLIED

SABRIL film–coated tablets containing 500 mg vigabatrin are supplied as follows:

- NDC 0088–0900–47: Bottles of 100 tablets
- NDC 0088–0900–55: Bottles of 500 tablets
- NDC 0088–0900–49: 100–ct UDIP®

Tablets are white, film–coated, oval, biconvex, scored, and debossed "SABRIL" on one side .

Store at Controlled Room Temperature, 20°C to 25°C (68°F to 77°F) and protect from light .

SABRIL® Tablets
(vigabatrin) 500 mg

Prescribing Information as of April 1997.

Hoechst Marion Roussel, Inc.
Kansas City, MO 64137 USA

MEMORANDUM

DATE: November 9, 1997

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

TO: FIle, NDA 20-427

SUBJECT: Supervisory Review of Response to Not Approvable LEtter for NDA 20-427, for the Use of Vigabatrin as Adjunctive Therapy in Patients with Epilepsy

BACKGROUND

NDA 20-427, for the use of vigabatrin, an irreversible GABA-transaminase inhibitor, in patients with refractory seizures, was submitted by Marion Merrell Dow, Inc., on 4/29/94. The application contained the results of two adequate and well controlled clinical trials as well as experience in several thousand patients.

Unfortunately, the data were inadequately presented in the application, and a Not Approvable letter was sent to the firm on 4/28/95. The letter outlined 2 general areas of deficiencies: 1) there was inadequate collection of safety information deemed critical to an adequate assessment of the safety profile of the drug, and 2) there was inadequate reporting and analysis of critical safety and effectiveness data.

In particular, the initial application contained safety experience from 3 distinct cohorts of patients: 1) a domestic cohort of 537 patients, 2) foreign patients who had data collected on CRFs or other presumably equivalent documents (N=1233), and 3) a cohort for which their data was entered into the database from secondary sources (N=1550). The Agency had determined that the first (domestic) cohort provided reliable, prospectively recorded safety data. At the same time, we concluded that data from the third cohort could not be relied upon to assess the safety of the drug, because it represented data that had not been gathered prospectively, was incompletely recorded, and could not provide

information on the ultimate outcome of many patients. It was on the second (CRF) database that the Agency focused its attention. In the Not Approvable letter, we asked the sponsor to gain access to the CRFs (at the time of our initial review they claimed that they did not have access for many of these, and our initial review of the CRFs that we did have for other studies suggested that the sponsor not infrequently made errors in transcribing data from CRFs into the database), as well as to provide information about the reasons for discontinuations in this cohort, as well as detailed information about incidence and causes of hospitalizations.

Further, the submission was deficient in the reporting of safety data, including inadequately reporting findings that our independent review discovered on CRFs (for the domestic cohort), as well as lacking coherent reports about specific safety concerns (e.g., no discussion of serious adverse events).

Regarding effectiveness, we had concluded that one of the two trials presented supported effectiveness (Study 25), but the second study (Study 24) was inadequately analyzed and reported for us to make an independent assessment.

Specifically, the review team had identified numerous deficiencies in the sponsor's analysis of Study 25, including misclassification of patients with important protocol violations (e.g., took additional concomitant AEDs, misclassification of numbers of seizures experienced, lack of inclusion of seizures during hospitalizations). Extensive efforts by our review team permitted the identification of these flaws in Study 25, and permitted us to re-analyze it appropriately. In the Not Approvable letter, we asked the sponsor to undertake a similar audit of Study 24, and to re-analyze it utilizing the amended data.

In addition, the Not Approvable letter contained several biopharmaceutic and Environmental Assessment comments.

On May 29, 1997, the sponsor responded to the Not Approvable letter; many subsequent amendments were submitted.

These submissions have been reviewed by Dr. Jim Sherry, medical officer

in the division (review dated 11/5/97), Drs. Burkhart and Boehm of the division's Safety Unit (reviews dated 11/7/97, and 10/28/97, respectively), Dr. Todd Sahlroot of the Division of Biometrics (review dated 10/31/97), Dr. Vijay Tammara of the Division of Pharamaceutical Evaluation I (review dated 9/11/97), and Dr. Guzewska, chemist, (reviews dated 12/14/95, and two reviews dated 10/24/97). The environmental assessment was performed by Dr. Berninger and Ms. Sager (two reviews dated 8/7/97).

In this memo, I will summarize the pertinent safety and effectiveness findings, and explicate the basis for my recommendations.

EFFECTIVENESS

The sponsor has proposed that the drug be approved "... as adjunctive therapy in the treatment of partial seizures in adults with epilepsy.".

As noted above, the Agency has previously determined that Study 25, a study comparing the effects of vigabatrin 1, 3, and 6 grams/day to placebo, was considered "positive", but that Study 24 could not at that time be considered so, until it was re-analyzed as requested. In the original NDA, the sponsor proposed that the drug be indicated for the treatment of partial seizures, with and without generalization.

It is critical to note that the protocols prospectively designated the primary outcome to be the effect of the drug on the combination of complex partial seizures (IB) and partial seizures that generalize (IC).

In the Not Approvable letter, though, the Agency noted that the evidence submitted did not permit us to conclude that vigabatrin was effective as a treatment for complex partial seizures that became generalized, (one of the types of seizures that wold have been included in a global claim for partial seizures) because the sponsor had submitted data on all partial seizures combined , but not for the individual types of partial seizures (simple and complex partial). As noted, the current proposal asks only for an effect on partial seizures (the language regarding generalization has been dropped by the sponsor). In addition, the Agency stated that the evidence does not support the conclusion that a daily dose of 6 gms

provides any additional seizure control beyond that afforded by a daily dose of 3 grams.

As both Drs. Sherry and Sahlroot note, the sponsor has audited their data and identified numerous patients whose data had to be amended. Specifically, a total of 54 patients had data that fell into 1 of 4 categories of misclassification as described either by the Agency or as constructed by the sponsor (inappropriate medical treatment for seizures, inaccurate seizure counts, a change in the dose of a concomitant AED, and reaching a protocol specified definition of increased seizure activity). Dr. Sherry has independently determined that 54 patients had data that fell into one of these categories, but he disagrees with the sponsor about into which specific categories a few of these patients' data fall.

According to Dr. Sahlroot, the sponsor's initial response to the NA letter was inadequate, because it excluded a significant amount of information inappropriately. Specifically, once the sponsor "accurately" identified patients who met the protocol violations described above, they excluded data from these patients from the point of the violation forward. Ultimately, based on conversations with Agency reviewers, intent to treat analyses were performed including all data and which used the revised seizure count data in a worst case approach. The following results were obtained:

	Median Baseline Frequency (IB + IC)	Median Frequency on Rx (IB + IC)
Placebo (N=90)	9.0	7.5
Vigabatrin (N=92)	8.3	5.5

The comparison yielded a p=value of 0.0143.

The previous analyses performed by the sponsor (in which data was excluded, as previously described) all yielded significant p-values.

While the overall results were strongly positive, it is of great interest to

examine the effects of treatment on individual seizure types (as discussed, to some extent, in the Not Approvable letter).

This is of critical importance because of the nature of the seizure types designated as primary in the protocol. Specifically, the types included in the primary definition include complex partial seizures that do not generalize (IB) and all partial seizures that generalize (simple partial seizures that generalize, and complex partial seizures that generalize-IC). This combination of seizure types does not lend itself to a meaningful or easily understood Indication section in labeling. It would be helpful, for example if we could conclude something about the effect of the treatment on **all** partial seizures (which the current definition does not include, because simple partial seizures that do not generalize are not included), or alternatively, conclude something about the treatment's effect on all simple partial seizures (which, again, are not all included), or on all complex partial seizures (which are all included, but the data for which are not analyzed separately).

While not all simple partial seizures are included in the primary data analysis, it would be reasonable, in my view, to permit an extrapolation from an effect of the drug on simple (or complex) partial seizures that generalize to an effect on simple (or complex) partial seizures that do not generalize (or vise versa); this is because we are not speaking here about an effect on generalization-a secondary event which is considered to reflect a complex series of neurologic events that differ markedly from the events leading to the initiation of a primary seizure-but an effect on the primary event-the simple (or complex) partial seizure. It is reasonable, in my view, to consider that the primary event is essentially the same, whether it goes on to generalize or not. I believe that this is especially reasonable considering that the drug effect we measure in these trials is the decrease in frequency, or **prevention of onset** of a primary seizure type. For this reason, were an effect shown, for example, on the frequency of simple partial seizures that generalize, I would feel comfortable extrapolating that effect to simple partial seizures that do not generalize, and, hence, to all simple partial seizures.

With these considerations in mind, the following results for individual seizure types of interest have been obtained (based on Dr. Sherry's Table

3, page 11 of his review):

Study 24

Seizure Type	Placebo Baseline	Placebo Endpoint	Vigabatrin (3 gm) Baseline	Vigabatrin (3 gm) Endpoint	P-value
IA	NA	NA	NA	NA	
IB	8.0	7.5	8.5	5.0	0.0006
IC	1.5	1.5	4.0	2.5	0.3881

NA-not enough patients to analyze

Study 25

IA	6.0	4.0	11.0	8.8	0.7511
IB	6.8	8.3	7.0	3.5	0.0014
IC	2.0	1.3	1.5	0.5	0.1828

As can be seen, although the studies were not designed or powered to examine the effects on individual seizure types, there clearly seems to be a differential effect on complex partial seizures that do not generalize (IB) compared to that seen on other seizure types. It is not unreasonable to conclude that the effect seen on the combined seizure types is largely the result of the effect on complex partial seizures. The data do permit serious questions to be raised about the effectiveness of the treatment on simple partial seizures (that do or do not generalize) because 1) any outcome in which these seizures are included (IA and IC) is negative, and 2) in the one study in which there were reasonable numbers of IA seizures (Study 25), there was no demonstrable effect.

While we have little affirmative evidence of vigabatrin's effect on complex partial seizures that generalize (these are a subset of IC seizures that have not been analyzed separately, but the numbers of IC seizures in general were sufficiently small that an analysis that looks at these seizures separately will likely be uninformative). Nonetheless, (reasoning

as I did earlier about extrapolating results from primary events that do not generalize to those that do), it seems reasonable to conclude that vigabatrin has been shown to be effective as adjunctive treatment for adults with complex partial seizures. For the record, I note that the data presented above were taken from the sponsor's analyses, which, as noted earlier, inappropriately excluded a significant amount of data. I recommend that the sponsor be asked to re-analyze the data appropriately, according to the rules applied by Dr. Sahlroot.

SAFETY

Dr. Boehm has conducted a detailed review of the safety data, and Dr. Sherry has provided a review of the neurologic findings, as they relate to any potential concomitant of the intramyelinic vacuolization seen in multiple animal species. In addition, he has reviewed the data that speak to the possible occurrence of a peripheral neuropathy. Dr. Burkhart has written a supervisory memo that summarizes the important safety findings.

Briefly, the sponsor has divided the non US data into several cohorts, depending upon whether or not data from studies were entered into the database from CRFs. Studies in which all patients had data prospectively collected on CRFs were considered to constitute the primary non-US database, and much of the safety review focused on this cohort. The total number of patients included in the US plus non-US primary database was 1726, and there were 3320 patients in the entire database.

The primary adverse events of interest (as well as the primary reasons for discontinuation) were related to the CNS , including dizziness, depression, fatigue, amnesia, paranoid reaction, thinking abnormal, agitation, confusion, psychosis, etc. A number of these terms, as in other NDAs for AEDs, were poorly defined.

Additional findings of interest (noted either in controlled trials, uncontrolled experience in the development program, or from post-marketing reports) included clinical findings consistent with peripheral neuropathy, hepatic failure, and ophthalmologic abnormalities. There were some relatively minimal attempts made to evaluate patients for the

possible occurrence of the vacuolization that was well documented in animals, with the sponsor's conclusion that there were no such occurrences. There were also some indications that vigabatrin use is associated with anemia.

Review of the safety database has revealed no bar to ultimate approval. However, as noted in the reviews by Drs. Sherry, Boehm, and Burkhart, there are still a number of questions that the sponsor must answer before adequate labeling can be written. Those issues are detailed in the attached Approvable letter and/or draft labeling.

BIOPHARMACEUTICS

In the Not Approvable letter, the Agency suggested that the sponsor perform formal interaction studies with vigabatrin and other commonly used AEDs (they had performed population pharmacokinetic analyses of the interactions from the clinical trial data). In addition, we asked that the sponsor study the effects of pH changes in the urine on the excretion of vigabatrin. Finally, the letter asked the sponsor to adopt certain dissolution specifications.

In his review of 9/11/97, Dr. Tammara agrees that the population pharmacokinetic approach to evaluating interactions taken by the sponsor is acceptable, given that vigabatrin does not undergo appreciable metabolism. Further, we are awaiting the results of a formal interaction study with phenytoin. If there is an interaction between vigabatrin and phenytoin, additional formal work may need to be completed. Further, the sponsor and OCPB have come to an agreement about dissolution specifications, which are slightly different (water instead of 0.1N H Cl as the medium) than the one proposed in the Not Approvable letter.

ENVIRONMENTAL ASSESSMENT

There are no outstanding problems.

SUMMARY AND RECOMMENDATIONS

The sponsor has submitted the results of 2 adequate and well controlled

trials that they believe provide substantial evidence that vigabatrin is effective as adjunctive treatment for partial seizures in adults with epilepsy.

Detailed analyses demonstrate that they have presented affirmative evidence of vigabatrin's beneficial effect on complex partial seizures that do not generalize. They have not directly demonstrated that the treatment has an effect on complex partial seizures that do generalize. However, based on reasoning described earlier, I believe it is reasonable to conclude on the basis of the evidence that the treatment has an effect on all complex partial seizures.

The sponsor has not demonstrated an effect on simple partial seizures that either do or do not generalize (indeed, what little evidence they have presented that has the potential to directly speak to the effect of vigabatrin on partial seizures suggests that it has none) . For this reason, I recommend that their proposed indication not be granted, but, instead, should be amended to state that vigabatrin is effective as adjunctive treatment for complex partial seizures in adults with epilepsy.

In addition, there are numerous questions about the safety database that the sponsor should be asked, and these are included in either the Approvable letter and/or the draft labeling.

For these reasons, I recommend that the attached Approvable letter with appended draft labeling be sent to the sponsor.

Russell Katz, M.D.

cc:
NDA 20-427
HFD-120

HFD-120/Katz/Leber/Sherry/Burkhart/Boehm/Ware
HFD-710/Sahlroot

DEPARTMENT OF HEAL . & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-427

OCT 27 1998

Hoechst Marion Roussel
Attention: M. Lorie Stewart
Mail Station H4-M2110
Kahsas City, Missouri 64134-0627

Dear Ms. Stewart:

Please refer to your new drug application (NDA) and to your amendment dated April 24, 1998, received April 27, 1998 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sabril® (vigabatrin) Tablets, 500mg.

Reference is also made to the Agency's Approvable Letter dated November 26, 1997.

We acknowledge receipt of your submissions dated:

May 21, 1998	August 25, 1998
June 4, 1998	September 11, 1998
July 29, 1998	September 23, 1998

We also acknowledge receipt of your submission dated October 20, 1998. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

The user fee goal date for this application is October 27, 1998.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act. Our review reveals that there is insufficient information to determine whether Sabril® is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling [21 CFR 314.125(b)]. The deficiencies may be summarized as follows:

Vigabatrin Associated Visual Field Defects

As you know, our review of your most recent submissions has revealed that Sabril appears to have the capacity to induce a number of adverse clinical phenomena referable to the visual system. Of most concern is the occurrence of a relatively stereotypical visual field defect, characterized by bilateral concentric constriction of the visual fields, with a

propensity to affect the nasal fields. While a number of sources of evidence strongly suggest that the finding is related to treatment with Sabril (including the results of epidemiological studies, spontaneous reports, and reports in the literature), the most compelling evidence derives from perimetry data obtained in the Finnish and Japanese patients. In this cohort, 38/136 patients (28%) had visual field defects of the type described, with 82% of these defects judged to be moderate or severe. Of particular concern is the fact that these patients were asymptomatic. This finding appears to be of sufficient severity and frequency to warrant the accrual of additional data prior to any consideration of marketing. Many of the most basic facts necessary to characterize the finding are still unknown, including the true incidence, the anatomic location of the lesion(s) underlying the finding, its relation to the dose and/or the duration of treatment, the course of the finding once it occurs, the sensitivity of any method of surveillance for the lesion, and the potential reversibility of the lesion.

Your 9/23/98 submission proposes that Sabril be marketed as a last resort agent under extremely restrictive conditions. We do not believe this is acceptable at this time because the risk is not yet adequately characterized and Sabril's effectiveness in last resort situations has not yet been documented. This may require additional effectiveness trials showing superiority of Sabril to other available AED(s) in a suitable population.

While we cannot at this time offer detailed guidance about the nature and amount of safety data that would be considered sufficient to support the approval of this application, it is likely that a study in large numbers of patients followed forward prospectively for a sufficient duration and monitored appropriately and that is designed to collect the data necessary to characterize the elements described above will be required. Of course, members of the Division of Neuropharmacological Drug Products will be happy to discuss these issues with you.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Melina Malandrucco, R. Ph., Regulatory Management Officer, at (301) 594-5526.

Sincerely,

Robert Temple 10/26/98

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Archival NDA 20-427 10/26/98
HFD-120/Div. Files 10/26/98
HFD-120/Leber/Katz/Burkhart/Boehm/Oliva/Fitzgerald/Rosloff/Malandrucco
HFD-860/Tammara 10/26/98
HFD-002/ORM
HFD-101/ADRA
HFD-95/DDMS
HFD-810/DNDC Division Director
DISTRICT OFFICE

NOT APPROVABLE (NA)

OCT 14 1998

MEMORANDUM

DATE: October 14, 1998

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD- 120

TO: File, NDA 20-427

SUBJECT: Supervisory Review of Response to Approvable Letter for NDA 20-427, for the use of Sabril (vigabatrin) in Patients With Partial Seizures

Background

On 11/26/97, the Agency issued an Approvable letter to Hoechst Marion Roussel, Inc., for NDA 20-427, for the use of Sabril (vigabatrin) in patients with partial seizures. In that letter, numerous questions related to further characterizing the safety profile of the drug were asked, as were questions related to the description of these findings in labeling.

The sponsor responded to this letter in 3 separate submissions: a safety update (1/20/98), a "complete" response to the Approvable letter (4/24/98, and which serves as the basis for the current User Fee deadline of 10/27/98), and a further discussion of ophthalmologic findings (7/29/98). All 3 of these submissions have been reviewed by Dr. Gerard Boehm, of the division's Safety Unit (review dated 8/24/98). In addition, the 7/20/98 submission of ophthalmologic data was reviewed by Dr. Oliva (review dated 8/28/98), and data related to peripheral neuropathy and MRJ were reviewed by Dr. James Sherry (review dated 8/25/98). Finally, Dr. Burkhart has written a supervisory review (review dated 10/6/98).

In the course of the Division's review of these submissions, serious concerns about the potential for Sabril to cause frequent, significant, perhaps irreversible, visual field defects (VFDs) were raised. As a result, the Division called the sponsor (8/27/98, a conversation in which Dr. Robert Temple, Director of ODE I, actively participated) to express these concerns and our view that the application could not be approved until additional data were submitted, reviewed, and determined to support the safe marketing of the drug.

In response to this call, the firm has made one additional submission, dated 9/23/98. In this submission, the sponsor proposed that the drug be marketed under very restrictive conditions (e.g., no journal ads, no detailing, no PDR placement, etc.). In a phone call to the sponsor on 9/24/98, the division informed the sponsor that we would still likely recommend that the application not be approved at this time.

In this memo, I will briefly review only the primary safety issue, (given that the other safety issues raised in our Approvable letter do not pose a difficult problem vis-a-vis the approvability of the application at this time), and offer my recommendations for action on the application.

Visual toxicity

As previously noted, the primary safety issue presented in the application now concerns the potential for Sabril to be associated with significant visual field defects.

According to Dr. Boehm, the sponsor reports on a total of 239 patients in whom reports of visual abnormalities have been recorded. Of these, 192 were reported to have visual field defects. These reports come from many sources, including clinical trials of various design (US and non-US) and post marketing sources. The vast majority of patients exposed to Sabril, in drug development cohorts as well as post marketing, have not had routine systematic assessments of their visual fields; as a result, most of the cases can be considered spontaneous reports which became known only after patient complaint. There are, however, several cohorts of patients treated with Sabril that have been systematically assessed with formal visual field testing.

Prospective cohorts

Study VI-PE-0192 was a randomized, parallel group, placebo controlled trial in children ages 4-16. The controlled portion of this trial lasted 17 weeks. Patients had formal testing of the visual system, including confrontational visual field testing, at baseline and at the end of the trial. In this study, no abnormalities were noted in either the treated or control groups.

After the 17 weeks, 44 patients entered an open, 28 week extension. Of these 44, 41 had visual system testing at the end of this extension. No abnormalities were noted.

One patient in this study, a 17 year old female, complained of visual difficulty during the extension trial, at which time her acuity was 20/25. At the end of the extension, her acuity was 25/25, with normal fields and a prolonged P100 latency with stimulation of the left eye on VEPs. Within several weeks of the end of the extension (she continued to be treated with commercially available vigabatrin), she developed pain and was noted to have visual field constriction. She apparently continued on treatment, subsequently developing pain and visual loss in the left eye after several additional months. At that time, she was noted to have nasal and temporal field constriction bilaterally, later described as a bitemporal hemianopsia. There was no further follow-up.

As far as I can tell from the reviews, there were no other data regarding visual field defects deriving from controlled trials.

The sponsor presented the results of systematic visual system testing in several other prospectively followed cohorts receiving Sabril.

Study VGPROO98 is an ongoing open label trial in adults in over 1000 patients. Of these, 146 had eye exams during earlier vigabatrin studies, and were therefore chosen to have repeat assessments. Unfortunately, visual field testing was not performed in these patients. However, one patient was noted to have had bilateral visual field defects 7 years after the initiation of treatment (by history, previous exams were normal, although it is not clear to me if these previous exams included visual field testing). A follow-up exam almost 6 months after the abnormality was noted was unchanged, although it is unclear when (if?) Sabril had been discontinued.

The sponsor also reported the results of systematic visual field testing in patients enrolled in 6 open, uncontrolled long term studies. Two of these studies were conducted in Finland, and were in patients receiving Sabril as monotherapy; the remaining 4 studies were conducted in Japan, in patients receiving Sabril as add-on therapy.

In these studies, patients were asked to undergo visual field testing at a single point in time (about 9 years after the start of the first study). A total of 219 patients were being treated in these 6 studies. Of these, 136 agreed to undergo testing. Two (2) of these patients had uninterpretable tests. Therefore, a total of 134 patients had useable data.

Formal visual field testing was performed on these patients, all of whom were asymptomatic (for the methodology used, see Dr. Oliva's review, page 2). Of the 134 patients with interpretable data, 38 (28%) had visual field defects. The data were independently reviewed by the firm's expert consultant, Dr. John Wild, of the UK. Of these 38, 31(82%) were considered moderate or severe. The constriction consisted of bilateral concentric constriction, worse nasally. The overall incidence was 5.9 cases per 100 patient-years. The distribution was reasonably similar between the 2 countries: 35% of patients in the Finnish studies, and 26% of patients in the Japanese studies had defects.

Another prospective cohort was evaluated by Krauss, et al, in an article "Vigabatrin associated retinal cone system dysfunction" (Neurology 1998;50:614-618). In this article, researchers at Johns Hopkins systematically evaluated the 4 patients they were treating in an HMR sponsored safety study (out of a total of 38 at their institution) who complained of visual symptoms. Of these 4, 2 complained of symptoms referable to visual field constriction, and 2 complained of blurred vision.

Three of these patients were noted to have formal visual field defects, and they all had cone system dysfunction. According to Dr. Burkhart (see his review, page 4), Dr. Krauss is currently assessing the remaining patients, who were asymptomatic. He has told Dr. Burkhart that he has assessed 10 control patients (matched by age and duration of epilepsy), and none have had demonstrable abnormalities.

Epidemiologically styled studies

The sponsor has presented the results of 2 epidemiologic studies.

The first study used a UK General Practitioner Database for this retrospective study. (My description of this study is taken entirely from that provided by Dr. Boehm in his review. There are a number of details about the methodology used that are not provided in Dr. Boehm's description; whether these details are provided by the sponsor is unknown to me). Patients in this database at the start date of the study with a diagnosis of epilepsy and no visual field defect recorded, as well as patients newly diagnosed with epilepsy during the study period and no recorded VFD, were included in the study.

For patients in whom a VFD was detected during the study, the day of detection was used as the index day; all AEDs they were receiving for the previous 120 days were recorded. For patients who did not develop VFDs, a day was randomly selected as an index day, and the same data as for cases was collected.

The sponsor sent questionnaires to the physicians of the patients with VFDs to collect the ophthalmologic data. These data were reviewed by 2 independent ophthalmologists, who classified the cases as probable/possible or probable.

A total of 16,447 patients were eligible for enrollment in this study. Of these, 54 had a VED recorded during the study period. In this study, the highest rate of VFD was associated with vigabatrin (31/10,000 patient-years for possible/probable cases, 10.3/10,000 patient-years for probable cases). The next highest rates of VFD were seen with carbamazepine (12.5/10,000 patient years for possible/probable cases, and 5.2/10,000 patient years for probable cases). It should be noted that the exposure to vigabatrin was considerably less than that for any of the other AEDs. For example, in this study, 285 patients were exposed to vigabatrin (968 patient-years), compared to 4,233 patients on carbamazepine, 15,248 patient years).

A second epidemiologic study was based on PEM data from the UK. This study compared experience among vigabatrin (10,178 patients), lamotrigine (11,316 patients), and gabapentin (3,100 patients). No cases of VED were found in the gabapentin treated group, no well documented case in the lamotrigine group, and apparently 5 cases were seen in the vigabatrin group. Of these 5 cases, one reportedly resolved, 2 continued after discontinuation of the vigabatrin, and there was no follow-up for the other 2. Details of the methodology of this study were not provided.

Other cases

The sponsor presents data about additional cases of VFD from other sources, namely post-marketing reports and various individual reports from various studies, compassionate use, etc. The number of such reports is not clear from the reviews of Drs. Boehm and Oliva. For example,

Dr. Boehm (page 31 of his review) lists 152"spontaneous" reports of any sort of visual abnormality; Dr. Oliva (page 3 of his review) lists 133 "spontaneous" reports from foreign sources. Dr. Boehm describes a total of 239 reports of visual abnormalities, Dr. Oliva describes a total of 221 reports.

According to Dr. Boehm, there were a total of 192 reports of visual field defects. Elsewhere in his review, he states that there were 27 spontaneous reports of VFD for which perimetry data was submitted, and that this represents about 14% of all spontaneous reports of VFD. This would be consistent with his statement that there were 192 reports of VFD (14% of 192=27), although the 192 are not all "spontaneous".

In any event, it appears that the number of perimetry documented spontaneous cases of VFD is 27. These 27 were also reviewed by Dr. Wild; he found 15 to be likely related to vigabatrin. As with the Finnish and Japanese data, he found these defects to be bilateral, concentric, more marked nasally. He offered the view that bilateral nasal VFDs are rare, and that the lesion was probably retinal.

According to Dr. Oliva (page 4 of his review), of the total 221 cases of visual abnormalities (I am not sure exactly how many of these are VFDs), vigabatrin was discontinued in 110 patients. Of these 110, the lesion was unresolved in 84. As he notes, the nature of the follow-up, etc., is unknown.

As described by both Drs. Boehm and Oliva, other visual and retinal abnormalities were noted.

Given the signal of ophthalmologic injury, the Division asked both the Epidemiology and Ophthalmologic Drugs review groups to address these issues.

Specifically, we asked the Epidemiology group to examine the SRS for similar reports for other recently approved AEDs. In a report dated 9/9/98, they note that there are no cases of VFDs reported in association with tiagabine, topiramate, and felbamate. One case of VFD was reported in association with valproate use. While there were numerous reports (mostly for valproate) of eye abnormalities, only one case of VFD was reported. A search of the literature also failed to find any cases of VFD is association with the use of these drugs.

In an ophthalmology consult dated 8/27/98, Dr. Wiley Chambers concludes that the lesion seen here is rare, not known to occur with other drugs, and might be significantly underreported, given concerns with the methodology used and the fact that there was no systematic assessment of asymptomatic patients. He also suggests that the character of the lesion is consistent with injury at perhaps multiple sites in the visual system, and not necessarily the result of a retinal lesion.

As noted earlier, the sponsor, aware of our reservations about approving the application in the face of these findings, submitted, on 9/23/98, a proposal for marketing the drug under the following restrictions:

No PDR placement ad
No journal ads
No Direct Mail programs to non-epileptologists
No commercial exhibits promoting Sabril
No sales force promoting Sabril
No direct to consumer or patient marketing

In addition, they propose announcing the drug's availability only to epilepsy centers, and working with the Agency to write restrictive labeling.

Beyond the ophthalmological findings, there were a number of other safety questions to which the sponsor responded; these are summarized in Dr. Burkhart's review. In particular, his comments on vigabatrin's capacity to cause liver injury are especially cogent.

Finally, Dr. Sherry has reviewed the MRI data and the evidence bearing on vigabatrin's capacity to cause peripheral neuropathy. In an attempt to further define this issue, the sponsor enlisted the aid of an expert, Dr. Cornblath, to construct a case definition and review potential cases of peripheral neuropathy. However, the sponsor did not provide requested information about the association of dose and/or duration of treatment to the onset, reversibility, etc. of the neuropathy, nor were adequate electrical studies provided. The sponsor did propose, though, that Phase 4 studies be performed to better characterize these aspects of any vigabatrin-induced neuropathy.

COMMENTS

The sponsor has submitted several sources of data that raise serious concerns about the capacity of vigabatrin to cause visual abnormalities of various type. This evidence is strongest for a drug induced visual field defect of fairly stereotypic type (bilateral concentric, predominately nasal). By most assessments, the lesion appears clinically to be retinal in origin.

Data from epidemiologically styled studies suggest that vigabatrin's ability to cause the lesion is, if not unique among AEDs, certainly unusual. However, as discussed in detail by Dr. Boehm, the nature of these studies is such that definitive conclusions about the rate of this lesion (absolute and comparative), as well as even its drug relatedness, cannot be made, although all evidence suggests that the rate of such a finding is extremely low in a similar population, suggesting, of course, that the lesion is treatment related.

The most compelling evidence for the existence, and estimated prevalence, of a Sabril induced lesion comes from the Finnish and Japanese data. In this study, 28% of asymptomatic patients had documented VFDs, 82% of which were gauged to be moderate or severe.

There is a great deal that is unknown about this lesion. As mentioned, the background rate (in particular, with other AEDs) is not known with any confidence, and so the relative risk of this event is impossible to know. In this regard, it is worth noting that I was informed by Dr. Cathy Peterson, of the Therapeutics Products Directorate of Health Canada, in a telephone conversation held 10/14/98, that a meeting was recently held by the Adverse Reactions Advisory Committee of the Australian drug regulatory authority on 9/25/98, at which reports of VFDs with AEDs was discussed. At this meeting, the committee discussed reports submitted by a single neurologist who he claimed that 50% of his patients on vigabatrin or tiagabine had constricted visual fields. Dr. Peterson faxed me a copy of a part of the confidential record of the committee's meeting. In this report is a list of 5 patients taking tiagabine in whom asymptomatic VFDs were noted (all of whom had received tiagabine for about 5 years and were receiving other AEDs). The report also contains a brief account of the sponsor's view (Sanofi Winthrop in Australia) that 4 of these cases were confounded.

Beyond this, however, we have no good data that speaks to the relationship of the occurrence and/or reversibility of the lesion to the dose and/or duration of treatment. Further, the sensitivity of the measures to detect the lesion early are unknown.

These lacunae in our knowledge about these fundamental parameters of this lesion make it impossible, in my view, to construct adequate labeling that would make the product safe in use. Specifically, despite the sponsor's proposal to severely restrict access to this drug, we still must be able to write labeling that adequately informs a prescriber about the risks associated with vigabatrin's use; given the lack of information about this risk, I do not believe that we can do this at this time. The sponsor has clearly not performed adequate tests by all methods reasonably applicable to show that the drug is safe for use under proposed labeling, as required by statute.

RECOMMENDATIONS

For the reasons stated above, I recommend that the application be Not Approved, and that the sponsor be required to perform studies in which large numbers of patients are adequately monitored (by appropriately sensitive methods) for a sufficient duration to evaluate the relationship of dose and duration of treatment to the occurrence of the lesion, and to document the incidence of the lesion as well as the comparative rates (perhaps to both a similar cohort treated with other AEDs as well as to an untreated cohort). Further, detailed study of the reversibility of the finding should also be undertaken, including adequately monitored follow-up of patients who develop VEDs. In addition, information about the risk of this event in association with other AEDs should be sought. Until this basic information is available, it would be difficult, in my view, to justify marketing.

When this additional data is received, the conditions of approvability can be further discussed. For example, approval might be contingent upon a demonstration of the superiority of Sabril to other available AEDs in a randomized controlled trial in which a direct comparison of the treatments is made.

Russell Katz, M.D.

cc:
NDA 20-427
HFD-120
HFD- I 20/Katz/Leber/BurkhartlBoehm/Oliva/Malandrucco

CLINICAL REVIEW
VIGABATRIN OPHTHALMIC ADVERSE EFFECTS

Application Type:	NDA
Submission Number:	22006 (Infantile Spasms); 20427 (Complex Partial Seizures)
Letter Date:	28 December 2007
Reviewer Name:	Ronald Farkas, MD, PhD
Through:	Norman Hershkowitz, MD, PhD Wiley Chambers, MD
Established Name:	Vigabatrin
(Proposed) Trade Name:	Sabril
Therapeutic Class:	Antiepileptic
Applicant:	Ovation Pharmaceuticals
Priority Designation:	P
Formulation:	Tablets and Powder
Indication:	Seizure disorder
Intended Population:	Children and Adults

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1. Introduction and Background

This review addresses the visual adverse effects of vigabatrin (VGB) in patients with complex partial seizures (CPS) (NDA 20427) and infantile spasms (IS) (NDA 22006). For VGB efficacy in these indications, see the reviews by Phillip Sheridan, M.D. For review of non-ophthalmic safety, see the reviews by Gerard Boehm, M.D.

VGB was first marketed in 1989 in a number of countries outside the U.S. Due to safety concerns about the potential for VGB to cause intramyelinic edema, FDA issued an approvable letter for VGB in 1997. However, shortly thereafter emerging data linking VGB with visual field constriction led FDA to issue a non-approved letter pending submission of adequate evidence of a favorable risk/benefit profile of VGB given the visual adverse effects. Information requested by FDA about the visual adverse effects of VGB included the following:

- *Character of adverse event*: Incidence, prevalence, location (e.g. central vs. peripheral visual loss), severity, latency, reversibility, and risk factors
- *Monitoring and Prevention*: Ability to detect and prevent adverse events in both adults and children

The sponsor states that the adverse visual effects of VGB are now well-characterized and that the current submissions contain adequate data and appropriate risk management to conclude that the drug has a favorable risk/benefit profile to support FDA approval in CPS and IS.

2. Executive Summary

Key sponsor conclusions about visual adverse effects of VGB are presented below, followed in bold by key review findings.

a. *Ophthalmic Adverse Effects in Adults*

1. VGB causes bilateral, concentric peripheral constriction of the visual field, ranging from mild to severe.
   Review agrees.

2. Central vision is preserved even in cases of severely constricted visual field
   Reviewer: **Central vision appears to be only *relatively* preserved. While *severe* visual acuity loss from VGB is rare, mild or even moderate acuity loss (20/25-20/50) may occur. Observable damage can also occur in the central retina.**

3. Visual field constriction does not begin immediately upon initiation of VGB-therapy but occurs slowly, with average onset after several years of treatment.

Review disagrees:

- **The time course of visual damage is highly variable among patients.**
- **Some cases occur after less than 2 months of VGB exposure, with the lower limit of time of onset not well-defined.**
- **It is important to distinguish between latency of onset and speed of progression of damage. Damage may not progress linearly over time, but instead may occur more precipitously.**
- **Peak incidence of field defect likely occurs at about 1 year.**
- **There is no reliable evidence for a 'safe' period of exposure in which visual damage will not occur.**

4. Most individuals treated with VGB who develop visual field constriction are unaware of its presence, but in a minority of cases, field defect is sufficiently severe to hinder daily activities.

Review findings partially agree.

- Even though many patients are unaware of the presence of visual damage, this in no way demonstrates that the visual damage doesn't have negative impacts on their function (see below).
- **Given the high percentage of patients that develop VGB visual damage, even a 'minority' of patients with more severe disability still reflects many people.**
- **Little data is available about visual ability in patients with VGB field loss. On the supposition that VGB field loss is in some respects similar to field loss from glaucoma, vigabatrin patients with more severe visual damage are likely to have difficulty with common daily activities. However, most patients likely would remain capable of independent self-care and conduct of necessary business. In children with IS, the functional consequences of given degrees of field loss are not as well understood, with case reports suggesting that visual disability in some cases can be profound.**

5. Careful questioning of VGB-treated individuals can reveal symptoms of functional visual deficits even in those who failed to spontaneously recognize them.

Review agrees.

6. Most studies support the finding of defect that occurs in approximately 50% of subjects or fewer.

Review findings generally agree. However, for the roughly 50% of patients that don't develop field defect after a number of years of VGB, some risk of late development of field defect might remain.

7. The field defect progresses to a maximal point, remains static, and does not progress inexorably to the central visual island.

Review findings disagree. Key questions about progression remain poorly understood:

- **While wide inter-individual variation exists, in many patients field defects progress over months to a few years to roughly 25° or even closer to fixation.**
- **While field defects have not been documented to progress to closer than roughly 10 degrees of fixation, even after a decade or more of VGB exposure, ongoing damage to the central retina may continue.**
- **The available data can not exclude the rare occurrence of severe central vision loss from vigabatrin.**
- **While field loss ranging from mild to severe can, in some patients, remain seemingly stable for months or even years despite continued VGB exposure, further constriction occurs in some patients.**
- **Importantly, some patients appear to have progressive field loss even after VGB is discontinued. The risk, time course, and potential degree of continued progression after stopping VGB are poorly understood.**

8. Improvement of the visual field defect is probably very rare, and can't be considered likely.

Review findings agree, stressing that even rare cases of improvement are not well documented.

9. Patients who develop a visual field defect generally experience a decrease in lateral vision from the normal 90 degrees to, on average, 71.1 degrees.

Review disagrees. The 'average severity' value presented by the sponsor is not based on reliable data. Moreover, 'average severity' is not a clinically useful measure of an adverse event of variable severity. While available data allows only rough estimate, by 5 years of exposure about 1/3rd of patients experience constriction, often to within 20 or 30 degrees of fixation, with perhaps 10% experiencing greater constriction, to roughly 10 or 20 degrees of fixation. It should be noted, too, that the sponsor's estimate is problematic because for any scotoma that is not absolute, defect size is dependent on technical factors that vary among the different perimetry methods used to examine vigabatrin patients, including stimulus size and intensity.

10. Uniform, highly sensitive screening tools, including confirmatory testing with a variety of techniques, ensure accurate assessment of field defects.

Review disagrees.

- **Perimetry is often *not* highly sensitive.**
  - **Perimetry is a subjective test that depends on the skill and experience of the patient and operator. The first one or several tests are often unreliable. Perhaps 20% of adult VGB patients may never be able to perform perimetry well enough to be monitored by that method. In perhaps a similar proportion of patients, perimetry may be possible, but with poor reliability. Inter-test variability often remains high even for patients**

experienced with perimetry, which may lead to a high risk of false-positive findings.
    - **Success of safety screening is intimately linked to the speed at which VGB damage progresses. It is not clear if damage progresses linearly over time, or if damage can occur precipitously after an unpredictable latency. Patients that progress precipitously may not be detected until damage has already occurred.**
- **Electroretinography (ERG) does not appear useful for early diagnosis of vigabatrin visual damage. ERG may be able to diagnose severe damage that has already occurred.**
    - **ERG appears less sensitive than perimetry for vigabatrin visual damage. ERG is often normal in patients with field defect.**
    - **ERG suffers from high inter-test variability and apparent poor specificity as a result.**
    - **Critically, the clinical correlate of any given degree of ERG decrease is poorly understood. Data is simply inadequate to determine the sensitivity or specificity of ERG testing for vigabatrin visual damage.**
- **Little data is available about the potential usefulness of screening methods other than perimetry and ERG, such as field-specific visual-evoked potentials (VEP).**
- **As severity of VGB damage increases, reliability of diagnostic methods may increase. Since even severe visual damage often remains asymptomatic, perimetry and ERG might be clinically useful to identify patients in whom VGB should be discontinued due to severe damage that has already occurred.**

b. *Ophthalmic Adverse Events in Infants and Children*

1. Children appear to develop the same peripheral VFD defect as adults.

Review generally agrees, noting that data from children is limited, and that important undiscovered differences may exist.

2. Diagnosis in very young or cognitively-impaired children can be technically challenging

Review agrees, stressing that sensitivity for detection of vigabatrin visual damage in children appears to be poor

3. Overall, studies suggest that VGB-induced VFD is somewhat lower in children than adults.

Data is inadequate to support this conclusion. Comparison of rates is not possible because vigabatrin visual damage can not be reliably diagnosed in children.

4. In infants, the characteristic electrophysiological abnormalities associated with VGB-induced visual field defect do not occur rapidly, with onset generally after one year of therapy.

Review disagrees. Issues of sensitivity and specificity aside, ERG testing was conducted at 6-month intervals in the studies on which this conclusion is based, and patients were required to have 2 abnormal results before being defined as abnormal; thus field defects would not be confirmed until after one year of therapy due to study design. In some of the patients tested after 3 months of VGB, abnormalities were found, but again, this does not provide evidence about potential onset even earlier, prior to the first ERG test.

c. *Risk Factors*

1. The question is unresolved whether visual toxicity is unpredictable ("idiosyncratic") or whether all subjects are vulnerable.

Review generally agrees. While there is little evidence that a single dose can cause visual loss, no 'safe' exposure is known.

2. Time of exposure and total dose are probably important risk factors.

Review generally agrees, stressing that at exposures for which data is available exposure and total dose are weak risk factors with limited clinical usefulness.

Reviewer Conclusions

- Many key questions remain unanswered about the characteristics of vigabatrin visual damage
- Current data allow a qualitative understanding of visual risks. Safety testing can *not* reliably prevent or lessen vigabatrin visual damage.
- Testing may more reliably detect severe visual damage, but the degree to which this would benefit patients is not clear..

Well-designed prospective, longitudinal studies needed to accurately characterize visual damage caused by vigabatrin were planned but never successfully conducted. Data submitted to FDA is mainly from less formally conducted, uncontrolled, potentially unrepresentative cross-sectional studies lacking full documentation. As a result, the available data supports only *qualitative*, not quantitative conclusions about the nature and extent of the visual damage caused by vigabatrin.

Vigabatrin causes both irreversible bilateral constriction of the visual field and, in at least some patients, mild or even moderate damage to central vision (rare cases of severe damage to central vision also can not be excluded). By about 5 years of treatment, roughly 1/3rd of patients will have visual field constriction, about evenly divided among mild, moderate, and severe constriction. Patients with more severe visual damage are expected to have increased difficulty with common daily activities, particularly those involving

mobility and orientation. Although many patients with less severe vigabatrin visual loss are seemingly 'asymptomatic,' symptoms of visual loss may be incorrectly attributed to such factors as clumsiness or drowsiness.

The peak incidence of vigabatrin visual damage occurs at about 1 year, but onset at a few weeks or months is not rare. While some evidence suggests a weak time and dose dependence of vigabatrin damage, no 'safe' exposure is known.

Importantly, there is little reliable data addressing if visual damage can worsen *after stopping* vigabatrin; of concern, individual cases suggest worsening can occur. Long term visual function of vigabatrin patients is also threatened by the presumably additive effects of such common eye diseases of aging as macular degeneration and glaucoma.

It is far more difficult to *prevent* vigabatrin visual damage than to detect damage that has already occurred. Essentially no data supports the effectiveness of safety monitoring for preventing vigabatrin visual damage, and neither perimetry nor ERG appear able to do so reliably. Visual loss similar to the 'natural history' of vigabatrin visual damage is likely to occur in many adult and pediatric patients despite safety monitoring.

Even in adult patients in whom perimetry might theoretically be useful, experience in other ophthalmic disease suggests that the sponsor's monitoring plan is inadequate. Of particular concern, the sponsor's plan does not account for the nearly universal 'learning effect' that would confound detection of visual damage. In addition, while the speed of damage progression is not well-understood, the proposed 6-month monitoring interval appears too infrequent. Theoretically, intensive early testing to establish a reliable baseline, followed by an ongoing increased testing frequency could improve detection of visual damage in patients that can perform perimetry adequately. However, such intensive monitoring might be impractical for many patients, thus subverting the theoretical gains.

3. Data Sources

Visual adverse events were assessed in the following for both CPS and IS:

- Efficacy studies and open-label extensions
- Phase 4 studies of visual adverse events
- Published case series and case reports
- Periodic Safety Update Reports (PSURs), 1995 (PSUR 1) to 2007 (PSUR 19)

Following are the major trials conducted by the sponsor that were evaluated in this review:

CPS Safety Studies

Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Safety-Subjects with Complex Partial Seizures	4020	Open, Multicenter Study of the Prevalence, Incidence and Clinical Course of Visual Field Defects in Adults and Children with Refractory Partial Epilepsy Treated with Antiepileptic Drugs	Multicenter, open, comparative, parallel group	Variable; subjects continued anti-epileptic treatment used at inclusion, unless the physician decided that a change was in the best interest of the subject	735 Enrolled 554 Included in safety analysis	Refractory Partial Epilepsy	Variable	First Subject Entered Mar, 1999 Last Subject Enrolled Apr, 2003 Report finalized June, 2006 Report amended Oct, 2006
Safety-Subjects with Complex Partial Seizures	4021	Assess the Clinical Course, Prevalence and Risk Factors of Visual Field Constriction	Single center observational open, follow-up study	Film coated tablet and non-coated tablet 500 mg; powder for oral solution sachets 500 mg, 1 g, 2 g, and 3 g; granules for oral solution sachets 500 mg and 1 g	30 Enrolled 30 Currently using or previously used VGB 26 Completed	CPS	Study Duration: 2.5 years Treatment Duration: 6-7 study visits per subject over 2.5 years	Last subject completed Dec, 2001 Report finalized June, 2002

Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Safety-Subjects with Complex Partial Seizures	R003	Study to Detect Early Visual Field Defects, Their Frequency and Clinical Course in First-Time VGB Treatment for Refractory Partial Epilepsy	Multicenter, non-comparative, prospective, observational cohort study	N/A	25 Enrolled 25 treated with VGB 10 Completed	Uncontroll-ed CPS	455 d mean duration (range: 2-988 d)	First subject enrolled Oct, 2000 Study ended Oct, 2003 Report finalized May, 2004

CPS Efficacy Studies

Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy – Subjects with Complex Partial Seizures	0101	Efficacy of Rational Polytherapy with Sabril vs. Carbamaze-pine or Phenytoin Monotherapy in the Management of Patients with Non-Refractory CPS (Complex Partial Seizures)	Multicenter, randomized, double-blind, placebo-controlled trial with 2 parallel groups	Oral 500 mg tablet VGB BID increasing weekly by 500 mg/d to a fixed maintenance dose of 3 g/d	268 enrolled 177 randomized to double-blind period (119 VGB; 58 placebo) 171 completed titration period (113 VGB; 58 placebo) 149 completed double-blind period (94 VGB; 55 placebo)	Partial Epilepsy	40-44 weeks: 12-week baseline; 4-week titration; 24-week maintenance; 4-week taper or transfer to open-label extension	Last subject completed May, 1997 Report finalized Oct, 1998
Efficacy – Subjects with Complex Partial Seizures	0118	Efficacy and Safety Evaluation of Oral Adjunctive VGB Therapy Compared to Placebo in Children with Uncontrolled CPS: a Dose Response Study	Multicenter, randomized, double-blind, placebo-controlled, parallel group	Oral VGB 20 mg/kg/d 60 mg/kg/d 100 mg/kg/d	173 Enrolled 126 randomized to receive study medication (94 VGB; 32 placebo) 108 Completed (80 VGB; 28 placebo)	Uncontroll-ed CPS	24-27 weeks 10-week baseline; 6-week titration; 8-week maintenance; 3-week taper or transfer to open-label study	Last subject completed (dosed) Sept, 1997 Report finalized Aug. 1998

Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy – Subjects with Complex Partial Seizures	0221	Efficacy and Safety of Oral Adjunctive VGB Therapy Compared to Placebo in Children with Uncontrolled CPS: a Parallel Group Study	Multicenter, randomized, double-blind, placebo-controlled, parallel group	Oral VGB Initial dose: 10-30 kg: 0.5 g/d (0.25 g BID) > 30 kg: 1.0 g/d (0.5 g BID) Maintenance dose: 10-15 kg: 0.5-1.5 g/d 16-30 kg: 0.5-2.0 g/d 31-50 kg: 1.0-3.0 g/d >50 kg: 1.5-4.0 g/d Dosage regimen: BID	127 Enrolled 88 Randomized (43 VGB; 45 placebo) 68 Completed (36 VGB; 32 placebo)	Uncontroll-ed CPS	23-26 weeks 6-week baseline; 10-week titration; 7-week maintenance; 3-week taper or transfer to open-label study	Last subject completed (dosed) July, 1997 Report finalized Sept, 1998 Amended April, 1999

Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy – Subjects with Complex Partial Seizures	0222	Efficacy and Safety of VGB 3 g/day vs. Gabapentin 1800 mg/d as Monotherapy in Patients with CPS	Multicenter, randomized, double-blind, double-dummy, parallel group	Oral VGB up to 3 g/d or gabapentin 1800 mg/d	44 Enrolled 19 Randomized 18 received study medication (9 VGB; 9 gabapentin) 3 Completed (1 VGB; 2 gabapentin)	CPS	29 weeks 8-week baseline; 5-week titration; 8-week withdrawal 8-week maintenance	Last subject completed (dosed) Sept, 1996 Report finalized Sept, 1998
Efficacy – Subjects with Complex Partial Seizures	0223	Dose-Response Study of Efficacy and Safety of VGB 1, 3, 4, and 6 g/day as Monotherapy in Patients with CPS	Multicenter, randomized, double-blind, dose-response, parallel group	Oral VGB 1, 3, 4, or 6 g/d BID	121 Enrolled 75 Randomized (17, 1 g/d; 18, 3 g/d; 19, 4 g/d; 21, 6 g/d) 13 Completed (2, 1 g/d; 3, 3 g/d; 4, 4 g/d; 4, 6 g/d)	CPS	30-35 weeks 8-week baseline; 6-week titration; 8-week withdrawal 8-week maintenance 5-week taper or transfer to open-label study	Last subject completed (dosed) Oct, 1996 Report finalized Dec, 1998

Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy – Subjects with Complex Partial Seizures	0192	Efficacy and Safety of Oral Adjunctive VGB Therapy Compared to Placebo in Children with Uncontrolled CPS: A Parallel Group Study	Multicenter, randomized, double-blind, placebo-controlled, parallel group	Oral VGB Initial dose: 10-30 kg: 0.5 g/d (0.25 g BID) > 30 kg: 1.0 g/d (0.5g BID) Maintenance dose: 10-15 kg: 0.5-1.5 g/d 16-30 kg: 0.5-2.0 g/d 31-50 kg: 1.0-3.0 g/d >50 kg: 1.5-4.0 g/d Dosage regimen: BID	55 Enrolled 55 randomized (28 VGB; 27 placebo) 48 Completed (22 VGB; 26 placebo)	Uncontrolled CPS	23-26 weeks 6-week baseline; 10-week titration; 7-week maintenance; 3-week taper or transfer to open-label study	Last subject completed Dec, 1994 Report finalized Sept, 1998
Efficacy – Subjects with Complex Partial Seizures	0098	Clinical Experience and Use of Sabril in Patients with Partial Seizures	Multicenter, open-label, flexible-dose, long term	Oral 500 mg VGB BID increasing weekly by 500 mg/d not to exceed 6 g/d	1264 Enrolled	Partial Epilepsy	6-24 months	Last subject completed Mar, 2000 Report finalized Dec, 2000

Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy – Subjects with Complex Partial Seizures	0242	Maintenance of VGB as Monotherapy in Patients with CPS	Multicenter, open-label, long-term, follow-up	Oral VGB 4g/d up to 6g/d	86 Enrolled 85 Evaluated for safety	CPS	Planned to be 52 weeks Study terminated	Last subject completed Oct, 1998 Report finalized Sept, 1999
Efficacy – Subjects with Complex Partial Seizures	0201	Maintenance Study of VGB as Adjunctive Therapy in Children with Uncontrolled CPS	Open-label, multicenter, long-term, follow-up	Oral VGB 40 mg/kg/d or 60 mg/kg/d up to the lesser of 100 mg/kg/d or 6 g	210 Enrolled 209 Evaluated for safety	Uncontroll-ed CPS	Planned to be at least 52 weeks Actual approximate-ly 3 years	Last subject completed Nov, 1998 Report finalized Dec, 1999

Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy – Subjects with Complex Partial Seizures	0294	VGB as Adjunctive Therapy in Children with CPS	Open label, multicenter, follow-up	Oral VGB Two dosing regimens depending upon which protocol was being extended 10-30 kg: 0.5 g/d (0.25 g BID) >30 kg: 1.0 g/d (0.5 g BID) or 10-15 kg: 1.0, 1.5 g/d 16-30 kg: 1.0, 1.5-2.0 g/d 31-50 kg: 1.5, 2.0-3.0 g/d >50 kg: 1.5, 2.0, 3.0-4.0 g/d Dosage regimen: BID	44 Enrolled 44 Received VGB 38 Completed	CPS	24 weeks	Last subject completed June, 1995 Report finalized Sept, 1998

IS Safety Studies

Toronto Study

Single center, open-label, retrospective and prospective case series of ≈ 200 children taking VGB for IS and CPS, focusing on ERG monitoring for VGB adverse visual effects. The study is ongoing.

Boston Children's Hospital Study
Single center, open-label retrospective case series of ≈ 50 children taking VGB for IS and CPS, focusing on ERG monitoring for VGB adverse visual effects.

IS Efficacy Studies

Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy - Subjects with Infantile Spasms	1A	Clinical Experience and Use of VGB (Sabril®) in Subjects with IS	Multicenter, randomized, single-blind study with an open-label, dose-ranging, long-term follow-up	Oral VGB Low-dose: 18-36 mg/kg/d High-dose: 100-148 mg//kg/d	226 Enrolled 221 Modified ITT Cohort 219 Entered flexible dosing period	IS	14-21 d, with long-term follow-up of up to 3 years	Last subject completed Apr, 2002 Report finalized Nov, 2005 Report Amendment June, 2006
Efficacy - Subjects with Infantile Spasms	W019	A Multicenter, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Safety and Efficacy of VGB vs. Placebo as First Line Therapy in the Treatment of Newly Diagnosed IS	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study with open-label follow-up period	Oral VGB at initial dose of 50 mg/kg/d with titration allowed to 150 mg/kg/d for 5 d, followed by 6 months of open-label VGB Placebo for 5 d, followed by 6 months of open-label VGB	40 Enrolled 40 Randomized (20 VGB; 20 placebo) 40 Completed double-blind phase 36 Entered open-label 28 Completed 24 weeks of study	Newly-diagnosed IS with no prior treatment	Baseline: 2-3 d Double-blind: 5 d Open-label follow-up: 6 months	Last subject completed Jan, 1996 Report finalized Mar, 1997

Type of Study	Study Identifier	Study Title	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy - Subjects with Infantile Spasms	FR03	VGB vs. Hydro-cortisone in IS due to Tuberous Sclerosis	Multicenter, randomized, open-label, comparative, response-mediated cross-over study	Oral VGB 150 mg/kg/d for 4 weeks (if no response, then cross-over to hydro-cortisone for 4 weeks) Hydro-cortisone 15 mg/kg/d for 4 weeks (if no response, then cross-over to VGB for 4 weeks) Long-term follow-up optional for both groups	VGB 11 Enrolled 11 Completed (No subjects crossed-over to receive hydro-cortisone) Hydro-cortisone 12 Enrolled 11 Completed (7 subjects crossed-over to receive VGB)	Newly-diagnosed and previously untreated IS due to tuberous sclerosis	2-month randomized period (No specific dosing data are available for the follow-up period, but some subjects were followed for ≥2 years)	Last subject completed Oct, 1994 Report finalized June, 1995

4. Ophthalmic Safety Data from Early Studies

In efficacy studies of children with IS, a large variety of visual abnormalities occurred in both VGB- and placebo-treated patients, ranging from strabismus to cortical blindness. The power of these studies to detect even large deleterious effects of vigabatrin on vision was thus low. For the current submission, the division reasoned that long-term ophthalmic exam data from the children in the original IS studies might be informative about long-term visual outcome in children treated with VGB. Of 279 originally enrolled patients, the sponsor was able to obtain some follow-up information about visual function for 55 (Table 1). None of these 55 patients had been noted by current caregivers to have severe VGB-related field defect, but 24 had been diagnosed with 'severe non-VGB related' field defect. Forty-eight patients were said to have normal vision.

Table 1: Long Term Vision of IS Study Patients

Investigator[a]	Total Enrolled	With Absence of Vision at Baseline[b]	With Follow-Up after Subject Exited Study	With Follow-Up Vision Exam Performed[c]	With Severe VGB-Related VFD	With Severe Non-VGB Related VFD	Normal Vision[d]
Appleton[e]	40	Unknown	10	3	0	0	3
Bebin	58	2	24	13	0	2	13
Chiron[f]	23	4	11	9	0	4	9
Conry	1	0	1	1	0	0	1
Crumrine	18	1	16	9	0	1	6
Elterman	47	0	13	13	0	4	9
Marks	6	1	6	0	0	1	Unknown
Mitchell	23	2	20	3	0	2	3
Shields	47	5	26	4	0	10	4
Trevathan (Bauman)	3	Not Available	No Follow-Up Data	No Follow-Up Data	No Follow-Up Data	No Follow-Up Data	No followup Data
Wyllie	13	Not Available	No Follow-Up Data	No Follow-Up Data	No Follow-Up Data	No follow-Up Data	No followup Data
Total	279	≥15	127	55	0	24	48

a Investigator participated in study 1A unless otherwise footnoted.
b Or near complete absence of vision, defined as light perception only
c Of those with vision at baseline
d By method or methods tested, depending upon subject included Goldmann perimetry, confrontation fields, measures of visual acuity or quadrant fixation testing, in various subjects
e Investigator for Study W019
f Investigator for Study FR03

[From Table 71, visualdysfunc.pdf, page 169 of 304]

Reviewer Discussion

Review of safety data from the original VGB studies confirms the findings of the original safety review that VGB is associated in CPS with a low incidence of at least severe *acuity* loss. It seems clear, too, that symptoms of visual field loss in CPS patients were not so gross as to be detected.

Since children, particularly those with IS, would not be expected to be able to report symptoms of visual loss, the original safety and efficacy studies in IS provide less

reassurance that severe visual loss did not occur in these patients. The long-term follow-up data available from the children in the original studies is too incomplete for reliable conclusions.

5. Ophthalmic Safety Studies in CPS

a. *Reviewer Introduction*

After postmarketing reports emerged associating VGB with visual field constriction, phase 4 studies were initiated to characterize this adverse effect. Several large studies were to be conducted prospectively, or with randomly selected retrospective samples designed to represent the overall VGB patient population. However, as detailed below, most studies were plagued by serious shortcomings in design and execution, including low enrolment, non-random patient selection, high dropout rate, poor quality assurance, and post-hoc analysis.

The sponsor's conclusions about the natural history of VGB visual damage in adults are based largely on study 4020, which is described below. However, due to multiple problematic study design and execution issues, this review concludes that most data from study 4020 is unreliable.

The 'pooled cohort' study described below is based on visual field exams at a single time point in a cross-section of several hundred patients enrolled in VGB clinical studies. The current sponsor did not submit detailed information from this cohort study, and did not rely upon it for major conclusions. However, this review considers the study particularly important because, while it is not a random population, it may represent a relatively unbiased view of field defect in patients with various VGB exposures.

Study R003 is particularly valuable as one of the few prospective studies of VGB visual effects. The study enrolled only 25 out of a planned 200 subjects, but despite the small number of patients, the study provides one of the only available estimates of the performance of perimetry in safety monitoring of patients starting VGB.

b. *Study 4020*

Study 4020 was an open-label, multicenter study at 46 centers in France, South Korea, Italy, Spain, and Australia conducted to examine the characteristics of the visual field defect associated with VGB. . Anti-epileptic treatment was selected by the treating physician.

The original study plan called for selecting a random sample of patients, but this plan was later abandoned. Investigators had knowledge of the severity of visual defect prior to patient enrollment, and excluded patients thought to have visual abnormalities not related to VGB, such as glaucoma.

Reviewer: Many profound biases could have been introduced by this patient selection. For example, visually disabled patients might be under-represented due to difficulty traveling to clinic.

Prior to enrollment patients had taken VGB for variable lengths of time, often several years, or had stopped VGB variable lengths of time in the past.

Reviewer: This confounded the sponsor's calculations of time to diagnosis and time of onset of visual damage.

Visual system tests:

- Perimetry
  - Static and kinetic perimetry were planned
    - The recommended static perimetry method was Humphrey Field Analyzer (HFA) 135 or 120 age-corrected 3 zone or Octopus 2 level and, whenever possible, Program 30-2 or 32 of the HFA, Octopus or equivalent.

  Reviewer: Consistent perimetry methods were not followed, for different patients or even when longitudinally following a single individual. This greatly hinders interpretation.

- Ophthalmic exam
  - Ocular history
  - Best corrected visual acuity (rated on a scale of zero to ten)

  Reviewer: The sponsor notes that visual acuity data was not properly recorded and not analyzable.
  - Manifest refraction
  - Ocular symptoms
  - Slit-lamp biomicroscopy
  - Intraocular pressure
  - Bilateral dilated ophthalmoscopy
  - Gonioscopy (if not done within the last year)
  - Evaluation of if ocular findings might explain the visual field results
  - Visual disability as assessed by questionnaire.
- Adverse event reporting

Endpoints:

- Estimated prevalence rates for peripheral VFD.

Major Inclusion Criteria:

- Age ≥ 8
- refractory partial epilepsy for at least one year

Major Exclusion Criteria:

- Patients with identified secondary ophthalmological disease of known etiology at inclusion were excluded.
- Progressive VFD of identified etiology unrelated to VGB

Reviewer: Importantly, the above 2 criteria might have excluded VGB patients with ophthalmic adverse events incorrectly classified as unrelated to VGB.

- Unreliable perimetric data

Reviewer: Patients with visual damage may be over-represented among patients with unreliable perimetric data, thus underestimating VGB visual damage.

The sponsor divided enrolled patients into groups for additional comparative analysis:

- Group 1: treated with VGB prior to study, and remaining on VGB
  - Average 4.2 years VGB treatment prior to entry
  - 38 children
  - 149 adults
- Group 2: previously treated with VGB but discontinued prior to study entry
  - Treated for average of 2.4 years
  - 47 children
  - 152 adults
- Group 3: subjects who never received VGB.
  - 7 of these subjects started VGB while on study, but for an average of only 4 months

On average the first field test in study 4020 occurred about 5 years after starting VGB.

Study populations

- 2,583 patients were screened
- 735 subjects were enrolled
- 524 subjects were considered evaluable (patients having at least a single conclusive visual field test)
- 354 subjects had an evaluable field at inclusion
- 46% of patients discontinued prematurely

Reviewer: In addition to initial non-random patient selection, patient attrition between screening and study completion was extremely high, and might have profoundly biased study results.

Data Analysis

- Prevalence was defined by Aventis as the number and percentage of subjects with field constriction on first conclusive examination. Two different definitions of conclusive examination were used. The strict definition was 'normal' or 'abnormal' and the broad definition also included 'inconclusive.' Abnormal was further categorized as abnormal of identified etiology and abnormal of unidentified etiology. Fields of unidentified etiology were further categorized as bilateral concentric peripheral constriction or other pattern.

  Reviewer: Notably, the study report discusses how an initial analysis of field defects was deemed unacceptable because too high a percentage of patients who had never taken VGB were found to have VGB-like visual field defects. This led to changes in the definitions used for abnormal fields. Such post-hoc

changes to analysis methods decrease the confidence that can be placed in study findings.

- Period prevalence was defined by Ovation as at least one occurrence of 'bilateral concentric peripheral constriction' (BCPC) upon entry into or over the course of the study.

- The submission describes how methods of field analysis were modified based on initial analysis of the data:

  "The metric properties of the outcomes are not yet known, although the interpretation of the results depends on these properties and this may lead to erroneous conclusions on clinical course. Therefore the inter-techniques agreement will be studied from the 5th IA [interim analysis] onwards to find out the extent to which different techniques lead to different conclusions."

  "There is no final statistical analysis plan, as the tests used will depend on the results obtained with the current plan. The statistics will evolve as required." [study4020.pdf, page 572-573 of 3105]

Data Integrity

Discussions from the study steering committee excerpted below offer insight into problems with study design and data analysis:

> "As a general consideration, the experts stressed the difficulty to obtain perimetries of good quality: only 10% Goldmann and 50-60% suprathreshold and threshold perimetries are of good quality." *October 1999*
> **Reviewer: Few of the visual fields were submitted to FDA, and reliability of findings could not be adequately evaluated.**
>
> "Concern [was] expressed by the neurologists regarding a "selection bias": current vigabatrin patients have already undergone visual field assessment(s). Since the vigabatrin is withdrawn in most cases where a typical VFD is diagnosed, as a consequence nearly all patients remaining under vigabatrin have no VFD." *September 1999*
> **Reviewer: Potentially also patients with mild defects would have preferentially remained on VGB, biasing the average to less severe defects.**
>
> "The company stressed again that they had concerns regarding the reliability of the data currently gathered by the 4020 study. The CPMP [Committee for Proprietary Medicinal Products, responsible for preparing opinions on questions concerning medicinal products for human use for the EMEA] had also expressed concerns over methodological issues and the data quality." *February, March 2002*

"It was noted that the majority of data presented was derived from centres in France and that the centres may have not used the recommended perimetry techniques or may not have carried out the tests under optimal conditions." *January 2003*
Reviewer note: Centers in France enrolled the majority of patients, 437/735

"Although at one point in the study there was an attempt to standardise the perimetry technique, not all centres complied. In addition, no allowance is made for increased patient compliance over visits (learning effect) or for the increased confidence of the expert in designating what is or isn't field loss. The importance of the latter may vary, depending on which technique was used. Time to onset is not equivalent to the time to detection. The clinical course also has to be considered. For a given patient this might only apply from when the perimetry was changed or, if the right technique was used in the first place, it might apply from baseline." *January 2003*

"The original patients included in France were generally evaluated using kinetic perimetry methods. These have since been largely superseded by static perimetry" *January 2003*
Reviewer: Even longitudinal data for individual patients appears suspect because the methods of perimetry changed during the course of follow-up. Depending on the ability of the patient and tester, a given perimetry technique can be more or less sensitive and reliable than another.

"Disparities in the frequency of visual field defects observed between countries, between the study populations and over time all indicate that bias may have been introduced into the study, affecting the representativity of the results." *June 2004*

"Much of the recruitment in countries other than France has occurred after the implementation of the educational programme aimed at training investigators in the optimal use and interpretation of perimetry testing." *June 2004*
Reviewer: Study quality control is not well described in the submission, but appears to be poor.

Disqualified Centers
A site in Italy was found to have committed scientific fraud, and the 18 patients enrolled from that site were not included in data analysis.

No data validation plan was developed for the study, and there was no data monitoring committee.

Major findings from study 4020.
The sponsor notes that the study authors concluded that a true prevalence rate could not be established from this study, due to limitations in study methodology, randomization issues, the exclusion of subjects with preexisting peripheral VFD, and the large proportion of subjects lacking conclusive perimetry data. The sponsor makes the following conclusions:

- Fields defined as having the typical 'bilateral concentric constriction' caused by VGB had more marked nasal severity.
  Reviewer: While this pattern of field defect often occurs, concern remains that other types of field defect might have been missed because they did not fit the 'expected' pattern.
- The prevalence of a confirmed Sabril-induced peripheral VFD was approximately 25% of adult patients and 15% of children receiving long-term Sabril therapy
  Reviewer: Even in this potentially biased sample, '*Confirmed*' field defects sets only a *lower limit* for the proportion of patients with field defect, and can not be considered a reliable estimate of the actual risk of developing visual field defect.
- Individuals who do develop VFD generally experience a decrease in lateral vision from the normal of 90 degrees to, on average, 71.1 degrees
  Reviewer: Average severity of defect is highly sensitive to bias from false positive fields showing apparent mild defects. Incidence of false positives is unknown in this study, but may be substantial because of the small number of fields completed by most patients and the fact that perimetry is subject to large patient learning effects and inter-test variation. Also, it should be noted that lateral vision is often the least affected by VGB; nasal fields were constricted to a median of 18 degrees, severely decreased from the normal of 60 degrees.
- Bilateral concentric peripheral constriction appeared to have deteriorated over serial perimetry assessments in 29% of overall cases. In patients with five field assessments, 12 of 33 adults (35%) still taking VGB deteriorated compared to 3 of 17 (13.0%) who never took VGB.
  Reviewer: The high incidence of deterioration in patients who never took VGB raises concern about a high false-positive rate. The higher progression rate in VGB patients versus controls still suggests progression occurs in patients on VGB, but the magnitude of progression can not be reliably estimated from this data. The submission notes that the sensitivity of the method used to determine progression is not known, and that this rate should be considered a preliminary estimate. Progression was only evaluated for fields that were already abnormal, and thus does not capture fields deteriorating from normal to abnormal.
- Risk factors for the development of BCPC visual field defects included treatment duration, average daily dose, and gender.
  - Males were ≈1.5 times more likely to have field constriction than females

  Reviewer: No clear bias was evident in the derivation of this number, and a number of other published case-series also suggest increased prevalence in males. However, non-random enrollment and other potential biases weakens confidence in this finding.
  - Logistic modeling of visual field loss identified a strong relationship between vigabatrin exposure and development of visual field defects, with the risk being greater the longer the cumulative treatment exposure. The model demonstrated progressive accrual of risk with continued exposure and revealed no evidence for a plateau over a ten-year period.

Reviewer: Since modeling is based on potentially biased data, results may not be reliable.

- The sponsor concluded that results from the ophthalmic disability questionnaire were inconclusive
    - The sponsor reports that at least one disability item was endorsed by 27% of children and 32% of adults, but the proportions were similar in subjects with abnormal visual fields (35%) and normal visual fields (30%).

  Review agrees.
- The average time to a confirmed peripheral VFD in patients exposed to Sabril was 6.3 years in adults and 6.5 years in children.

  Reviewer: This is strongly biased by the time between starting VGB and enrolling in the study, and does not reflect the biology of VGB adverse visual effects.
- The earliest onset of the peripheral VFD was 12 months in adults and 16 months in children.

  Reviewer: The average time of VGB treatment before enrollment was 2- to 4 years, such that the study was poorly designed to measure earliest onset of field defect. This estimate provides only an upper bound of when field defect develops, not a lower bound.

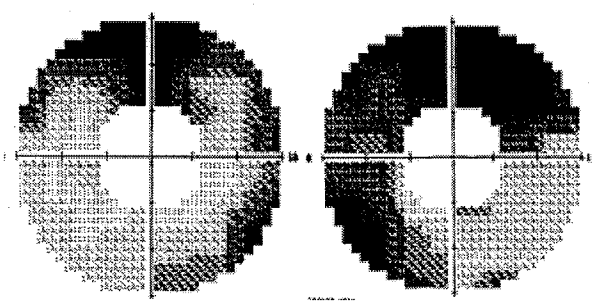
Additional findings

- There was a strong association between the presence of field constriction and the use of the recommended static perimetry technique

Reviewer: Reliable perimetry depends on the skill of both the patient and the operator. While this finding suggests that static perimetry may be more sensitive than kinetic perimetry for detecting VGB-induced field defects, it may also reflect differences in execution of kinetic versus static perimetry.

Cases of interest

Case 1
Subject 006, Center 3
63 days of VGB use
Peripheral fields (30-60 degrees), show ring scotoma with temporal sparing, consistent with most common pattern of VGB-associated field defect.



Reviewer: This case suggests onset of VGB visual field loss at 2 months or less.

Cases 2 and 3
Reviewer: The difficulty of perimetric monitoring in epilepsy is illustrated by the narratives of these 2 cases (paraphrased from submission), which are typical of many case reports in study 4020:

Site 17, subject 17

> This 18 year old man had taken VGB 1g/day for 6 years prior to enrollment, and continued the same dose during the study. He had an ocular history of amblyopia, strabismus, and nystagmus. The first field test was technically limited. Results of visits 2 and 4 were inconclusive. Visits 5, 6, and 7 showed a field defect related to his right neonatal intracranial hemorrhage. The sponsor noted that 'underlying visual disorder makes it difficult to interpret any vigabatrin related defects in this subject.'

Subject 023

> This 28 year old male had a history of vigabatrin usage 1000-1500 mg/day for about 1 year, stopping prior to the start of study 4020. He had no symptoms per questionnaire initially but later reported he noticed difficulty in lateral vision to the left and right, and noticed worsening of vision for shapes, and had vision disorder when walking in the street. His initial visual fields were read as normal at visits 1, 2, and 4. Visits 3 and 5 were technically correct but outcome inconclusive. His visual field at visit 6 was read as VGB-attributed visual field loss.

Reviewer discussion of study 4020.
Study 4020 suffers from multiple serious shortcomings in study design, execution, and analysis. The method of selection of study population was susceptible to multiple types of bias, perimetric data was collected using inconsistent methods (even within-patient), and data analysis methods were modified post-hoc, potentially biasing findings towards prior expectations. As a result, this review finds most of the data and conclusions unreliable. This is particularly true for estimates of incidence, prevalence, and severity.

c. *'Pooled Cohort Study'*

As described briefly first in PSUR 5, a cohort of VGB users was assembled from a variety of studies (Table 2) and tested for visual field defect. The cohort apparently consisted of 367 of the total 403 VGB-exposed patients from these studies. Of the 367 patients, 335 had usable visual fields, while the remaining 32 were excluded from analysis as either unreliable or uninterpretable.
Reviewer: Perimetry data from a high percentage of a defined group of study patients exposed to VGB for varying lengths of time was thus apparently captured.

Table 2: Studies contributing to cohort study of field defect

Country	Study Number	Phase	Treatment Regimen	Vigabatrin N=403	Non-Vigabatrin N=112
Finland	71754-3-W-007	III	Vigabatrin monotherapy	11	
	097.335	III	VGB monotherapy	23	
Japan	JGVG-CL-201*	IIa	VGB add-on therapy	3	
	JGVG-CL-202	IIb	VGB add-on therapy	33	
	JGVG-CL-301	III	VGB add-on therapy	37	
	JGVG-CL-302	III	VGB add-on therapy	29	
US	VGPR0098	IIIb	VGB add-on or monotherapy	39	11
US	201			70**	
UK	VIGAB/4001	IV	VGB add-on or monotherapy	26	5
Canada	Ottawa	IV	VGB add-on or monotherapy	37	
Spain	Valencia	IV	VGB add-on therapy	30	
Germany	BRD/S2	IV	VGB add-on or monotherapy	32	39
Germany	M071754/4017	IV	Non-GABA-ergic AED		42
Germany	Pilot study	IV	Non-GABA-ergic AED		15
Australia	Matched pairs	IV	VGB add-on therapy	33**	

* Includes one patient on compassionate use; ** include a total of 36 children <14

Baseline variables including age, duration and cumulative dose of VGB, duration of epilepsy, and weight differed among the studies (Table 3)

Reviewer: Baseline differences among studies weaken confidence in modeling derived from combined analysis.

Table 3: Baseline Characteristics in Cohort Study

	Male gender		Age (yrs)		Duration of vigabatrin Rx (yrs)		Duration of epilepsy (yrs)		Weight (kg)		Cumulative dose (kg)	
	N	(%)	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Adults												
Finland	11	39	36.4	15.7	6.1	2.2	9.7	7.3	73.9	16.0	5.9	3.2
Japan	102	49	31.5	11.1	2.4	1.9	24.2	9.9	57.9	10.2	2.1	2.0
US	32	52	27.8	16.0	3.1	1.5	-	-	-	-	4.3	2.5
UK	10	40	29.8	10.9	5.4	2.1	22.6	11.5	74.6	15.9	4.3	2.5
Germany	19	50	40.6	10.8	2.7	2.5	-	-	-	-	2.3	2.4
Canada	15	52	33.5	11.4	2.8	1.8	-	-	-	-		
Spain	16	59	32.6	14.0	2.8	1.6	16.0	13.5	-	-	2.4	1.7
Australia	18	50	31.7	12.4	4.2	2.3	18.5	11.2	-	-	3.8	2.4
Total Adults	**223**	**49**	**32.2**	**12.8**	**3.1**	**2.2**	**21.5**	**11.2**	**65.4**	**16.2**	**3.8**	**2.4**
Children	12	44	9.6	2.0	2.5	1.4	-	-	-	-	3.0	1.7

Visual fields were measured with a variety of instruments and examination techniques. Each patient underwent field exam at only one time point, with repeat exam if abnormality was suspected or if the results were deemed unreliable (as described in Wild et al., 1999[1]). The PSUR states that fields were assessed independently of drug exposure using a pre-specified algorithm.

As described in PSUR 5, of the 335 usable patients, 105 had visual field loss. The prevalence of VGB field defect was 31% (95% CI 25-36%), and for patients with more than 3 years of treatment was 36% (95% CI 29-43%). The severity of field loss ranged between a localized nasal defect between 30 and 40 degrees from fixation to severe concentric constriction. Field defect was considered to be 'profound' in about 1/3 of patients.

Reviewer: Severity was further graded on a 4-point scale of increasing severity, but the correlation of the 4-point severity scale with degrees of field loss was not provided in the study description in the PSURs. The sponsor indicated that the severity scale was defined in Wild et al., 1999. However, this publication described a 3-point scale of mild, moderate, and severe field defect, not a 4-point. It is not clear if 'grade 1'

[1] Wild, J.M. et al.. Characteristics of a Unique Visual Field Defect Attributed to Vigabatrin. Epilepsia 1999;40:1784-1794.

represents normal field, as the sponsor asserts. To summarize the grading method of Wild et al.[2], mild defect was to within about 30 to 35 degrees of fixation, moderate was within 20 to 25 degrees, and severe was closer than 15 or 20 degrees to fixation. The field severity in this study was grade 1 for 20 patients (22%), grade 2 for 29 (31%), grade 3 for 25 (27%), and grade 4 for 18 (20%).

For 165 evaluable patients unexposed to VGB, the overall prevalence of visual field defect was zero (upper 95% CI 2.2%)
Reviewer: It is striking that none of the control patients was diagnosed with a field defect. While findings were not described in detail, specificity may have been kept high by requiring field defects to be fairly severe before being called positive. This is supported by the grading scale, which somewhat surprisingly considered a deficit to within about 30 or 35 degrees of fixation to be only 'mild.'

In PSUR 7, data was added to this study for an additional 119 patients, for a total of 454 evaluable adult vigabatrin patients. In this larger cohort, 112 had a vigabatrin-attributed VFD.
Reviewer: The prevalence of VGB field defect was strikingly lower in the patients added between PSUR 5 and PSUR 7. There were only 7 cases in the additional 119 patients (6%) in PSUR 7, compared to 105 out of 335 patients (31%) reported in PSUR 5. It is not clear if factors such as shorter exposure in the added patients could explain this difference.

PSUR 7 reported that in 27 children ≤12 years old, prevalence of VGB field defect was 19% (95% CI 6%-38%).

Analysis of field severity by treatment duration showed that mean severity score was similar, about 2.5 on the 4 point severity scale, across groups exposed for a range of years from <1 to >7. Likewise, there was little relationship between cumulative VGB dose and field severity (Table 4).

[2] Wild, J.M. et al.. Characteristics of a Unique Visual Field Defect Attributed to Vigabatrin. Epilepsia 1999;40:1784-1794.

Table 4: Mean Field Severity by VGB Duration and Cumulative Dose

Treatment duration	Grade of VFD severity	
	N	Mean
<1 year	2	2.5
1 – 3 years	18	2.1
3 – 5 years	45	2.5
5 – 7 years	26	2.5
> 7 years	8	2.5
Total	**99**	**2.4**

Cumulative VGB dose	Grade of VFD severity	
	N	Mean
<1 kg	5	2.6
1 – 3 kg	27	2.4
3 – 5 kg	26	2.3
5 – 7 kg	15	2.5
> 7 kg	13	2.9
Total	**86**	**2.5**

Reviewer: This result should not be taken as evidence that an *individual* patient's defect stays of moderate severity even after many years of exposure. A more likely explanation is that the average stability of the cohort derives from some patients developing field defects early and progressing rapidly, combined with others developing field defects later and progressing more slowly. Thus, at <1 year, 2 patients who were presumably very sensitive to VGB adverse effects already developed moderate field defects. At year 2, even if these patients worsened, the *group* average would stay about the same if additional patients with newly developed *mild* field defects then entered the average. The average field severity of patients *with field deficits* wouldn't strikingly worsen until all at-risk patients developed field defect, thus halting the influx of less severely affected patients over time. In contrast, the average severity of *all patients* would behave more intuitively, worsening steadily with increasing exposure.

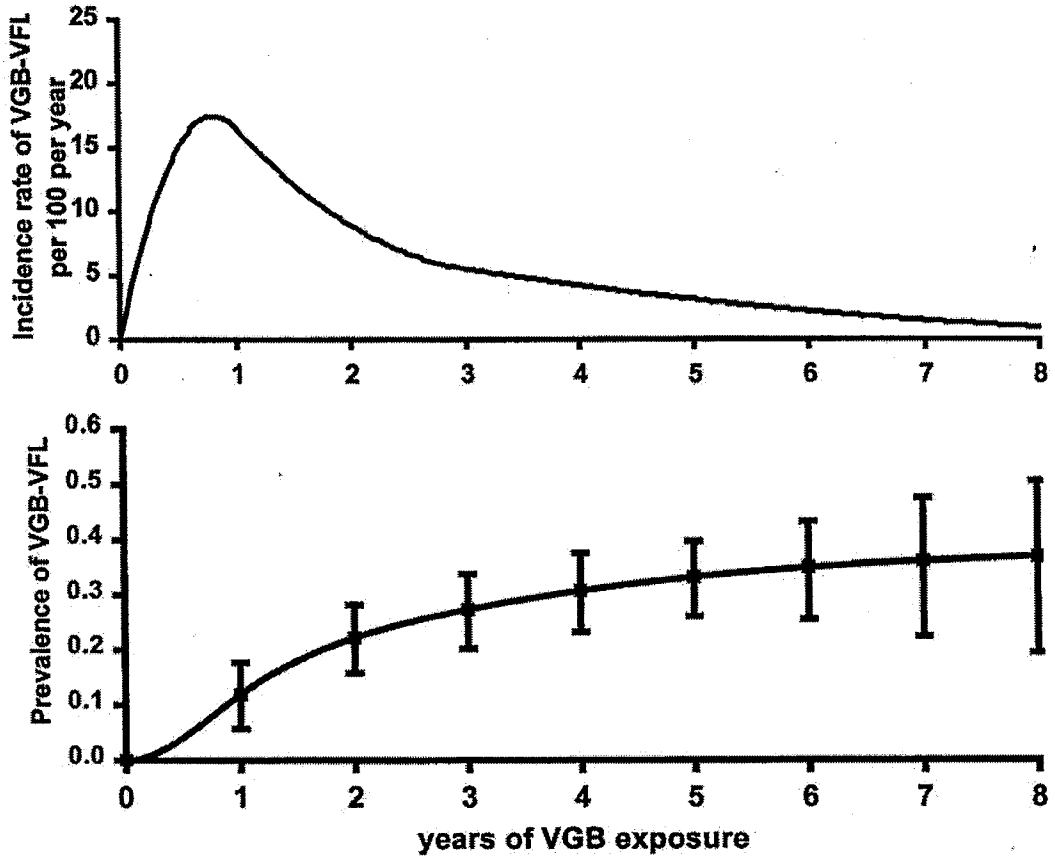
The PSUR notes that "only 8% of the patients tested had spontaneously complained of symptoms that could be related to the visual field defects."

Since patients in this cohort were tested after treatment with VGB for varying lengths of time (Table 5), it was possible for the sponsor to estimate the time to onset (Figure 1) and cumulative dose (Figure 2) to onset of visual field defects using a statistical approach that estimated the most likely time before the visual field test that the defect would have occurred. The maximum incidence of field defect occurred early, at less than 1 year, and then declined slowly over 8 years, but still with additional occurrences.

Table 5: VGB Dose and Duration at Time of Visual Field Test

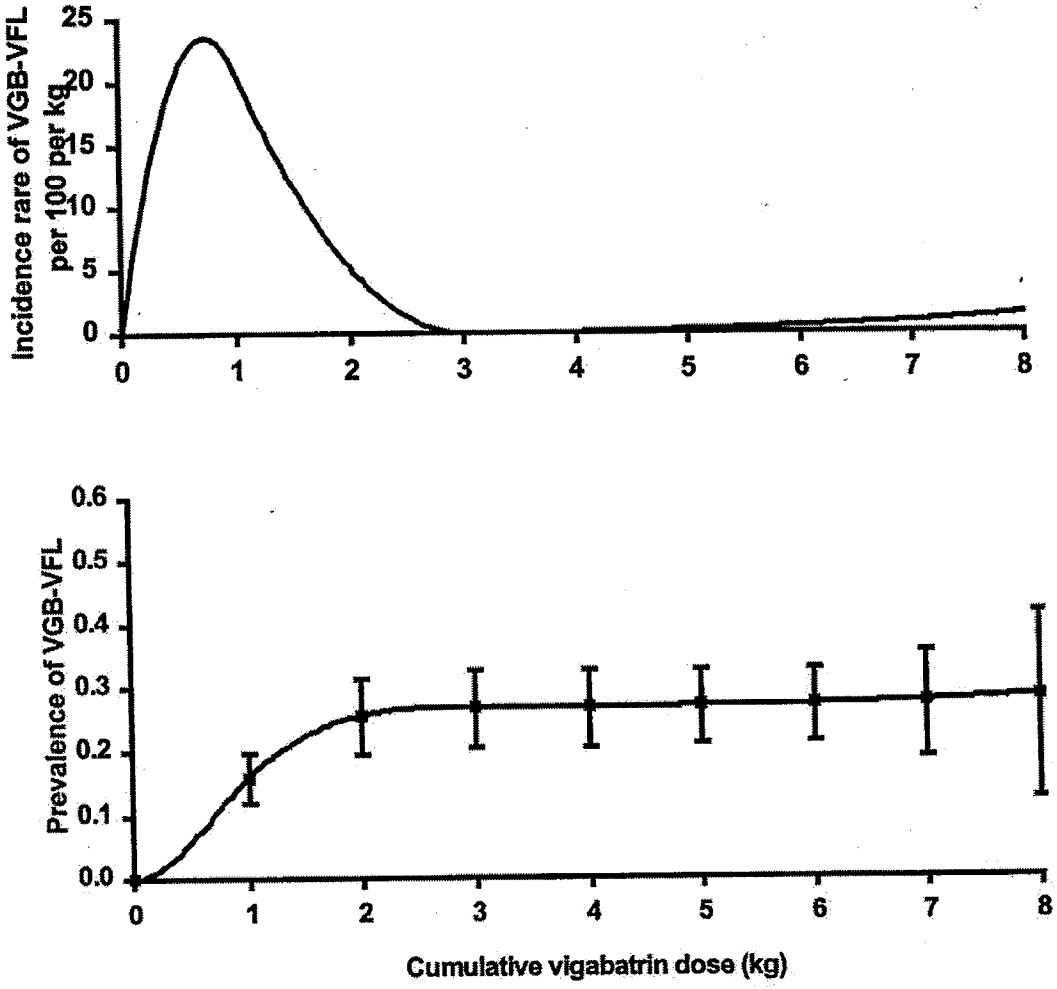
Cumulative VGB dose	Subjects	Duration of VGB therapy	Subjects
0-0.5 kg	79	0-0.5 year	64
0.5-1 kg	46	0.5-1 year	50
1-2 kg	54	1-2 year	59
2-3 kg	58	2-3 year	52
3-4 kg	50	3-4 year	84
4-5 kg	42	4-5 year	41
5-6 kg	37	5-6 year	57
6-7 kg	18	6-7 year	23
7-8 kg	13	7-8 year	10
8-9 kg	7	8-9 year	3
9- kg	12	9- year	8
Total	**N=416**	**Total**	**N=451**

Figure 1: Incidence and Prevalence of VGB Field Defect by Duration of Exposure



Reviewer: The data indicate a rapidly increasing risk of field defect in the first few months of VGB exposure, with risk of developing field defect still present for patients exposed for 8 years, albeit at a decreasing yearly rate.

Figure 2: Incidence and Prevalence of VGB Field Defect, by Cumulative Dose



Reviewer: Cumulative exposure is correlated with time of exposure in this population. Since cumulative dose is both a function of daily dose and time on treatment, the greater flattening of the dose curves compared to the time on treatment curves argues against a strong dose-dependence of risk of field defect, at least in the relatively narrow range used in these studies.

Risk Factors

Field defect occurred in 31% of all males (70/112) and 17% of all females (40/112). This increased prevalence in males was present in all countries from which patients were enrolled (Table 6).

When duration of VGB was stratified by high (>3 g/day) and low (<1.5 g/day) dose, the incidence rate for the high dose peaked at 0.75 years, while the incidence rate for the low dose peaked after 2.3 years.

Reviewer: This finding highlights the need to consider risk factors not only for occurrence of field defect, but also for time to onset of field defect.

The risk of field defect increased with duration of VGB use, but this finding was confounded by effect of cumulative VGB dose.

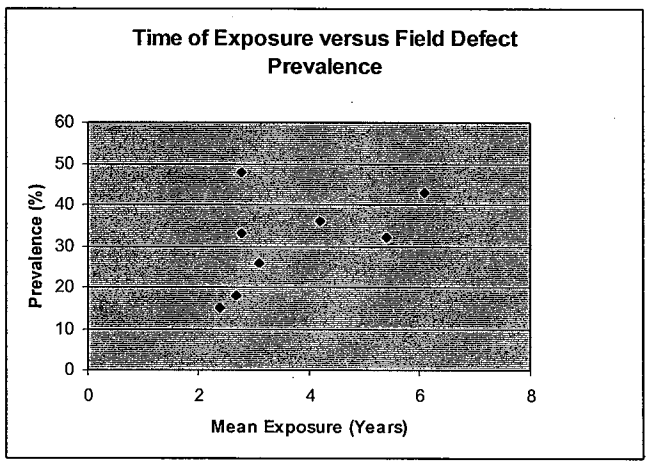
Type of epilepsy or ethnic origin was not reported to be a risk factor (Table 6).

Table 6: Field Defect by Country and Gender, Cohort Study

Country	Vigabatrin attributed VFDs			
	Male gender n=223	Female gender n=229	Total VFD	Total* N=454
Finland	6 (55%)	6 (35%)	12 (43%)	28
Japan	19 (19%)	12 (11%)	31 (15%)	208
US	11 (34%)	5 (17%)	16 (26%)	61
UK	5 (50%)	3 (20%)	8 (32%)	25
Germany	5 (26%)	2 (11%)	7 (18%)	38
Canada	9 (60%)	5 (36%)	14 (48%)	29
Spain*	6 (38%)	3 (27%)	9 (33%)	29
Australia	9 (50%)	4 (22%)	13 (36%)	36
Total	**70 (31%)**	**40 (17%)**	**110 (24%)**	**454**

*Gender unknown for 2 patients

Reviewer note: Baseline characteristics and exposure differed by country. For example, duration and cumulative dose in Japan was lower than in other countries, possible explaining the lower prevalence of field defects. The chart below shows prevalence of field defect in each country plotted against average years of exposure, and suggests that increase of field defect prevalence with exposure time may explain differences among countries.



In smokers or ex-smokers (N=111) no difference in relative risk of field defects was found (relative risk 0.9, 95% CI 0.5-1.5).

Reviewer Conclusions and Discussion, Cohort Study
While this study was not described in detail in the submission, several key characteristics of the study suggest that important insight can be gained into the VGB-induced visual field defect.

Most importantly, the study captured interpretable fields from a high percentage, perhaps close to 80%, of an identifiable cohort of patients that had been exposed to VGB for various lengths of time (although the cohort still reflects only those patients who had not dropped out of previous studies). This allowed the sponsor to model incidence and prevalence of field defect by time and total exposure. This model must still, however, be considered with caution because it is derived from combined data from studies of patients with different baseline characteristics and exposures, ranging from ≈2 years in Japan to ≈6 years in Finland.

While little information was provided about perimetric methods or data analysis, the low (zero) incidence of any field defects in the unexposed control population, and high incidence of severe field defects in VGB patients suggests that false-positive results were not a major confounder despite the fact that each patient was only tested at one time point. It appears that false-positives were kept low by not diagnosing even mild field defects until constriction to within about 30 or 35 degrees of fixation. Thus, the 'true' incidence of field constriction, as judged against normal fields that would be expected to be about 60 degrees on average, might have been underestimated by the study.

The following conclusions are drawn from this study:

- The incidence model suggests that visual field defects may begin within only weeks or a few months of starting VGB treatment.
- Peak incidence appears to occur after treatment of less than 1 year.
- ≈1/3 of patients developed visual field defects in the first few years of VGB use.
- ≈1/3 of field defects are severe, encroaching to within about 20 degrees of fixation.
- A continued risk of developing field defect extended past 8 years exposure, the limit of the data.
- Risk of field defect appeared higher (or occurred earlier) in men than in women.

d. *Study R003*

This non-comparative, *prospective* observational study enrolled 25 subjects from 4 centers in Canada (out of a planned 200 subjects). Subjects were treated with vigabatrin according to the clinical judgment of the investigator in accordance with the indication of VGB. The decision to treat patients with vigabatrin was independent of the trial protocol.

Static perimetry and ERG were performed every 3 months for all adult patients, and were evaluated by central evaluators. Suprathreshold perimetry using 120 point [60 degree] 3-zone strategy was the perimetry method of choice.

The median cumulative dose of VGB was about 1,100 g, and the median duration of treatment was about 500 days (range 2 to 988 days)

Seven patients (28%) developed visual field defect (Table 7). In 4 of these 7 the defect was graded as mild, while in 3 the defect was deemed moderate at first diagnosis.
Reviewer: The correspondence of severity grades to degrees of field constriction is not specified. John Wild was consulted for visual field interpretation, suggesting that as in the cohort study described above, mild defect corresponds to constriction to within about 30 to 35 degrees of fixation, and moderate corresponds to constriction to within about 20 to 25 degrees of fixation.

Table 7: Study R003 Serious Adverse Events

Subject number	Age/ Sex/ Race (i)	Adverse event as coded	Period (ii)	Exposure (iii)	Cumulative dose at SAE onset (g) (iv)	Duration of event (days)	Possible relation to vigabatrin	Intensity (v)	Action (vi)	Outcome (vii)
0300001	37/M/Asian	*Visual field defect	Post	680	1506.0	123	No	Mld		R w/o seq
0300005	40/F/White	*Visual field defect	On		2118.5		Yes	Mod	D/Cevn	Ongoing
0405001	50/F/White	*Depressed mood	On	11	7.5	20	Yes	Sev	D/Cevn	R w/o seq
		*Restless legs syndrome	On	11	7.5	20	Yes	Mod	D/Cevn	R w/o seq
		*Hallucination, visual	On	11	7.5	20	Yes	Mod	D/Cevn	R w/o seq
		*Convulsion	Post	37	18	3	No	Mod	Other	R w/o seq
0405003	43/F/White	*Mood swings	On	14	82.5	70	Yes	Mod	D/Cevn	R w/o seq
		*Visual field defect	Post	148	82.5		Yes	Mod		Ongoing
0405006	33/M/White	*Visual field defect	On	706	1553.0		Yes	Mld	N/C	Ongoing
0405007	32/M/White	*Visual field defect	On	402	1908.5		Yes	Mld	N/C	Ongoing
0405010	58/M/White	*Visual field defect	On	254	423.5		Yes	Mod	D/Cevn	Ongoing
		*Convulsion	Post	519	631.5	1	No			Death
0405011	32/F/White	*Drug hypersensitivity	On	1	1.0		Yes	Mod	D/Cevn	R w/o seq
0415008	52/F/White	*Visual field defect	On	444	867		Yes	Mld	N/C	Ongoing

Note:
(i) Sex: M=male, F=female
(ii) On = On-treatment; Post = Post-treatment
(iii) Day of study medication when event occurred
(iv) Cumulative dose calculated from Appendix C.1.2 Listing 17
(v) Mld = mild; Mod = moderate; Sev = severe
(vi) N/C = no change; D/Cevn = discontinued due to the event
(vii) R w/o seq = recovered without sequelae
Key to symbols: * = serious adverse event; + = alert term; & = sponsor assessment of possible relationship differs from that of investigator assessment given in table

The following patient is particularly remarkable for showing that field defect can develop rapidly, escape perimetric diagnosis until of moderate severity, and totally escape ERG diagnosis.

Subject 405003
The subject is a 44 year old woman who took VGB for 63 days, beginning at 500 mg/day and increasing to 2000 mg/day, with a cumulative dose of 82.5 g. Her initial baseline static field test was outside of normal limits, but on repeat testing was "within normal limits". Two months after study medication was discontinued for a non-ophthalmic adverse event, visual field testing showed moderate superior nasal defects. Repeat exam confirmed the field defect.

ERG did not detect retinal abnormality (Table 8):

Table 8: Flicker, subject 405003

Treatment day	Flicker (μV)
-28	49
28	55
56	57
148	57
317	69

Only one subject (0405010) had a visual field defect detected by ERG examination. The subject had an asymptomatic bilateral nasal peripheral acquired field defect that was considered to be moderate in intensity.

Reviewer Discussion

While this study was small, it is valuable for several reasons. The study was prospective, and should represent a less biased patient sample. Patients were monitored with perimetry in a manner similar to what might occur in clinical practice, thus providing an estimate of how successful safety monitoring might be at detecting early field constriction. ERG flicker testing was also conducted, providing information on how field defect correlates with ERG. This review concludes the following from this study:

- Visual field defect occurs in about 1/3rd of patients after less than 2 years of treatment.
- Early onset of visual field defect is common. In patient 405003, field defect was detected after only 63 days of treatment (including titration period starting at a low dose of 500 mg/day) and a cumulative dose of 82.5 g. Importantly, the defect diagnosed after 63 days likely did not *occur on the day of diagnosis*, but rather developed some time *before* diagnosis. This suggests that this field defect of moderate severity developed at *less than 63 days* of treatment. If the study had been larger, likelihood suggests that outliers would have been identified even earlier after initiating VGB. Patient 405010 had onset of field defect of moderate severity after only 254 days and a cumulative dose of 423.5 g, again with true onset of the defect likely at less than the time to diagnosis.
- *Perimetry appears unable to reliably detect mild field defects.* Only 4 of 7 defects were identified while mild. The remaining 3 were not detected until of moderate severity. Moderate severity defects under the grading scale likely used in this study correspond to constriction to within about 20 or 25 degrees of fixation.
- *ERG appears ineffective at detecting retinal damage corresponding to mild or even moderate field defects.* None of the mild defects and only 1 of 3 moderate defects were detected by ERG.

e. Study 4021

This was an open-label observational study conducted in a single center in Finland. The study enrolled 29 current or previous VGB patients from a single center, who were either still undergoing therapy or had discontinued due to VFD. Nine of 29 patients had a visual

field defect attributed to VGB, and 1 had a field defect attributed by the investigator to other causes. Seven of 18 patients who underwent ERG had abnormalities, but the investigator concluded that concordance between ERGs and peripheral VFD could not be confirmed due to methodology used for the ERG assays. Over 2.5 years of follow-up, 14 patients were monitored. Nine had no apparent change in visual fields, one demonstrated progressive field loss in one eye, and 4 showed apparent lessening of field defect, but the investigator concluded that reliable evaluation of progression or regression could not be made owing to variability in field assessments.

Reviewer discussion
Few reliable conclusions can be made from this data. If anything, the study adds supports that ERG findings are difficult to correlate with perimetry, and that perimetry is difficult to perform reliably.

f. *Study 4103*

The study called for 170 patients from 5 countries, but only 2 centers enrolled 23 subjects, and the study was terminated.

Reviewer discussion
Little can be concluded from this study

g. *Sabril/Sabrilex (Scope) Study*

This was a survey study designed to assess the compliance of VGB prescribers in the European Union (EU) with guidelines for ophthalmic monitoring of patients given VGB. The survey was completed by patients, but only 22% responded. The study was terminated early and deemed not to have met objectives.

Reviewer discussion
Insufficient response renders the study uninterpretable.

h. *Glasgow study*

This study is only briefly described in the submission, but is noted to be the same as McDonagh et al.[3]. The sponsor presents data on color vision and visual acuity from 56 patients on VGB and 49 previously on VGB. Compared to patients either on other GABAergic drugs or never on GABAergic drugs, there were no apparent differences in color vision or visual acuity associated with VGB.

Reviewer discussion

[3] McDonagh et al., Peripheral retinal dysfunction in patients taking vigabatrin. Neurology 2003;61:1690-1694.

Insufficient data is presented in either the submission or the publication to judge the reliability of study findings (see additional discussion under Visual Acuity, section 10a).

6. Ophthalmic Safety Studies in Infantile Spasms and Children

a. *Toronto Study (Westall)*

This ongoing study was conducted by Carol Westall who heads the vision testing laboratory at the Hospital for Sick Children in Toronto. The sponsor has supported the study since 2005. No formal study protocol was available for review.

The majority of IS patients in the region are treated at this center, and the sponsor asserts that the study subjects should therefore be representative of the overall population of VGB-treated IS patients.
Reviewer: Speculatively, a center highly specialized in the technically difficult ophthalmic exam of IS patients may provide more reliable diagnosis than might be provided in less experienced centers that might provide the bulk of care to U.S. patients.

Ophthalmic exam including ERG was conducted every 6 months, although ongoing examinations now occur every 3 months (the sponsor notes that this is a limitation in interpretation of these data).

The study had both a prospective and retrospective component. Prospective patients had baseline exams near the time of initiating VGB, while retrospective patients were followed after varying times of VGB treatment.

Study population:

- 246 total infants (most with IS)
- 117 with baseline and at least one post-baseline exam (prospective arm)
- 85 with at least one exam, but no baseline exam (retrospective arm).
- 179 treated with VGB, with 117 discontinued VGB during study
- Median age of all subject at most recent ERG test was 2.2 years

Reviewer: **While this study was relatively large and had a prospective arm, patients were not followed very long, such that important questions about defect progression or functional outcome can not be addressed.**
Table 9 displays the number of visits for prospective and retrospective patients. The average patient had just over 2 exams, and was followed for between 6 and 12 months (Table 10).
Reviewer: While this study was relatively large and had a prospective arm, patients were not followed very long, such that important questions about defect progression or functional outcome can not be addressed.

Table 9: Number of Post-Baseline ERG Tests, Toronto Study

Number of Post-Baseline ERG tests	Prospective (N=117) n (%)	Retrospective (N=85) n (%)	Prospective + Retrospective (N=202) n (%)
1	28 (23.9)	21 (24.7)	49 (24.3)
2	28 (23.9)	19 (22.4)	47 (23.3)
3	26 (22.2)	19 (22.4)	45 (22.3)
4	17 (14.5)	10 (11.8)	27 (13.4)
5	13 (11.1)	7 (8.2)	20 (9.9)
6	3 (2.6)	3 (3.5)	6 (3.0)
7	1 (0.9)	1 (1.2)	2 (1.0)
8	0 (0.0)	3 (3.5)	3 (1.5)
9	1 (0.9)	1 (1.2)	2 (1.0)
10	0 (0.0)	1 (1.2)	1 (0.5)

Note: Prospective subjects have a baseline ERG and at least one post-baseline ERG.
Retrospective subjects have no baseline ERG.
t_visits_after.sas

Table 10: Duration of VGB Therapy, Toronto Study

Duration of Therapy	Prospective (N=117) n (%)	Retrospective (N=85) n (%)	Prospective + Retrospective (N=202) n (%)	Baseline Only (N=44) n (%)
>1 wk-<3 mo	9 (7.7)	7 (8.2)	16 (7.9)	42 (95.5)
3-<6 mo	18 (15.4)	8 (9.4)	26 (12.9)	1 (2.3)
6-<12 mo	37 (31.6)	19 (22.4)	56 (27.7)	1 (2.3)
12-<18 mo	16 (13.7)	9 (10.6)	25 (12.4)	0 (0.0)
18-<24 mo	18 (15.4)	9 (10.6)	27 (13.4)	0 (0.0)
24-<30 mo	9 (7.7)	5 (5.9)	14 (6.9)	0 (0.0)
30-<36 mo	3 (2.6)	3 (3.5)	6 (3.0)	0 (0.0)
3 yrs	2 (1.7)	6 (7.1)	8 (4.0)	0 (0.0)
4 yrs	2 (1.7)	5 (5.9)	7 (3.5)	0 (0.0)
5 yrs	1 (0.9)	5 (5.9)	6 (3.0)	0 (0.0)
6 yrs	2 (1.7)	2 (2.4)	4 (2.0)	0 (0.0)
7 yrs	0 (0.0)	2 (2.4)	2 (1.0)	0 (0.0)
8 yrs	0 (0.0)	2 (2.4)	2 (1.0)	0 (0.0)
10 yrs	0 (0.0)	2 (2.4)	2 (1.0)	0 (0.0)
11 yrs	0 (0.0)	1 (1.2)	1 (0.5)	0 (0.0)

Note: Prospective subjects have a baseline ERG and at least one post-baseline ERG.
Retrospective subjects have no baseline ERG.
Note: Duration of therapy measured from first dose to last dose. A missing last dose is taken as ongoing therapy, in which case duration is measured from first dose to last ERG visit. Subjects with last ERG visit prior to first dose have duration of 0.
t_demog1.sas

Of the patients already taking VGB before first exam, 49 of 85 began ≤ 6 months previously.

In the prospective cohort, most subjects (77%) had an ERG on the day of first dose or within the week immediately following the first dose. Eight of the 117 patients in the prospective cohort had ERG >2 months after starting VGB, and another had ERG >1 month after starting VGB.

In the sponsor's analysis, a replicated abnormality on ERG testing was defined as abnormality on two consecutive exams, and a sustained abnormality was defined as abnormality observed on the *last* two examinations.
Reviewer: The true sensitivity and specificity of ERG testing is not reflected in these definitions. A 'sustained' abnormality is in *no respects* equivalent to a 'true positive.' ERG results suffered from high noise, such that two consecutive abnormal results could have occurred by chance alone. Available data is fundamentally insufficient to determine the relationship of the sponsor's measures to true test performance. .

Significant change was defined as 30 Hz flicker amplitude less than lower limit of age matched control data (2.5th percentile) *or* a significant worsening of the ERG (change in ERG between visits is greater than normal inter-visit change).
Reviewer: 'Significant worsening' was not adequately defined, for example as a certain percent decrease.

The definition of an ERG abnormality also took into account that each ERG session could produce interpretable results from one eye, both eyes, or neither eye. The Toronto investigators developed a 'decision matrix' to define replicated or sustained abnormalities given the various combinations of results that could arise from two eyes over two ERG exams (Table 11).

Table 11: ERG Abnormality Decision Matrix

Toronto ERG Abnormality Analysis: Decision Matrix for Replicated and Sustained Abnormalities						
Left eye	Right eye	Left eye	Right eye	Patient-level assessment for replicated or sustained abnormality	Rule	Description of rule
Normal	Normal	Anything	Anything	Normal	A	Normal in both eyes at a visit precludes two abnormals in a row.
Normal	Abnormal	Normal	Abnormal	Abnormal	B	One eye consistently abnormal on the two visits
Normal	Abnormal	Normal	No data	Normal	D	No evidence of abnormality at either visit, or abnormality not confirmed
Normal	Abnormal	Abnormal	Normal	Normal	D	
Normal	Abnormal	Abnormal	Abnormal	Abnormal	B	
Normal	Abnormal	Abnormal	No data	Abnormal	F	
Normal	Abnormal	No data	Normal	Normal	D	
Normal	Abnormal	No data	Abnormal	Abnormal	B	
Normal	Abnormal	No data	No data	n/a	n/a	These cases, where both eyes provide no data, are listed as a formality and are not applicable. That is, if there is no data on either eye at a particular visit, it's as if that visit didn't exist and the algorithm has to search for a different visit to examine.
Normal	No data	Normal	Normal	Normal	A	
Normal	No data	Normal	Abnormal	Normal	D	
Normal	No data	Normal	No data	Normal	D	
Normal	No data	Abnormal	Normal	Normal	D	
Normal	No data	Abnormal	Abnormal	Normal	D	
Normal	No data	Abnormal	No data	Normal	D	
Normal	No data	No data	Normal	Normal	D	
Normal	No data	No data	Abnormal	Normal	D	
Normal	No data	No data	No data	n/a	n/a	
Abnormal	Normal	Normal	Normal	Normal	A	
Abnormal	Normal	Normal	Abnormal	Normal	D	
Abnormal	Normal	Normal	No data	Normal	D	
Abnormal	Normal	Abnormal	Normal	Abnormal	B	
Abnormal	Normal	Abnormal	Abnormal	Abnormal	B	
Abnormal	Normal	Abnormal	No data	Abnormal	B	
Abnormal	Normal	No data	Normal	Normal	D	
Abnormal	Normal	No data	Abnormal	Abnormal	F	This takes a conservative point of view. Although there is no confirmation of the abnormality in one eye because there is missing data, we accept the occurrence of the abnormality in the other eye at the second exam as surrogate confirmation to declare the patient abnormal.
Abnormal	Normal	No data	No data	n/a	n/a	
Abnormal	Abnormal	Normal	Normal	Normal	A	
Abnormal	Abnormal	Normal	Abnormal	Normal	B	
Abnormal	Abnormal	Normal	No data	Normal	D	
Abnormal	Abnormal	Abnormal	Normal	Abnormal	B	
Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	B	
Abnormal	Abnormal	Abnormal	No data	Abnormal	B	
Abnormal	Abnormal	No data	Normal	Normal	D	
Abnormal	Abnormal	No data	Abnormal	Abnormal	B	
Abnormal	Abnormal	No data	No data	n/a	n/a	
Abnormal	No data	Normal	Normal	Normal	A	
Abnormal	No data	Normal	Abnormal	Normal	D	
Abnormal	No data	Normal	No data	Normal	D	
Abnormal	No data	Abnormal	Normal	Abnormal	B	
Abnormal	No data	Abnormal	Abnormal	Abnormal	B	
Abnormal	No data	Abnormal	No data	Abnormal	B	
Abnormal	No data	No data	Normal	Normal	D	
Abnormal	No data	No data	Abnormal	Abnormal	F	
Abnormal	No data	No data	No data	n/a	n/a	
No data	Normal	Normal	Normal	Normal	A	
No data	Normal	Normal	Abnormal	Normal	D	
No data	Normal	Normal	No data	Normal	D	
No data	Normal	Abnormal	Normal	Normal	D	

Reviewer: The matrix assigns the label 'normal' or 'abnormal' in situations in which there appears to be little certainty as to the clinical condition of the patient. For

example, a patient is 'normal' if the left eye is normal on two consecutive exams, while the right eye is abnormal on the first and 'no data' is available for the second exam.]

The following are the major findings and conclusions of the sponsor:

- There is a high background rate of abnormality on 30 Hz flicker (37%) and cone b-wave (18%) in children not exposed to VGB
  Reviewer: Importantly, the sponsor does not discuss how testing would be interpreted in patients with abnormal baseline exams, who constitute a high percentage of all patients.
- Most subjects on VGB retained normal ERG parameters over 2 years
  Reviewer: Findings do not support the validity of this observation. While high inter-test variability prevented concluding with certainty that most subjects had *abnormal* ERG parameters, this is not equivalent to concluding that the subjects retained *normal* ERG parameters. At least one 30 Hz flicker abnormality occurred in 63% of subjects. The incidence of "sustained abnormality" was 25%, but this might provide only a *lower bound* on the true incidence of abnormal ERG (although since specificity appears low, the number also may not be reliable even as a lower bound).
- No subjects experienced single abnormal ERG from VGB before 3.1 months
  Reviewer: Findings do not support the validity of this observation. This result reflects *testing interval*, not necessarily time to onset of abnormality. Most patients weren't tested until after 6 months of VGB, and this patient wasn't tested until 3.1 months. (Of note, VGB has an initial pharmacological effect to increase ERG flicker voltage. This effect could delay apparent onset of abnormal ERG).
- For prospective patients, mean time to detection of ERG abnormality was 15.6 months.
  Reviewer: Time of onset of ERG abnormality would, on average, be earlier than time of detection. Most patients were examined every 6 months, so time to onset might be estimated by subtracting half the inter-test interval from the time of detection, yielding about 13 months.
- In the VGB-treated subjects who developed sustained abnormalities, the average times to sustained 30 Hz flicker and sustained cone b-wave abnormalities were 27 and 36 months, respectively.
  Reviewer: Findings do not support the validity of this observation. 'Sustained abnormality' is not an adequate measure of time to onset of ERG abnormality, but describes abnormality on the *final two* examinations, and thus depends on *time to the final two examinations*, not necessarily time to onset of the abnormality.
- Visual field abnormalities potentially related to VGB were found in 5 of 63 children (8%).
  Reviewer: Findings do not support the validity of this observation. Visual field was mainly tested by confrontation. The sensitivity of confrontation field testing is likely low in this population.
- No VGB-induced reductions in central visual acuity were found.

Reviewer: Findings do not support the validity of this observation. Most subjects were not tested or gave no response at any visit. When testing was conducted, mainly Teller acuity was used, which might not have detected acuity loss that was not relatively severe.

- Since a sizeable number of infants with IS have an age-adjusted abnormal reading at a single visit, to confirm VGB induced retinal injury requires 2 serial abnormal examinations
  Reviewer: Findings do not support the validity of this method. While the specificity of the flicker test was not discussed, it appears to be relatively low; the odds of two false positive results in a row is therefore fairly high. ***Critically, since serial testing is conducted, the odds of any two tests out of many being false positive is even higher.*** **Of similar concern, given a risk of false-negative results, to 'confirm' a true retinal injury would sometimes require fully four (or more) tests, not two; a 'true positive' followed by a 'false negative' would then require two more 'true positives' to 'confirm' retinal damage. With 3-month intervals between tests, a year of treatment and continued visual field deterioration would pass before diagnosis.**
- Significant correlation of male sex with effect on flicker response was not found
  Review findings agree. While it's difficult to explain a negative result, large test variability might have obscured any gender effect.
- Defects did not seem to appear after drug was discontinued.
  Reviewer: The data is inadequate to address the question. Almost no patients had more than 1 ERG exam after stopping VGB. At least 10 patients showed lower flicker results after stopping VGB, with some patients changing from 'normal' to 'abnormal' (e.g. patient 14IWL).
- Some subjects normalized parameters while still on drug and remained normal following discontinuation.
  Reviewer: This finding may only represent artifactual 'normalization' compared to earlier 'false positive'.

Individual Cases

Reviewer: 30-Hz data flicker data is presented below for 3 representative patients in the Westall study. The data raise concern about test performance and clinical interpretability. Apparent inter-test variability suggests that false-positive and false-negative findings would be common, and that early diagnosis of retinal damage would not be reliable. The third example gives the impression that test results decrease exponentially, as might be expected of VGB damage. Importantly, however, this case does not represent early diagnosis, only potential confirmation of irreversible retinal damage. (Of note, while this last example appears to show steady progression, it might actually represent only a chance pattern).

Subject 1528X

30 Hz flicker decreased from ≈120 μV to ≈65 μV after 6 months, a 50% decrease that would seem to indicate significant retinal damage (

Figure 3). However, VGB was continued, and the ERG then decreased further, to ≈35 μV at 1.5 years, at which time VGB was stopped. *Importantly, stopping VGB after the third exam would seemingly have failed to diagnose VGB early, since about 75% of the flicker voltage was already apparently lost to VGB damage.* At 2 years, however, the test returned to ≈100 μV, and stayed ≈100 μV at 2.5 years. Even looking at the full set of tests retrospectively, it is not clear if the changes in flicker values represent VGB toxicity or other types of variability.

Figure 3: Subject 1528x ERG Flicker

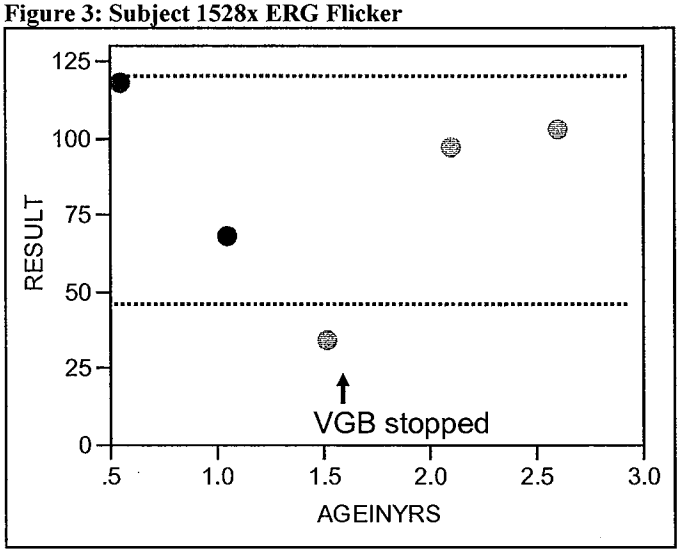


Figure 3: Upper and lower limit of normal are approximately represented by the red lines (normal age-related increase in values not shown). Red circles represent flicker result for left eye, and green for right eye. 'Result' is 30 Hz flicker result, in microvolts, versus patient age in years.

Subject 15AX2

Baseline flicker was below lower limit of normal, but VGB dosing continued. Data points appear scattered, and prevent clear clinical interpretation, even considering all 7 exams.

Figure 4: Subject 15AX2 ERG Flicker

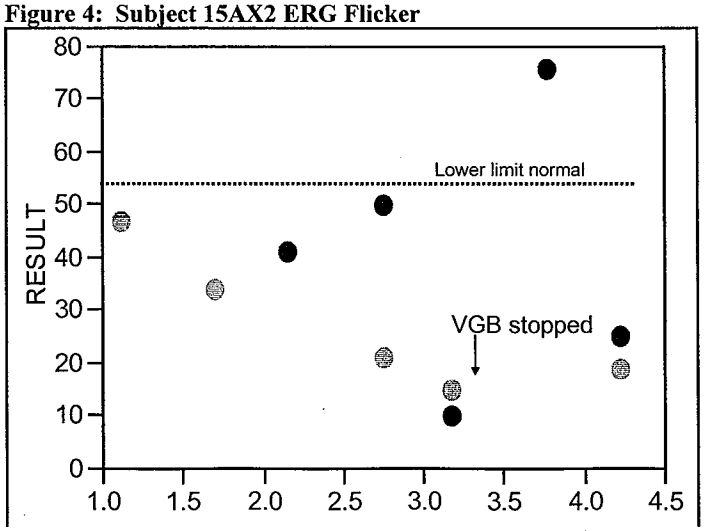


Figure 4: Lower limit of normal is approximately represented by the red line (normal age-related increase in value not shown). Red circles represent flicker result for left eye, and green for right eye. 'Result' is 30 Hz flicker result, in microvolts, versus patient age in years.

Subject 153OG

A series of decreasing test values for this patient might represent VGB damage. VGB was continued, and testing might only have confirmed irreversible retinal damage.

Figure 5: Subject 1530G ERG Flicker

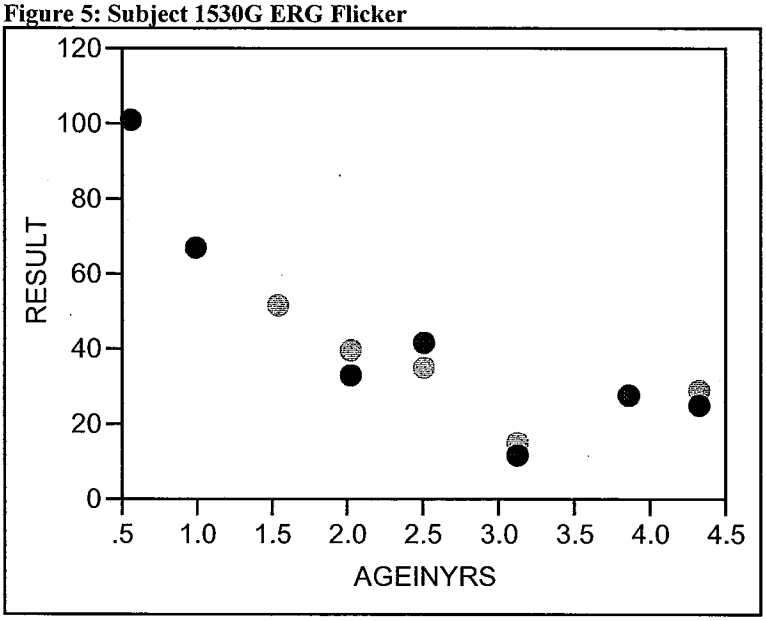


Figure 5: Red circles represent flicker result for left eye, and green for right eye. 'Result' is 30 Hz flicker result, in microvolts, versus patient age in years.

Westall Group Publications

Buncic JR et al., Characteristic retinal atrophy with secondary "inverse" optic atrophy identifies vigabatrin toxicity in children. Ophthalmology 2004;111:1935-42.

This paper concluded that the central as well as the peripheral retina is damaged by VGB:

- The macula is relatively spared, although superficial retinal light reflexes indicating wrinkling of the innermost retina suggest early macular toxicity as well.
- This pattern of atrophy also supports the notion of diffuse, but differential, involvement of peripheral and central retinal cells and the ganglion cell layer.
- Peripheral retinal atrophy occurs initially, with progression to involve the central retina with time.

This paper also detailed 3 cases that offer insight into the clinical monitoring of children on VGB.

- Case 1 suggests that ERG can fail to detect visual field constriction in children. This 10-year old girl took VGB 2.5 g/day for 4 years before first ERG exam. Goldman fields showed constriction to central 20 to 30 degrees in both eyes. ERG was within normal limits.
- Case 2 suggests that clinically disabling visual field defect can develop relatively precipitously after many years of VGB treatment. A 13-year old autistic, non-verbal boy with generalized tonic-clonic seizures had been treated with VGB 1 g/day for 6 years prior to ERG monitoring. First ERG was 'mildly abnormal' (of note, flicker was not recorded because of 'technical difficulties'). No visual difficulties were observed by the parent at the time. The patient returned to the clinic after 18 months. The parent now noted the patient was bumping into things and seemed not to see where he was walking. ERG was markedly reduced. Visual acuity was preserved to ≥20/40. The macula showed some involvement of both the nerve fiber layer and deeper layers.
- Case 3 illustrates several issues: a) practical difficulty of interpreting ERG findings, b) clinical disability from VGB in children, and c) potential progression of damage after stopping VGB. A 13-month old boy with trisomy 21 and IS since age 9-months had a normal ERG after 5 months of 500 mg/day VGB. At 11 months, ERG showed some reduction from the previous, but was still 'well within normal limits.' However, at 16 months the ERG 30-hz flicker was 'decreased dramatically to become 55% lower than age-expected.' VGB dose was decreased, but at 24 months the patient was noted to stare straight ahead, and to respond more to sound than to visual cues. The parent reported the need to attract the child's attention downward to his food at mealtimes by tapping on his plate. The ERG 30-hz flicker was similar to previous, but cone response had decreased to 42% below normal. The macula showed wrinkling and irregular thickness. VGB was stopped, but 3 months later the ERG showed further reduction in both eyes.

Reviewer Summary and Conclusions, Westall Experience

Large inter-test variability appears to limit the precision with which ERG can characterize or monitor for VGB-induced retinal injury, particularly for mild or moderate defects. Consistent with this, inter-test variability of ERG in normal volunteers suggests that a 50% decrease in flicker amplitude can be needed to detect a true decrease with 95% confidence (Fishman et al, 2003[4]).

As discussed in more detail in Section 7, sensitivity of ERG for even moderate vigabatrin visual damage appears to be low. Some published reports suggest that ERG might be more reliable for detecting severe vigabatrin retinal damage (for example, Harding et al., 2004, also discussed in section 7). However, testing would then be confirming damage rather than contributing to its prevention.

[4] Fishman GA et al., Short term intervisit variability of ERG amplitudes in normal subjects and patients with retinitis pigmentosa. Retina 1997;17:33-7.

Inter-test variability is particularly problematic when ERG is used for serial monitoring. False-negative or false-positive results are almost inevitable with repeat testing simply due to probability. Confirmatory testing for any single result is necessary, but delays diagnosis while retinal damage worsens. To speculate, increased frequency of ERG monitoring at intervals less than the proposed 3 months might improve the performance of ERG testing, but this would need to be studied.

The lack of data correlating ERG to visual field remains extremely problematic in clinical interpretation. Case 3 above suggests that decreased ERG flicker to just 55% below normal, essentially the level of first reliable detection of defect, can cause visual disability in children with IS.

b. *Boston children's hospital*

Retrospective data was collected from 47 children between 3 and 52 months of age treated at Boston's Children's Hospital. Most patients had only a single ERG test.

Descriptive statistics compared patients with 6 months of exposure to those with greater than 6 months of exposure to VGB.

The mean 30 Hz flicker amplitude was 77.6 μV (± 24.5μV) for those who were tested ≤6 months after the first VGB dose compared to 54.7 μV (±20.4μV) for subjects tested > 6 months after the first dose of VGB.

Reviewer discussion
Lack of serial exam data limits conclusions from this study. Findings support a positive correlation between exposure and severity of retinal damage.

c. *Study 4102*

This was a cross-sectional observational study of the prevalence of visual field defect in young children exposed to VGB. Thirty-nine children from 3 centers were enrolled, 3 with IS and the remaining with partial seizures.

Standard perimetry was used in 12 patients, H-stimulus was used to evaluate 35 patients, and ERG was used in 26 patients. On average, the patients received 1,400 mg/day for 2.2 years. Peripheral VFD was found in about 1/3 of patients.

Reviewer discussion
Only a brief description of study findings was provided by the sponsor. H-stimulus is noted by the sponsor as a potential method of monitoring VGB retinal damage, but insufficient data or analysis was provided for evaluation.

d. *Study 0201*

This was a 1 year open-label, follow-up, long-term maintenance study of vigabatrin as adjunctive therapy in 210 children with uncontrolled complex partial seizures. The study enrolled patients previously in study 0118 and 0221. Visual field exams (kinetic or static), ERGs, and VEPs were performed to characterize VGB effects. The VGB dose was adjusted to achieve the "optimum" dose for each patient. The total daily dose did not exceed 100 mg/kg/day or 6g, whichever was less.

ERG flicker amplitude decreased on average from 83 μV to 69 μV in patients followed longitudinally for 1 year (N=88). Flicker amplitude decreased in more than twice as many eyes as it increased (Table 12).

Table 12: Flicker Amplitude, Study 0201

	Flicker	
	Right eye (n=80)	*Left eye (n=81)*
Increase	8.8	8.6
Decrease	16.2	22.2

Table 12: Percent of eyes showing >44% change in flicker amplitude [From 'Study 0201a3.pdf]

13/69 with visual field tests had at least possible constriction. 11 of these 13 had progression of ERG abnormalities during the study. 23 of 51 patients with normal fields also showed ERG progression.

Snellen visual acuity was measured at baseline and end of study. The sponsor notes that acuity results could vary based on the subjective nature of the test, skill of examiner, and proper spectacle correction. There were 13 patients with greater than 2-line change in acuity in one or both eyes: 6 patients with a positive change, and 6 with a negative change.

Reviewer discussion

ERG findings support a positive association between VGB exposure and retinal damage, but the sensitivity and specificity of ERG testing didn't appear to be high enough for a useful clinical test (apparently false-positive ERG progression occurred in nearly half the patients).

7. ERG/Visual Field Correlation

ERG is an objective test of retinal function that does not require patient effort. The sponsor proposes ERG as the primary method of monitoring for VGB adverse visual events in young children and adults who are unable to perform perimetry. The sponsor asserts that specific ERG abnormalities, particularly 30 Hz flicker, have been shown to correspond with the VGB-induced VFD. The sponsor cites in particular the following published studies:

- *Comaish IF, Gorman C, Brimlow GM, et al. The effects of vigabatrin on electrophysiology and visual fields in epileptics: A controlled study with a discussion of possible mechanisms. Doc Ophthalmol 2002;104:195-212*

  Reviewer: Moderate correlation (r = 0.65) was found with cone maximal response b-wave amplitudes. However, a clinical test based on this strength of correlation would have poor sensitivity and specificity (as illustrated below in the discussion of Miller et al., 1999, which presented more detailed data).

- *Krauss GL, Johnson MA, Miller NR. Vigabatrin associated retinal cone system dysfunction: Electroretinogram and ophthalmologic findings. Neurology 1998;50:614-8.*

  Reviewer: This paper does not give adequate information to determine strength of association between ERG findings and visual field defect.

- *Harding GFA, Wild JM, Robertson KA, et al. Electro-oculography, electroretinography, visual evoked potentials and multifocal electroretinography in patients with vigabatrin-attributed visual field constriction. Epilepsia 2000;41:11:1420-31*

  Reviewer: 7 of 8 patients in the study had severe field constriction to within 10-15 degrees of fixation. The findings therefore don't address the sensitivity of ERG for detecting VGB before it is severe, which would much of the point of safety monitoring. Of note, the multifocal ERG data from patients with severe field constriction showed damage to the macula.

- *McDonagh J, Stepehen, LJ, Dolan FM, et al., Peripheral retinal dysfunction in patients taking vigabatrin. Neurology 2003;61: 1690-1694.*
  The sponsor asserts that this study documented that the VFD corresponds with abnormalities of flicker response.

  Reviewer: The referenced study does not support a strong correlation between visual field defect and flicker response; most patients with visual field defect had flicker response in the normal range (Figure 6).

Figure 6: Visual Field/ERG Correlation, McDonagh Data

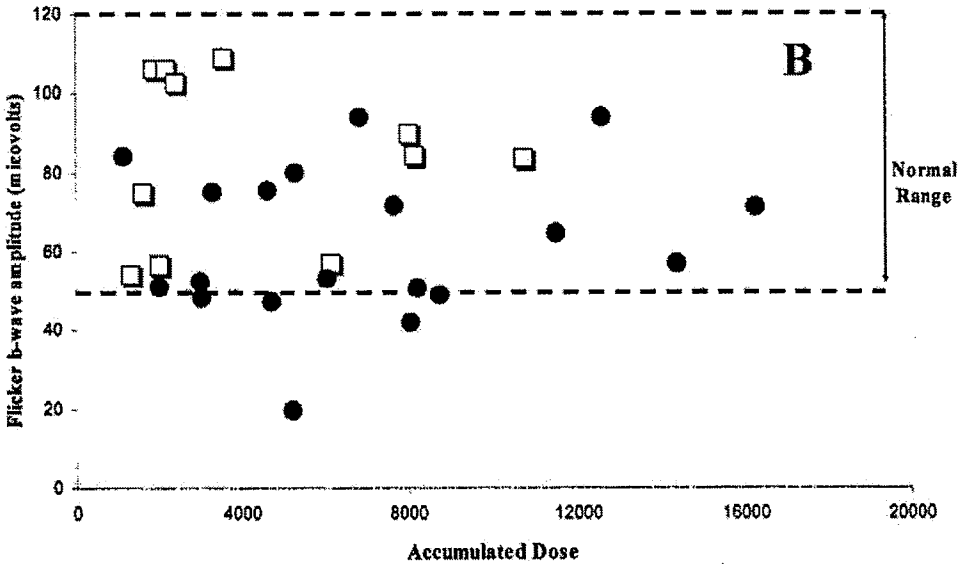


Figure 6: VGB patients with (solid circles) and without (open squares) bilateral visual field defects.

- *Miller NR, Johnson MA, Paul SR, et al. Visual dysfunction in patients receiving vigabatrin: Clinical and electrophysiologic findings. Neurology 1999;53:9:2082*

  This study found a correlation between ERG flicker response and degree of visual field constriction (Figure 7), with $r \approx 0.68$.

  Reviewer: While this r-value indicates a moderate correlation, it does not appear to be high enough to allow reliable conclusions about visual field based on flicker ERG data. For example, if 40 μV is considered upper limit of normal based on the control patients (Figure 7, triangles), then most VGB patients would be considered abnormal, even though nearly half the patients would have visual field results indistinguishable from normal (>50 mean radial degrees). Lowering the upper limit to 20 or 30 μV doesn't particularly improve the test, since that voltage could correspond to a visual field ranging from severely affected to normal.

Figure 7: Field/ERG Correlation, Miller et al., 1999

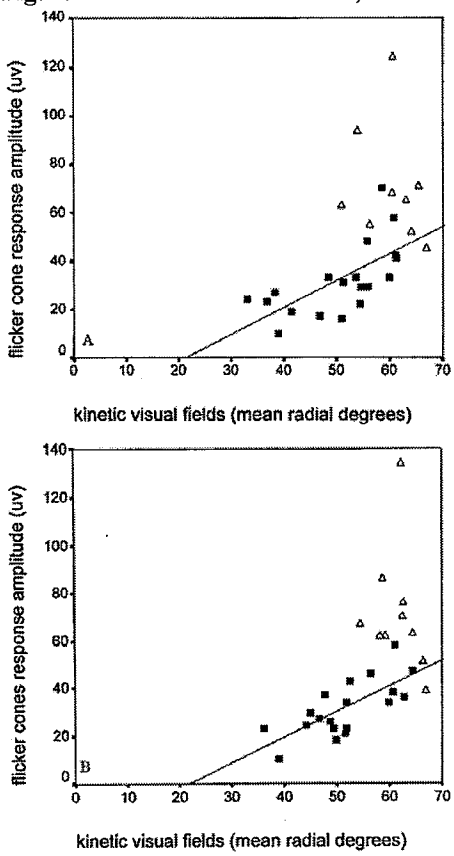


Figure 7: Filled squares are VGB patients, and triangles are controls. Right (top) and left (bottom) eyes shown separately.

- *Ponjavic V, Andreässon S. Multifocal ERG and full-field ERG in patients on longterm vigabatrin medication. Doc Ophthalmol 2001;102:63-72*

  The sponsor asserts that this paper reported that full-field ERGs are effective in monitoring the reduction in b-wave amplitude in patients over time. The paper reported that in 12 patients, 100% of patients with field defects had reduced 30 Hz flicker amplitude in at least one eye and that no patients with normal fields had reduced 30 Hz flicker amplitude.

  Reviewer: The field defects were severe. The findings therefore do not address how ERG might perform in early detection of VGB visual damage.

- *Brigell MG, Wild JM, Ruckh S. The effect of vigabatrin on visual function data from a long-term open-label add-on trial in patients with uncontrolled partial seizures [abstract]. Neurol 2000;54;S3:A308*

The sponsor asserts that Brigell used a combination of flicker amplitude and latency measurements of cone system and reported a 71% sensitivity of the ERG to monitor for the presence of the peripheral VFD in their patients.

Reviewer: This report is a brief meeting abstract, without adequate detail for interpretation.

- *Parks S, McDonagh J, Dolan F, Dutton GN, Keating D, Brodie M.J. Separating the transient physiological effects and retinotoxic effects of vigabatrin related retinal dysfunction using the wide field multifocal ERG. Invest Ophthalmol Vis Sci 2003;44:2721 [Abstract]*

  The sponsor asserts that this report found that 30 Hz flicker amplitude was the most sensitive predictor of peripheral VFD, with a threshold of <0.52 microvolts, the predictive value had a sensitivity of 100% and a specificity of 75%. Adding photopic a-b wave amplitude or the first oscillatory potential, the specificity could be increased to 83%.

  Reviewer: This report is a brief meeting abstract, without adequate detail for interpretation.

Reviewer Discussion, ERG Flicker Testing
This review finds little evidence that serial ERG monitoring would allow for reliable early diagnosis of VGB retinal damage. The available data suggest that ERG testing for anything other than severe VGB retinal damage would likely generate a high proportion of false-negative and false-positive results.

8. H-Stimulus

H-stimulus is a VEP method that compares peripheral and central retina. The stimulus consists of a central area from 0-5 degrees, an annulus of neutral density, and an outer stimulus form 30-60 degrees. The child needs to be cooperative and to look at the central stimulus. The sponsor asserts that it has been validated for assessing peripheral VFD in children 3 to 10 years of age with a sensitivity of 75% and a specificity of 87.5%,

The sponsor indicates that this technique is in use in Europe and Canada, and can also be used in adults with cognitive difficulties who cannot provide reliable perimetry data. The sponsor supports these assertions by citing the work of Harding, with two publications based on the same patients (Study 4102 in this submission is also based on the same patients. Only 4 pages of information were submitted for study 4102):

- Harding GFA, Robertson K, Spencer EL, et al. Vigabatrin: Its effects on the electrophysiology of vision. *Doc Ophthalmol* 2002;104:213-29

- Harding GFA, Spencer EL, Wild JM, et al. Field-specific visual-evoked potentials. *Neurol* 2002;58:1261-5

The study examined 39 children with epilepsy treated with VGB. The paper states that a number of the children were cognitively impaired, and that 35/39 could complete the task. The authors note that H-stimulus correctly identified 3 out of 4 children with abnormal visual fields, and 6 out of 7 with normal fields. No information was provided about the severity of the visual field abnormalities.
Reviewer: This study does not contain adequate information to determine if H-stimulus would be useful in detecting early VGB visual damage. Sensitivity and specificity estimated from the small number of subjects still suggests that false-negative and false-positive results may hinder clinical use.

Reviewer Conclusions and Discussion
H-stimulus is discussed only briefly in the submission as a potential method for monitoring for retinal damage. Insufficient data was provided to adequately evaluate the method. Data was available from only one investigator, on only 4 children with a documented field defect. No information was provided about the severity of the visual field abnormalities, so it was not possible to determine if H-stimulus would be useful for early detection of VGB damage. The method requires patient cooperation, and would not be usable in many VGB patients, particularly those with IS. Also, many of the children started on VGB are under 3 years old and would not be eligible for the test on that basis.

9. Postmarketing Adverse Events Reports

Vigabatrin was initially approved in 1989 outside the United States, in Europe, Australia, Korea, Canada, and other countries. Adverse events occurring both in phase 4 studies and from spontaneous reports are included in Periodic Safety Update Reports (PSUR).

Estimated patient exposure was roughly 50,000-150,000/year between 1992 and 2005, peaking in 1998 and declining thereafter. Exposure data for the first 6 months of 2006 was expressed as 5.4 million treatment days.

The sponsor reports that information to estimate duration of VGB therapy prior to onset of visual field defect was provided in 519 postmarketing reports (54.1%). There were 23 reports of VFD within the first 6 months of the reported drug start date. In 9 of the 23 reports, the VFD onset was reported to be on the same date as the initiation of VGB therapy. Of the remaining cases, the earliest time from drug start date to reported event of VFD was 5 days. There were 13 additional cases that reported time to onset in less than 6 months. The sponsor concludes that insufficient information is known about the cases to adequately characterize the events or determine relationship to VGB.
Review agrees.

The PSURs generally contain a few reports of 'serious and unlabeled' events potentially representing visual adverse effects of VGB that are different from visual field constriction, as represented by the following examples:

- Patient 199710789
  A 43 year old woman taking VGB for 4 years developed macular degeneration, and diminished vision in left eye.
- Patient 95001315
  A 47 year old man developed bilateral optic nerve atrophy proceeded by blurred vision after 21 months of VGB. The macula appeared normal. Visual fields showed concentric, binasal constriction.
- Patient 199710611
  A 60 year old many taking VGB 2 g/day for 5 years developed 'senile macular degeneration' that the investigator assessed as related to VGB. Other findings included abnormal color vision and bilateral visual field constriction with tessellated fundus in the periphery. The patient experienced no ocular symptoms.

Reviewer discussion.
VGB has rarely been associated in postmarketing adverse events reports with visual field defect within only a few days of initiation. However, it is not possible to determine from the available data the degree to which these reports represent false-positives, a common problem with testing for VGB field defects

There are few reports suggesting *severe* central acuity loss from VGB. To speculate, given the high level of awareness of VGB visual adverse effects, and the high degree to which central acuity loss would be symptomatic, it seems likely that more cases would have been reported if severe acuity loss occurred commonly.

10. Key Characteristics of VGB Visual Damage

a. *Visual Acuity*

The sponsor argues that central visual function is only rarely, if ever decreased from damage by VGB. The sponsor bases this conclusion in large part on result from study 4020, the Glasgow study, and the Westall Study.

The acuity data from study 4020 appear to be of poor quality. The submission states that "a retrospective quality control of the data revealed potential ambiguities in the recording of visual acuity and refraction."

The Glasgow acuity data is presented only as summary statistics. While the data suggest that average visual acuity is not affected by VGB, the data does not exclude decreased acuity in a subset of VGB patients. Also, the overall protocol for the Glasgow study is not presented in sufficient detail to determine reliability of findings.

The Westall study was not able to record acuity from most patients, and only suggests that some children taking VGB likely retain at least near-normal visual acuity.

Reviewer discussion
The studies cited by the sponsor to support that visual acuity is not affected by VGB do not address the issue with much precision. Review of the overall safety database suggests that *severe* decrease in visual acuity from VGB is rare if it occurs at all. In contrast, some case series suggest that mild decrease in acuity may occur from VGB. For example, Miller et al.[5] found 20 of 32 VGB patients to have visual acuity of 20/20 or better, while 12 of 32 had acuity ranging from 20/25 to 20/60 in one or both eyes. Matched control patients, in contrast, had normal acuity. Some degree of deficit in color vision also occurred in the patients of Miller et al.

b. *Non-retinal visual system injury*

Autopsy data including histology is available from a single patient with VGB field defect. The retina was severely atrophied, but there was no evidence for intramyelinic edema in brain sections.

Reviewer discussion
VGB clearly causes retinal and optic nerve injury. While the optic nerve injury might result solely from loss of retinal ganglion cells, direct toxicity to the optic nerve can not be excluded. Visual evoked potentials generally do not show conduction delay in cases of VGB field defect, but while this suggests that intramyelinic edema is not occurring, it does not rule out other toxic effects of VGB directly on the optic nerve. Damage to higher visual centers has not been identified, but has not been studied in detail.

c. *Reversibility*

The sponsor argues that little is known about the extent to which VGB-induced VFD improves after discontinuation of VGB, but acknowledges that in most reports loss of function has remained after stopping VGB.

Reviewer discussion
Although measurement error in field testing can be considerable, VGB visual field defects appear to be essentially irreversible. There is no persuasive evidence that clinically meaningful recovery can occur.

d. *Latency*

The sponsor argues that visual field constriction does not begin immediately upon initiation of VGB-therapy but occurs slowly, with average onset after several years of treatment. The sponsor cites results from study 4020, stating that the earliest time to onset from that

[5] Miller NR et al., Visual dysfunction in patients receiving vigabatrin. Neurology 1999;53:2082

study as 12 months. The sponsor also states that Kinirons et al (2005)[6] found in a longitudinal study of 93 adults that earliest onset occurred at 13 months.

Reviewer Discussion
This review concludes that there is little reliable data about the risk of early onset of vigabatrin visual damage. In study 4020, average time of VGB treatment before enrollment was 2- to 4 years, such that the study was poorly designed to measure earliest onset of field defect. Kinirons et al. state that the majority of patients in their study had been taking VGB for a number of years before testing, and that little data was available on how quickly constriction develops.

As discussed under individual studies above, some patients appear to develop constriction after less than 2 months of VGB treatment. For example, subject 405003 from the prospective study R003, and subject 006 from study 4020 each appeared to develop field defect after less than 2 months of VGB treatment.

The 'Pooled Cohort' study discussed above suggested that the peak incidence of field constriction occurred at just less than 1 year. This is supported by study R003, in which 5 of the 7 field defects were diagnosed before or shortly after 1 year of treatment.

The uncertain sensitivity and specificity of ERG testing in children prevents reliable estimate of latency of visual damage, as discussed in detail above under the Toronto Study.

e. *Progression with Continued VGB use*

The sponsor notes that the prevalence of VFD increases in subjects who continue VGB therapy. While some published reports found no progression of VGB damage with continued use of VGB, others suggested deterioration occurs if VGB is not stopped. The sponsor notes that study 4020 showed deterioration of fields while subjects were on VGB, but not following discontinuation of the drug. However, the sponsor points out that inconclusive or unconfirmed perimetry results hinder interpretation.

Reviewer discussion
Progression of VGB damage appears to occur in both adults and children that continue VGB treatment; normal patients develop field defects, and existing field defects worsen. However, the degree and proportion of patients progressing has not been reliably quantified. For example, study 4020 found that 35% of patients with field defects that remained on VGB progressed, compared to 13% who never took VGB. While most or all of the 'progression' in patients never on VGB was likely attributable to testing variability, the much higher rate of progression in patients continuing VGB indicates that progression likely occurred in subjects remaining on drug.

[6] Kinirons et al., Vigabatrin retinopathy in an Irish cohort: Lack of correlation with dose. Epilepsia 2006, 47:311-317.

Notably, field loss appears to develop over a short period of time in some patients, and then to slow or even stop despite continued VGB use. For example, Best and Acheson (2005) identified 16 patients who continued taking VGB for at least 5 years (range 5-12 years) despite having developed field defects. Patients were followed with serial kinetic fields for an additional 18-43 months while continuing VGB. Mean visual field remained fairly constant, about 37 degrees, over the course of the study, but one of the 16 patients deteriorated. That patient had been treated with 1.5 g/day VGB for 8 years before enrollment, and deteriorated from a 36 degree to a 23 degrees field over 19 months of study. This case suggests that even for patients with seemingly stable field defects, progression to severe defects may occur relatively suddenly, and may not be preventable by visual field monitoring.

The time course of field progression is of critical importance in safety testing. With gradual deterioration, periodic testing might detect early damage, allowing drug to be stopped before severe damage develops. In contrast, if damage occurs rapidly and then remains fairly constant, periodic testing may not effectively catch early damage, and instead may only confirm that severe damage has already occurred. Adequate data on which to base screening recommendations is lacking about the time course of field progression.

f. *Progression after Stopping VGB*

The sponsor notes that VGB-induced VFD clearly does not progress inexorably after the defect has occurred, and that most reports indicate no progression of VGB field defect once drug is stopped. However, the sponsor cites several publications suggesting progression can occur despite stopping VGB (for example, two cases reported by Malmgren et al.[7]). The sponsor also notes that visual field in one patient in study 4020 (subject 016-067) appeared to progress after stopping VGB. The patient was first examined 2.5 years after discontinuation of VGB, and was found to have lateral field to 36 degrees. On repeat testing 1.5 years later lateral vision was about 15 degrees. The sponsor suggests that this case illustrates that progressive visual defects may occur in some individuals many years after exposure. However, the sponsor indicates that since only a small number of late onset peripheral defects or cases of pre-existing defects have been reported, a causal relationship between VGB therapy and progression of defect due to VGB cannot be established without further study.

Reviewer discussion

Even slow worsening of vision, or worsening in a minority of patients after stopping VGB, would greatly increase the overall risk of the drug to vision. Evidence is clear that in *most* patients, vision does not *rapidly* deteriorate after stopping VGB. Critically, however, available data does not reliably address the potential that many patients may slowly worsen, or that rare patients may quickly worsen after stopping VGB.

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[7] Malmgren K, Ben-Menachem E, Frisén L. Vigabatrin visual toxicity: Evolution and dose dependence. Epilepsia 2001;42:609-15

Meaningful reassurance derives from the fact that in almost 2 decades of marketing, thousands of exposures in trials, and marketing exposure of roughly 350,000 patients, there is little reliable evidence of severe visual deterioration after stopping VGB. Unlike field defect, severe bilateral *acuity* loss is almost invariably symptomatic, and seemingly would have been reported. Importantly, however, this reassurance must be tempered by the fact that severe acuity loss in VGB patients might often be wrongly attributed to glaucoma or macular degeneration. Since glaucoma and macular degeneration are common in the general population, careful comparison to expected incidence would be necessary to detect even fairly large increase in risk.

Over several decades after VGB exposure, the issue of progression of VGB damage can't meaningfully be separated from the 'true' occurrence of glaucoma or macular degeneration. Expectation would be that the overall clinical course of otherwise unrelated eye disease would be more severe in combination with pre-existing VGB damage. For example, *central* vision loss from age-related macular degeneration might result in loss of *almost all* vision in VGB patients with pre-existing *peripheral* loss. The prevalence of ARMD increases rapidly with age, from about 2% in the sixth decade, to about 10% in the seventh, and 30% in the eighth.

g. *Exposure*

The sponsor notes that extreme ranges of dosing and duration of therapy have been shown to be associated with VFD, and that in some ways the adverse event resembles an idiosyncratic drug reaction. Since many individuals do not develop a VFD after years of treatment and many kilograms of drug, it is clear that toxicity is not simply dose-related. However, the sponsor notes that many, but not all studies have found an association between severity, duration of use, total dose, and less clearly, higher daily dose.

The sponsor proposes that if exposure time is short enough, on the order of a few days or weeks, there would be little risk to vision while efficacy of VGB could be established in the patient.

Reviewer discussion

For the exposures studied, a weak positive correlation appears to exist between field damage and time of exposure, cumulative dose, and daily dose. Since a broad range of exposures is associated with VGB damage, the correlation is not likely to be useful clinically at exposures commonly used in epilepsy.

As a special case, the sponsor proposes that very short exposure of only a few days or possibly weeks carries little risk of visual damage. Since VGB hasn't been used in this way, no direct evidence addresses the issue. While the range of VGB exposures associated with visual damage is remarkably large (including postmarketing reports of onset on the first day of treatment), there is no convincing evidence of 'paroxsysmal visual loss' from a single or very few doses of VGB. At some minimum exposure, risk of consequential visual damage likely approaches nil; however, the risk at any given exposure is unknown.

h. *Gender*

The sponsor notes that several studies have found the risk of VGB field defect to be about 1.5-fold higher in males versus females.

Reviewer discussion
Increased risk in males has been found in several studies. However, since studies were not adequately controlled, the possibility remains that the finding was due to undetected bias.

i. *Mechanism of retinal injury from VGB*

The mechanism of retinal injury from VGB is unknown. VGB inhibits GABA-transaminase, and leads to increases in retinal and vitreal concentrations of GABA in animals. High levels of GABA, however, have not been demonstrated to be retinotoxic. Vigabatrin has been associated with extensive pathological changes in all portions of the retina, including the ganglion cells and other cells in both the inner and outer retina.

11. Functional Correlates of VGB Field Loss

The sponsor notes that most patients with VGB field loss are asymptomatic, and suffer no significant functional impairment, but that in a minority of cases, field defect is sufficiently severe to hinder daily activities. The sponsor concludes that functional impact of the defect is relatively small since central, high acuity vision is spared.

Questionnaires probing for symptoms of visual disability demonstrated no evidence that the presence of VGB field loss conferred any functional impairment, but the sponsor acknowledges that investigators thought the questionnaires not to be validated measurement instruments, and to have poor sensitivity and specificity.

Reviewer discussion
Most patients with VGB field loss are asymptomatic, but little reliable data addresses the proportion with symptoms, or the severity of patient disability. A proportion of seemingly asymptomatic patients may actually be symptomatic from field loss, but not realize that symptoms are of visual origin, instead attributing them to clumsiness or drowsiness. In other cases, field loss may be experienced by the patient as blurry vision or oscillopsia. Patients who are initially asymptomatic frequently become symptomatic after diagnosis of visual field defect, potentially after realizing the true cause of their problems.

Overall visual ability might reasonably be considered as the relatively independent sum of central acuity and extent of peripheral visual field. Central acuity is critical for functions like reading and recognizing faces, while peripheral field is critical for functions associated with mobility and orientation. Studies of the impact of visual field loss in glaucoma patients may be relevant for understanding the impact of field loss from VGB, although visual field loss in glaucoma is often asymmetric, both between eyes and between superior and inferior hemifields, such that remaining field in one eye or hemifield could compensate

for loss in the other. Theoretically, disability from VGB might be greater because field loss is bilateral and symmetrical. With such caveats in mind, field loss from glaucoma has been shown to increase the likelihood of bumping into objects, and to decrease walking speed. Importantly, however, even bilateral glaucoma is not usually associated with needing help from others for self-care (e.g. eating, bathing), doing household chores, shopping, or doing necessary business (Freeman et al., 2008[8]). Figure 8 suggests that overall visual function, as measured by an instrument querying about difficulty with tasks such as reading, driving, walking, and preparing meals, is on average maintained even with severe binocular field loss. ***Importantly, however, a significant minority of glaucoma patients report difficulty with visual tasks even with 50% or more of visual field preserved.***

Figure 8: Activities of Daily Vision Scale Versus Binocular Visual Field in Glaucoma

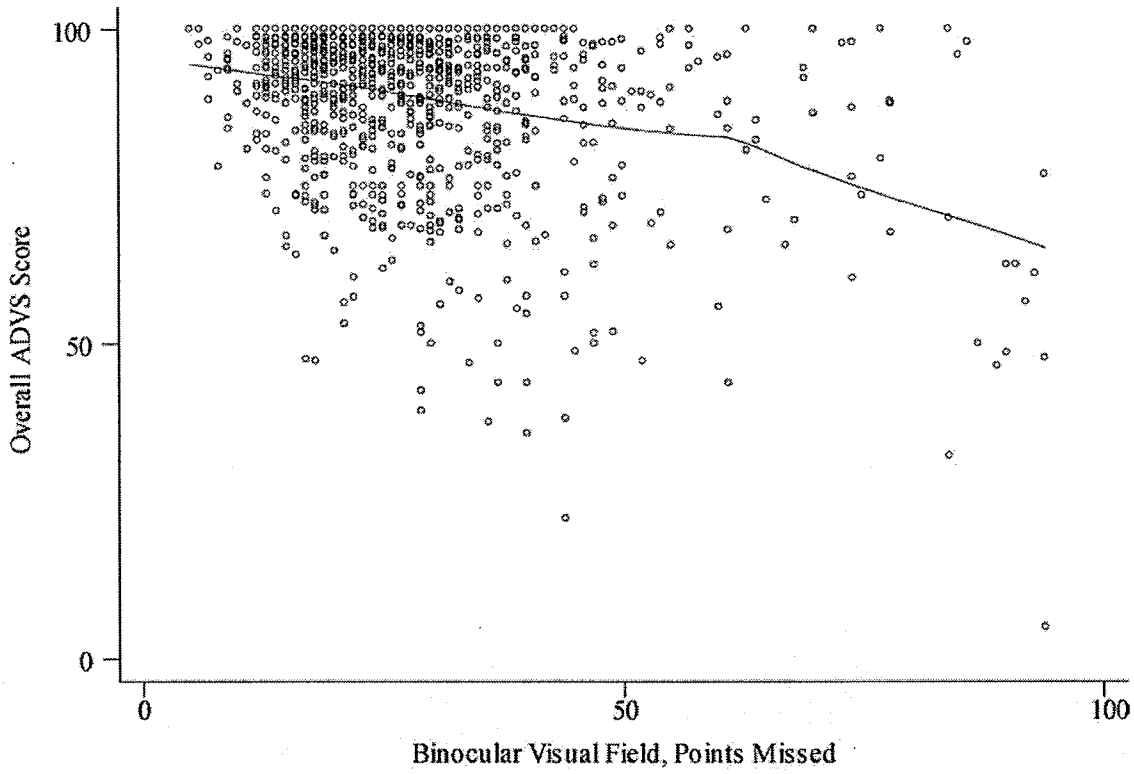


Figure 8: Scatter plot of overall Activities of Daily Vision Scale score by binocular visual field score, represented by 96 points to 60 degrees in the periphery. From Freeman et al., 2008

The relationship between visual loss and clinical disability depends on how well adaptive behaviors can be used to compensate for the visual loss. Impaired visual function can limit a person's ability to perform a specific activity, but it does not necessarily limit that person's ability to achieve the goal of that activity. Therefore, the overall negative impact of visual field loss for a given patient might be less than limitations in specific activities would at first suggest. Of concern, some patients with epilepsy, particularly patients with

[8] Freeman EE et al., Glaucoma and Quality of Life. Ophthalmology 2008;115:233-238.

IS and mental retardation, might be less able to compensate for visual field loss than glaucoma patients. Little data is available to address this issue, but case reports from the Toronto group suggest that visual disability from vigabatrin in IS patients can be profound[9].

Particularly as patients with VGB field loss age, the risk of falling may be expected to increase compared to persons with full visual fields. In the elderly, mobility problems are also associated with loss of independence, depression, and overall decrease in health.

As a final note, while for legal purposes (e.g. the U.S. Social Security Administration) an eye that has a visual field limitation to 20 degrees is considered as having visual acuity of 20/200 and of meeting the definition of legal blindness, there is no clinical basis for such a correlation.

12. Pregnancy

The sponsor indicates that it still remains unclear whether prenatal VGB exposure carries a risk for ophthalmic dysfunction. Ophthalmic abnormalities have been reported in the offspring of mothers using VGB during pregnancy, including strabismus, optic nerve pallor, nystagmus, and visual inattention.

A single published report describes ophthalmic exam results of two children exposed prenatally to VGB (Sorri et al., 2005[10]). These children showed no clear ophthalmic abnormalities, although perimetry and field-specific VEP were borderline.

Vigabatrin is excreted into breast milk in low concentrations. Based on vigabatrin breast milk concentrations from one patient, it was estimated that 0.3% of a daily maternal dose of 2 g daily would have been excreted into breast milk.

Reviewer discussion
Pre-natal exposure to VGB has not been clearly associated with visual damage, but the issue has not been studied in any detail.

13. Ophthalmic Safety Monitoring Plan in Adults

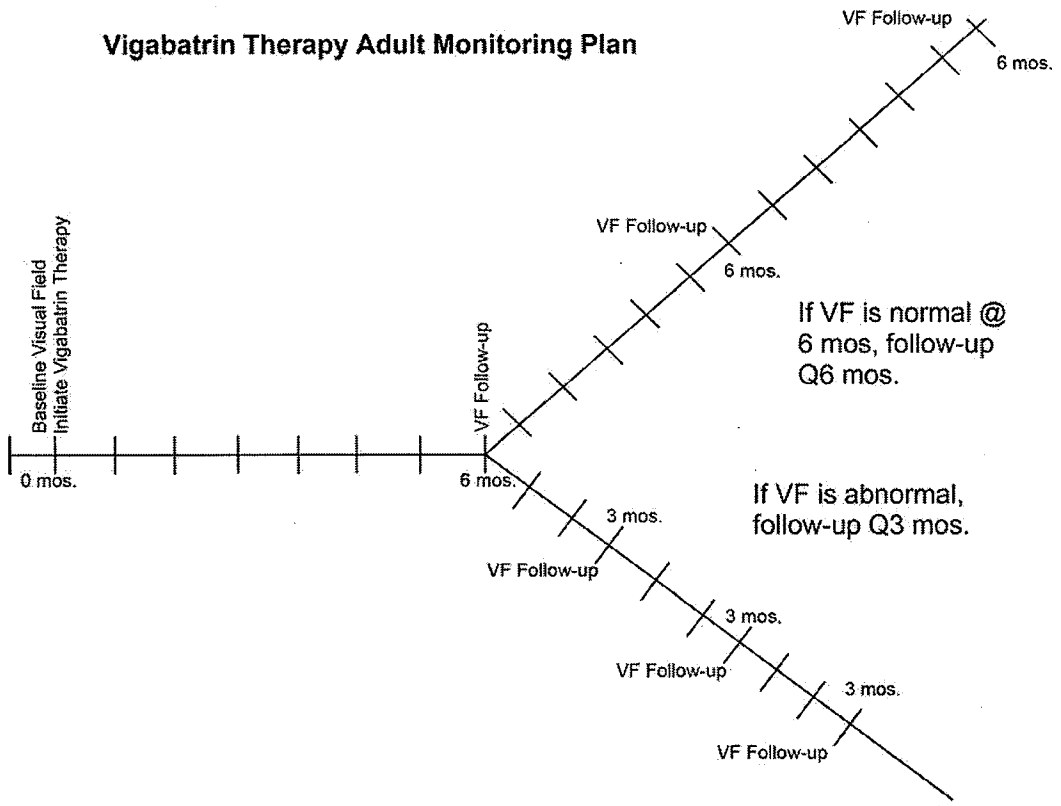
The sponsor asserts that either static or kinetic perimetry is sensitive and specific enough to be used to establish baseline and monitor peripheral vision in patients taking VGB. The following is the sponsor's ophthalmic safety monitoring plan for adults:

> Patients should have baseline evaluation of vision by a testing method appropriate for their cognitive state. For the great majority of patients, that would mean some

[9] Buncic et al., Characteristic retinal atrophy with secondary 'inverse' optic atrophy identifies vigabatrin toxicity in children. Opthalmology 2004;111:1935-1942.
[10] Sorri et al., Ophthalmologic and neurologic findings in two children exposed to vigabatrin in utero. Epilepsy Res 2005;65:117-20.

variety of perimetry examination such as static or kinetic perimetry. Appropriate methods have been published for perimetry as well as techniques suitable for cognitively impaired patients and will be in materials made available by Ovation Pharmaceuticals to vision specialists, neurologists and all others involved in caring for people with epilepsy.

Repeat examinations should occur every 6 months, unless abnormalities consistent with the VGB–induced peripheral VFD are found, in which case the patient should return for confirmatory testing. If VGB is to be discontinued, vision testing should be performed at the time of discontinuation or shortly thereafter. Formal vision testing thereafter should be performed only if clinical testing raises a suspicion of defect or if the patient reports any problems which might be related to a visual defect. The patient should be actively queried for any difficulties which may be due to a field defect.



Reviewer discussion, Ophthalmic Safety Monitoring in Adults
The potential effectiveness of the ophthalmic monitoring program for identifying early VGB damage and preventing severe damage remains essentially unknown. Most of the available data about VGB visual injury addresses detection of pre-existing field defects, not prevention of field defects, and thus contribute little to understanding the effectiveness of safety monitoring. Very limited (and poorly documented) data from the small prospective study R003 suggest that monitoring every 3 months might be able to detect moderate, but not early VGB damage; 3 of 7 defects were apparently not identified until fields had constricted to within about 20 or 25 degrees of fixation. Testing every 6 months, as proposed by the sponsor, might presumably worsen the performance of safety testing compared to study R003.

The time course of field progression is of critical importance in safety testing. With gradual deterioration, periodic testing might detect early damage, allowing drug to be stopped before severe damage develops. In contrast, if damage occurs rapidly and then remains fairly constant, periodic testing may not effectively catch early damage, and instead may only confirm that severe damage has already occurred. Susceptibility to VGB visual damage varies widely among patients. Adequate data on which to base screening recommendations is lacking. While frequent testing might improve the performance of safety monitoring, this would need to be demonstrated.

Perimetry is a difficult test for patients to perform, with a large learning effect. Anecdotally, successful perimetry is significantly more difficult in epilepsy patients, and 20% of patients may not be monitorable at all with perimetry. Wild et al.[11] in a discussion of perimetric monitoring for VGB field loss note that "the results of perimetry can often be inconclusive and frequently require one or more confirmatory repeat examinations, even though the results of the subsequent tests can remain equivocal."

This raises the additional problem of obtaining reliable perimetry *when initiating* therapy with VGB. The first field exam that a patient performs often does not accurately reflect the extent of the visual field, or yields uninterpretable results. If the baseline results do not accurately reflect the intact field, detection of VGB damage over time would also not be accurate.

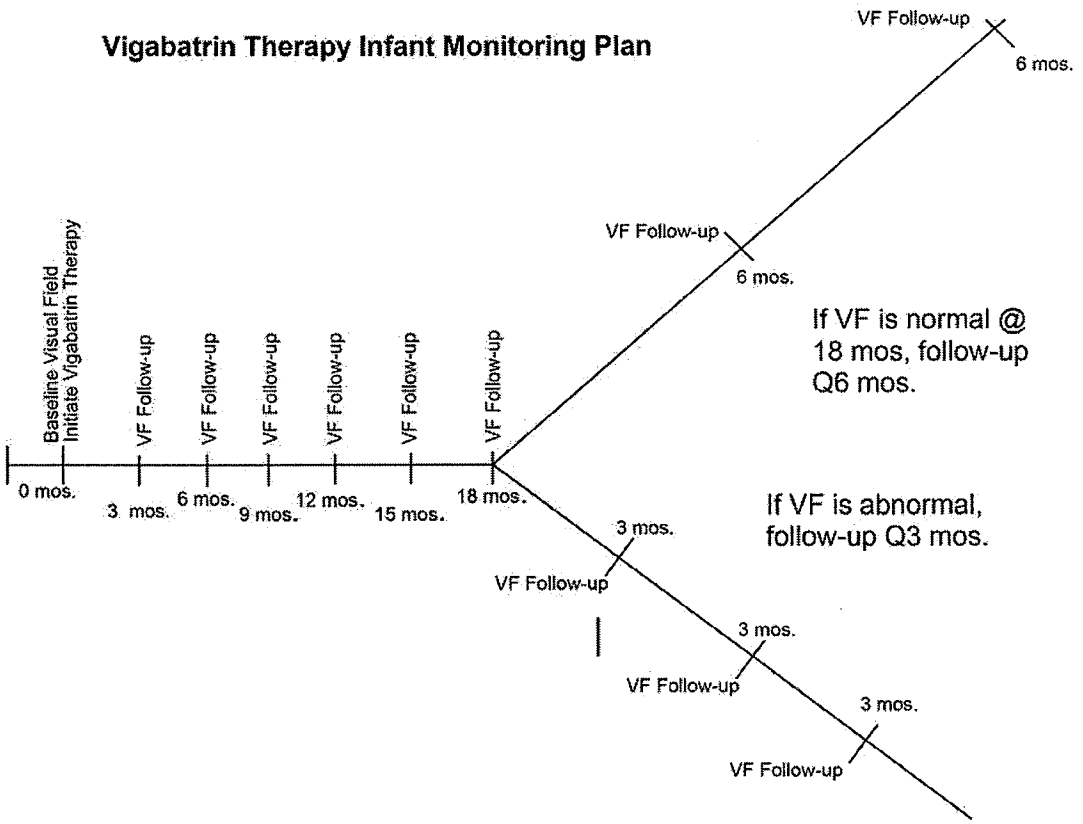
14. Ophthalmic Safety Monitoring Plan in Children

The following is the safety monitoring plan submitted by the sponsor for infants and young children:

> *Infants*:
> A baseline ERG evaluation with methods suitable for age should be performed. That baseline examination may occur up to 2 weeks before VGB therapy to a

[11] Wild, JM. Detecting Vigabatrin Toxicity by Imaging of the Retinal Nerve Fiber layer. Invest. Ophth. Visual Sci 2006;47:917-924.

maximum of 3 months after initiation of therapy, although examination close to the onset of therapy is best. The evaluation should then be repeated every 3 months for the first 18 months, and then repeated every 6 months thereafter unless an abnormality is discovered. If abnormal, a repeat exam in 3 months and repeat exams at 3-month intervals if still abnormal are recommended. No testing is necessary in some clinical situations, such as in patients in whom vision is absent or when other clinical factors eliminate the need for visual testing. Examples of such cases would be in cortically blind children or infants in whom other conditions reduce the likelihood of a visual defect having an impact on function. Because of the potential relationship between the incidence of peripheral VFD and the total lifetime dose of VGB, patients should be given regular visual examinations throughout the entire course of therapy. If a peripheral VFD or retinal abnormality is identified in a patient, it is important to perform confirmatory testing in a timely fashion. If a defect is confirmed, both patient/caregiver and clinician should review both the benefits of therapy and the risk of visual injury to make a timely decision on continuation of therapy.



Reviewer Discussion, Ophthalmic Safety Monitoring in Children
The sponsor focuses on ERG 30 Hz flicker as the safety test of choice for VGB visual monitoring in subjects unable to perform perimetry. This review finds that monitoring with ERG flicker has not been established as an effective method for monitoring VGB retinal damage. The Westall data appear to show large inter-test variability, suggesting that sensitivity and specificity are low, and that ERG would not be able to reliably diagnose VGB retinal damage until at best severe (Section 6a). The correlation between ERG and field loss is weak, (section 7), such that once abnormality is detected it might correspond to a large range of severity.

Studies on older children and adults who could perform perimetry suggest that ERG often fails to identify field defects. In study R003, ERG was able to detect zero of 3 mild defects, and only 1 of 3 moderate defects. In the Toronto study, a 10 year old girl with field constriction to within 30° of fixation had a normal ERG.

CLINICAL SAFETY REVIEW

Application Type	NDA Amendment
Submission Number	020-427
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Letter Date	12/28/08
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Reviewer Name	Gerard Boehm, MD, MPH
Review Completion Date	7/09/08
Established Name	Vigabatrin
(Proposed) Trade Name	Sabril
Therapeutic Class	Anitepileptic
Applicant	Ovation
Priority Designation	S
Formulation	Oral
Dosing Regimen	BID
Indication	Refractory CPS
Intended Population	Adults

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The Executive Summary-Safety Review

This review considers the overall safety of vigabatrin, excluding visual field defects and Intramyelinic edema (IME)/MRI abnormalities. Data on visual field defects are reviewed by Dr. Ronald Farkas, and IME/MRI abnormalities are reviewed by Dr. Phillip Sheridan, in separate memos.

Vigabatrin is an orally administered irreversible inhibitor of gamma-aminobutyric acid transaminase. Ovation's current submission is a safety update for the NDA seeking approval for vigabatrin for the treatment of refractory complex partial seizures in adults. Ovation submitted a separate NDA seeking approval for the use of vigabatrin in the treatment of Infantile Spasms (IS). The safety data specific to that submission are reviewed in a separate document.

Vigabatrin has a long and complicated regulatory history including numerous regulatory submissions, three advisory committee meetings, and a sponsor change. FDA put the development program on hold in the 1980s due to the finding of intramyelinic edema IME in several animal species. After resuming development, the sponsor submitted the vigabatrin NDA to FDA in 1994. The Division completed its review in 1995 and the application was found not approvable, due mainly to deficiencies in the presentation of safety data. The sponsor submitted an amendment to the NDA that addressed the identified deficiencies and vigabatrin received an approvable letter in 1997. The sponsor subsequently withdrew the application, prior to vigabatrin approval in the US, due to the finding of permanent visual field defects in a notable percentage of treated patients. Ovation acquired the the rights to vigabatrin from Aventis and submitted the amendment to the NDA that is the focus of this review.

Vigabatrin is currently approved for use in over 50 countries. Vigabatrin was first approved in the United Kingdom in 1989. Vigabatrin is approved in most countries in the European Union as well as Canada and Mexico.

There are numerous FDA approved treatments for epilepsy. No approved epilepsy treatment is completely efficacious. Many epilepsy drug treatments are associated with substantial and in some cases life threatening toxicities.

Vigabatrin related IME was a major preclinical safety finding. IME, manifested as microvacuolization in the brain, has been identified in mice, rats, dogs, and less consistently in monkeys. These findings led to a clinical hold for the development program and 3 advisory committee meetings. Another preclinical finding of note was retinal degeneration observed in albino rats but not in pigmented species.

The current vigabatrin submission summarizes pooled safety data from 15 controlled and uncontrolled trials including 2,148 subjects from studies in adults with CPS, children with CPS, IS, and safety studies evaluating visual field defects. The data included in these analyses come from studies that were not reported in previous regulatory submissions. In addition to presenting pooled analyses (Overall population), Ovation presented analyses of safety data from these 15 studies that stratified patients into the following subpopulations: adult subjects, pediatric (non IS) subjects and the IS subjects. At the request of the Division, Ovation also submitted Integrated

data analyses of pooled data from 80 epilepsy trials, including over 4,000 vigabatrin exposed subjects dating back to the original NDA. The Division requested these analyses to allow estimation of adverse event risks based on the available data and to allow examination of adverse event risks over time and across submissions.

Considering only the data in the current submission, the number of patients exposed to vigabatrin in phase II/III combined controlled and uncontrolled trials exceeds ICH guidelines and investigators exposed adequate numbers of subjects to the intended recommended doses. The current amendment submission includes safety data for 2,148 subjects exposed to vigabatrin in the combined controlled and uncontrolled trials. Ovation reported that for the studies included in the current submission 1,112 epilepsy subjects were exposed to a vigabatrin dose between 3 to <4g/day for at least 6 months, and 587 subjects were exposed to a vigabatrin dose between 3 to <4g/day for at least 1 year.

Division reviewers have identified deficiencies in the sponsors' presentations of adverse events over the course of the vigabatrin development program. These deficiencies have included lack of supporting information (narratives, CRFs) in applications, use of sources other than CRFs to capture data, including data from studies with no prespecified protocol, and the use of separate databases to capture serious adverse events. When these deficiencies have been identified, the sponsor has attempted to address them and the results have been generally acceptable. Narrative summaries of serious adverse events or AEs leading to discontinuation were generally of poor quality and often containing insufficient information to completely characterize the event being described.

The most commonly reported causes of death in the Integrated data pool of epilepsy study subjects were seizures (n=22), SUDEP (n=18), and respiratory events (n=4). In a comparative mortality analysis of 12 pooled controlled trials data, there were 4 deaths among vigabatrin subjects (n=952) and none among placebo subjects (n=393). The reported causes of death generally were those expected in the studied populations.

The most common SAEs among vigabatrin subjects in the Integrated data pool of epilepsy study subjects were visual field defect (6.8%, 324/4737), convulsions (2.8%, 132/4737) and status epilepticus (1.6%, 77/4737). The overall SAE risk was higher for vigabatrin subjects compared to placebo subjects in analyses of controlled trials data. In an analysis of pooled controlled trial data, vigabatrin subjects had a higher SAE incidence for status epilepticus (vigabatrin 2.9/100PY, placebo 2.0/100PY), depression (vigabatrin 2.2/100PY, placebo 2.0/100PY), confusional state (vigabatrin 1.8/100PY, placebo 0), pneumonia (vigabatrin 1.3/100PY, placebo 0), and fatigue (vigabatrin 1.1/100PY, placebo 0).

The most common AEs leading to discontinuation among vigabatrin subjects in the Integrated data pool of epilepsy study subjects were depression (1.5%, 71/4855), and convulsion (1.4%, 68/4855). Vigabatrin subjects discontinued from controlled trials for AEs more frequently than placebo subjects. In a pool of controlled trials, depression (vigabatrin 3.2/100PY, placebo 1/100PY) headache (vigabatrin 3.0/100PY, placebo 2.0/100PY), agitation (vigabatrin 1.5/100PY, placebo 0), confusional state (vigabatrin 1.3/100PY, placebo 0), and status epilepticus

(vigabatrin 1.1/100PY, placebo 0) led to discontinuation more commonly among vigabatrin subjects than control subjects.

Common AEs that occurred more frequently among vigabatrin subjects and in some cases that exhibited evidence of a dose response relationship included fatigue, somnolence, sedation, irritability, gait disturbance, dizziness, headache, nystagmus, tremor, coordination abnormal, parasthesia, hypoesthesia, confusional state, amnesia, memory impairment, disturbance in attention, depression, disorientation, diplopia, weight increased, edema peripheral, tremor, vision blurred, and diplopia.

Vigabatrin use was associated with development of edema. In analyses of pooled controlled trial data, the risk of edema was higher among vigabatrin subjects compared to placebo subjects. Dose response analyses of controlled trials data suggested an increasing risk of edema peripheral and generalized edema with increasing vigabatrin dose but not other edema related adverse events. Edema adverse events were not classified as SAEs and infrequently led to discontinuation. The edema AEs did not appear to be related to cardiac, renal or hepatic AEs and did not appear to be associated with increased creatinine, low serum albumin, or proteinuria.

Evidence supports an increased risk for depression with vigabatrin but there is insufficient evidence to support an increased risk of suicidal behavior. Data from 12 pooled controlled studies document an increased risk for depression related SAEs among vigabatrin subjects, although the number of SAEs was relatively small. In addition, data from these trials suggest an increased risk for depression AEs leading to discontinuation among vigabatrin subjects compared to the subjects randomized to other treatments. There did not appear to be a clear dose response for depression related AEs.

Vigabatrin was associated with increased risk of peripheral neuropathy signs and symptoms. In the original NDA, risks for parathesia and hyporeflexia adverse events were 3 times higher among vigabatrin subjects compared to placebo subjects. Vigabatrin studies were not designed to systematically evaluate potential cases of peripheral neuropathy and did not include nerve conduction studies, quantitative sensory testing, or nerve biopsy.

There have been cases of liver injury resulting in death or transplant in patients treated with vigabatrin but it is not clear if vigabatrin is causally related to these cases. Confounding factors such as concomitant medications, and prolonged duration of vigabatrin use prior to liver injury, make it difficult to assess the role of vigabatrin in these events. There were no cases of transaminase elevations >3x ULN with total bilirubin >2.0mg/dL in the vigabatrin development program, and there was no increased risk of transaminase outliers among vigabatrin subjects in an analysis of pooled controlled trial data. These laboratory results must be interpreted in light of the understanding that vigabatrin causes *decreases* in serum transaminases (see below).

Vigabatrin was associated with an increased risk for a number of CNS AEs including somnolence, sedation, coordination abnormalities and confusional state. The occurrence of these events could impair a patient's ability to perform tasks such as driving or operating machinery.

Lab data suggest that vigabatrin subjects experienced declines in hemoglobin and hematocrit that were not seen in subjects that received placebo. Despite these laboratory findings, vigabatrin subjects did not appear to experience high frequencies of concerning clinical events. A search of the development program identified only 2 vigabatrin subjects that experienced unexplained declines in hemoglobin below 8g/dL and or hematocrit below 24%. In addition, there appeared to be few post marketing reports of anemia adverse events. The sponsors did not collect sufficient information to classify the observed anemia events.

Vigabatrin causes reductions in serum transaminases (ALT>AST), presumably through its effect as a transaminase inhibitor. In one analysis, 94% of vigabatrin treated study subjects had a 60-100% maximum decrease in their ALT compared to baseline and 4% had an ALT result of 0. The magnitude of the declines appeared to be dose related. This effect could hinder the ability to monitor patients for hepatotoxicity.

Vigabatrin use is associated with weight gain. Data from controlled trials demonstrated that vigabatrin treated subjects had a higher mean increase in weight from baseline than did placebo treated subjects. In addition, vigabatrin subjects had a higher risk of gaining >=7% of baseline body weight. In the Integrated database, 10.2% (415/4077) of vigabatrin subjects had a weight increased AE. The long term impact of vigabatrin associated weight gain on cardiac disease or blood pressure outcomes is not known.

Due to the small number of analyzed ECGs, lack of specified timing in relation to dose, and lack of pre-specified measurement methodology, Ovation's analyses of ECGs collected during vigabatrin clinical trials are insufficient to assess the effect of vigabatrin on cardiac repolarization. Preclinical data did not appear to suggest an effect of vigabatrin on ion channels or repolarization.

Recommendations
Any ongoing or planed vigabatrin clinical trials should incorporate monitoring of hemoglobin, hematocrit, serum iron, transferrin, ferritin, reticulocyte count, red cell morphology, red cell indices, haptoglobin, urine hemoglobin, and erythropoietin.

Any ongoing or planned vigabatrin clinical trials should incorporate hematologic testing during post-treatment washout in order to assess rate of recovery from reduction of hemoglobin and hematocrit.

Ovation should conduct a thorough QT study in humans. This could be conducted as a phase IV commitment.

If approved for pediatric indications, Ovation should collect data that address the effect of vigabatrin on growth and development.

Ovation should closely follow up any spontaneous reports of liver injury. Follow up should include complete description of the case, outcome information, lab test results, biopsy results,

and post mortem test results. In addition, Ovation should submit any serious liver injury cases as 15-day reports.

Ovation should incorporate the labeling language that will be requested by the Division.

7 Integrated Review of Safety

Background

Vigabatrin has a long and involved regulatory history. Vigabatrin's first sponsor (Marion Merrill Dow) filed the original IND in February of 1980. In 1983, the Division suspended clinical investigations due to the finding of intramyelinic edema (IME) in rats, dogs, and possibly monkeys. IME manifested histologically as microvacuolization, most notably in the cerebellum, reticular formation, and optic tracts. In 1984, following an advisory committee meeting on IME, the Division required the sponsor to collect additional information about IME prior to resuming clinical testing. In 1985 the sponsor provided data related to IME and following another advisory committee meeting the Division decided that prior to resumption of clinical testing, the sponsor would have to identify a non-invasive test capable of detecting IME at an early stage in humans. In late 1989, following yet another advisory committee meeting, the Division allowed clinical testing to resume with the sponsor monitoring subjects for IME using visual evoked potentials and MRI. In 1989, vigabatrin was approved for marketing in the United Kingdom. Clinical testing resumed in the United States in 1990.

The sponsor submitted the vigabatrin NDA to the FDA on 4/29/94 and the Division deemed that application Not Approvable on 5/28/95, primarily for quality related issues with the non US studies safety database. The sponsor neither submitted with the NDA nor had available for audit/review the Case Report Forms (CRFs) for most of the non US studies that contributed safety data. In addition, the NDA lacked complete dose and duration of exposure data for non US studies subjects, and did not include narrative summaries of serious adverse events and discontinuations for these subjects.

In response to the issues raised in the Not Approvable letter, the sponsor collected and reviewed available CRFs from non US study sites. Some CRFs were located and others were not. Using the available data, the sponsor assembled the safety data for resubmission. In another development, the January 1997 issue of the BMJ published 3 post marketing case reports from the UK of patients treated with vigabatrin that developed bilateral concentric visual field loss.

On 5/31/97, the sponsor (now Hoechst Marion Roussel) filed an Amendment to the NDA that responded to the shortcomings identified by the Division in the Not Approvable letter. To address the Division's concerns about non-US studies lack of CRFs, the sponsor created three separate cohorts of non-US studies safety data. The first cohort was comprised of data from non-US studies for which CRFs were available for all subjects, where data was designated to be captured by a prospectively written protocol and where data was contemporaneously captured in the CRF. These data were termed the non-US studies primary safety data. In instances where some but not all CRFs were located for a given study the data for patients with CRFs were

grouped into the second cohort called Secondary data. A third cohort included data for those patients for whom CRFs were not located (non-CRF data).

Upon completion of the NDA Amendment review, the Division issued an Approvable letter for vigabatrin and identified several safety issues requiring additional exploration. The approvable letter requested a separate review of safety data for pediatric patients treated with vigabatrin, additional information regarding a variety of topics in the proposed labeling, and updated information regarding visual field defects. The sponsor provided another safety update in 1/98 and responded to the requests in the approvable letter on 4/24/98.

Due to the finding of visual field defects in patients treated with vigabatrin, the sponsor withdrew the application prior to the Division's final regulatory decision. The sponsor subsequently met with the Division on several occasions to discuss visual field defect findings with vigabatrin and explore avenues for approval but that sponsor (at this time Aventis) decided to abandon the application.

Ovation acquired the US rights to vigabatrin and on December 23, 2005 filed an Amendment to the NDA application for FDA approval for vigabatrin for treatment of refractory complex partial seizures in adults. The Division deemed the submission an incomplete response for reasons related to deficiencies in the format and content. Ovation attempted to address these deficiencies in a 10/10/06 submission. Ovation filed their NDA for vigabatrin for the treatment of infantile spasms on 10/17/06. These submissions were also deemed incomplete and Ovation submitted responses in March of 2007. Shortly thereafter, the Division became aware of publications describing MRI findings suggestive for intramyelinic edema in children treated with vigabatrin. The Division met with Ovation and informed them that additional information about these findings would be required prior to accepting the vigabatrin applications. Ovation conducted additional analyses and re-filed their submissions for both refractory CPS in adults and IS on 12/28/07.

7.1 Methods and Findings

7.1.1 Deaths

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

Through the 12/31/95 cutoff date for the NDA Amendment, the sponsor identified 11 deaths from the completed US and non US primary safety data clinical trials. The sponsor also identified 9 deaths from the secondary safety data clinical trials and 8 deaths from the non-CRF safety database (from trials where CRFs were not available). In addition, the sponsor identified 32 deaths from clinical trials that were ongoing at the time of the amendment cutoff date. The sponsor re-categorized these 32 deaths (ex. to completed primary study category or post

marketing trial category, etc.) in subsequent submissions, after the trials were completed (Source, Amendment review 10/28/97, pp. 14-18; Safety Update Table 9-21).

For the 11 deaths in vigabatrin treated subjects from completed US and non-US primary data studies in the NDA amendment, 7 were from US clinical trials and 4 from non-US primary studies. The crude mortality rate for vigabatrin treated subjects in the US studies was 1.11/100 PY (7/630PY; 1.3%, 7/537) and for the non-US primary studies was 0.9/100PY (4/449PY; 0.3%, 4/1,189). For the US studies, the reported causes of death were seizures (n=3), drowning, coronary artery disease, trauma, and suicide. The causes of death for the non-US primary studies were pneumonia, infection, fall, and motorcycle accident (Source, Amendment review 10/28/97, pp. 14-16, Appended exposure table). In controlled US trials, one death (0.5%, 1/222, suicide) occurred among vigabatrin subjects and none (0/135) among placebo subjects. No deaths were reported from non-US primary controlled trials.

The sponsor identified 9 vigabatrin subject deaths from completed studies included in the secondary data group and 8 vigabatrin subject deaths from the non-CRF data group. The reported causes of death for the secondary and non CRF databases included sudden/unwitnessed (n=3), suicide (n=3), coronary artery disease (n=2), aspiration/seizure, status epilepticus, seizure, lung cancer, colon cancer, congestive heart failure, trauma, progression of underlying disease, and unknown.

In addition to the clinical trial deaths, the NDA Amendment included deaths identified from post marketing reports and from compassionate use programs. For the most part, the causes of death reported from these non-clinical trial data sources (cutoff date 12/31/95) were similar to causes reported above, although there were 6 deaths due to hepatic failure. In 4 of these cases the patient was treated with vigabatrin for 1-6 years prior to the development of hepatic failure. In one of the remaining cases, liver failure occurred in the setting of multi-organ failure, following cardiac arrest. The remaining case summary did not identify any strong confounding factors but included only limited clinical details. I summarize those cases in an appendix to this review (Source Amendment Review 10/28/97, pp. 18-19).

Safety Update (1/1/96-3/15/97)

The sponsor identified a total of 22 deaths from completed US and non US primary trials in this Safety Update (Safety Update table 9-24). The crude mortality risk for this group was 1.3% (22/1,667). The reported causes of death were seizure (n=8), status epilepticus (n=2), intracranial hemorrhage (n=2), drowning (n=2), cardiac arrest (n=2), SUDEP, aspiration, lung cancer, myocardial infarction/ventricular fibrillation, myocardial infarction/ GI bleed, and valvular heart failure. (Safety Update table 9-24).

The sponsor identified 22 additional deaths from sources other than primary data trials (completed and ongoing Japanese trials, post marketing trials, and miscellaneous sources-Safety Update Table 9-24). The reported causes of death were drowning (n=6), accident/trauma (n=3), suicide (n=2), seizure/aspiration, seizure/fall/suffocation, status epilepticus/pneumonia, heart failure, oligodendroglioma, sepsis/cardiac arrest, SIDS, CMV infection, bronchopneumonia,

pneumonia/respiratory failure, and fulminant hepatitis. The hepatitis death occurred in a 3 year old female patient being treated with vigabatrin and phenobarbitone and liver histology was reportedly consistent with a toxic etiology and the report stated that other causes of hepatic injury had been excluded (no specific test results reported).

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Ovation reported 16 deaths from completed trials in the Overall Safety Population (0.74%, 16/2,148). Four deaths were related to epilepsy/seizure; 3 related to myocardial infarction; 3 related to respiratory causes (pneumonia and respiratory arrest; pneumonia and urinary tract infection; and pulmonary hemorrhage secondary to pulmonary angiomatosis respectively); 3 cancer related (pulmonary carcinoma with pneumonia and multiple organ failure; carcinoma; and adenocarcinoma respectively), 1 related to hepatic necrosis with multisystem organ failure; 1 cause not reported; and 1 sudden death. The narratives for the myocardial infarction deaths suggested that these were sudden and or unwitnessed events and contained insufficient information to support the diagnosis of myocardial infarction. The death due to hepatic necrosis with multisystem organ failure occurred in a 17 year old female who had been treated with vigabatrin for 20 months and developed status epilepticus the evening after undergoing an intracranial monitoring procedure in preparation for possible lobectomy for seizures. She was treated with antiepileptics, mechanical ventilation, pressors and broad spectrum antibiotics. The subject died and a post-mortem report described the cause of death as extensive hepatic necrosis with multisystem organ failure. Ovation provided narrative summaries for the Overall Safety Population deaths identified in the 12/28/07 submission and I summarize information from those narratives in an appendix to this review.

Pediatric Subpopulation (non IS, age 3-<16)

Ovation reported no deaths among the 444 pediatric patients that were part of the Overall Safety Population (12/28/07 Submission, p.151).

IS Subpopulation

Ovation identified four deaths among the IS patients that were part of the Overall Safety population. The reported causes of death were pneumonia, pulmonary hemorrhage, cardiac arrest, and sudden death.

Integrated Data

Ovation's Integrated Data summary of deaths includes only those deaths from epilepsy clinical trials. Ovation's presentation consisted of a table that listed the total number of deaths and the number of deaths by cause. The table includes the following 3 columns: prior data, current data, and combined data. I provide that table below.

The causes of deaths listed for the Prior Data in the Integrated analysis table below cannot be compared to causes listed in previous submissions because the events have been re-coded using MedDRA. The previous submissions did not use the same coding dictionary to categorize adverse event verbatim terms that was used for the Current data. In order to provide the Integrated analyses, Ovation had to re-code the adverse event verbatim terms in the previous submissions so that the events could be categorized in a uniform manner. Ovation explained that they re-coded the adverse event verbatim terms from previous submissions using MedDRA version 8.0 (Amendment p.33).

The 42 deaths identified from Prior Data include deaths from the NDA Amendment and 1998 Safety Update. Ovation includes 18 deaths from completed primary and secondary data sources in the NDA Amendment (two deaths noted above were not included in this analysis because one was from a clinical pharmacology study and another from a tardive dyskinesia study, Response to Reviewer Questions 2/11/08). Ovation also includes the 22 clinical trial deaths reported in the 1998 Safety Update. The final 2 deaths in the Prior Data column were reported as from an ongoing study in the 1998 Safety Update and are included now by Ovation in their final accounting of deaths (Response to Reviewer Questions 2/11/08).

The Current data deaths are the 16 deaths reported by Ovation in the current Amendment Submission.

The Combined Data total includes the Prior data deaths (n=42, as described above), the Current Data deaths (n=16), and 5 additional deaths identified by Ovation that were reported from ongoing studies in the Safety Update but not reported elsewhere (see footnote of table for explanation).

Table 67. Subject Deaths Integrated Data

Adverse Event Related To Subject Death	Prior Data (N=3441) n (%)	Current Data (N=2148)[a] n (%)	Combined Data (N=4855)[a] n (%)
Total	42 (1.22)[a]	16 (0.74)	63 (1.30)
Seizure (all)	15(0.44)	4 (0.19)	22 (0.45)
SUDEP	16 (0.47)	2 (0.09)	18 (0.37)
Respiratory events	0	4 (0.19)	4 (0.08)
Aspiration	3 (0.09)	0	3 (0.06)
Cancer	0	3 (0.14)	3 (0.06)
Cardiovascular events	0	3 (0.14)	3 (0.06)
Coronary artery atherosclerosis	3 (0.09)	0	3 (0.06)
Drowning	2 (0.06)	0	2 (0.04)
Hypoxia	2 (0.06)	0	2 (0.04)
Myocardial infarction*	1 (0.03)	0	2 (0.04)
Trauma*	1 (0.03)	0	2 (0.04)
Acute Myocardial infarction	1 (0.03)	0	1 (0.02)
Brain hypoxia	1 (0.03)	0	1 (0.02)
Bronchopneumonia	1 (0.03)	0	1 (0.02)

Cardiac arrest	1 (0.03)	0	1 (0.02)
Cardiac valve disease	1 (0.03)	0	1 (0.02)
Cardiogenic shock	1 (0.03)	0	1 (0.02)
Cerebral hemorrhage	1 (0.03)	0	1 (0.02)
Completed Suicide	1 (0.03)	0 (0.00)	1 (0.02)
Confusional state	1 (0.03)	0	1 (0.02)
Congestive cardiomyopathy	1 (0.03)	0	1 (0.02)
Dyspnea	1 (0.03)	0	1 (0.02)
Gastric hemorrhage	1 (0.03)	0	1 (0.02)
Gastric ulcer	1 (0.03)	0	1 (0.02)
Hemorrhage intracranial	1 (0.03)	0	1 (0.02)
Hepatic events	0	1 (0.05)	1 (0.02)
Hepatic neoplasm	1 (0.03)	0	1 (0.02)
Injury Asphyxiation	1 (0.03)	0 (0.00)	1 (0.02)
Lung cancer metastatic	1 (0.03)	0	1 (0.02)
Lung neoplasm malignant	1 (0.03)	0	1 (0.02)
Malignant glioma	1 (0.03)	0	1 (0.02)
Multiple organ failure	0 (0.00)	1 (0.05)	1 (0.02)
Pulmonary oedema	1 (0.03)	0	1 (0.02)
Subdural hematoma	1 (0.03)	0	1 (0.02)
Sudden death	1 (0.03)	0	1 (0.02)
Tachycardia	1 (0.03)	0	1 (0.02)
Ventricular fibrillation	1 (0.03)	0 (0.00)	1 (0.02)
Ventricular tachycardia	1 (0.03)	0	1 (0.02)
Unknown	0 (0.00)	1 (0.05)	1 (0.02)

[a]The following 5 subject deaths were reported in 1998 SU as deaths in "ongoing" studies, and therefore not reported in rest of this current SU. However, for completeness and accuracy in accounting for all the deaths in the combined analysis, the following 5 deaths are included under the "combined" total data but not reported elsewhere in the current SU: Subject 1349-0007 from study 0101 cause of death was Unwitnessed Death: Possible seizure and pulmonary edema. Subject 1344-0002 from study 0101 cause of death was Unwitnessed Death: Cerebral hypoxia due to a seizure. Subject 1507-1001 from study 242 cause of death was Head injury secondary to motor vehicle accident. Subject 1541-0003 from study 242 cause of death was Unwitnessed Death: Seizure disorder. Subject 1545-0004 in study 242 cause of death was Unwitnessed Death: Myocardial Infarction. These 5 causes of death are not present in Table 66, however 5 is added to the existing prior and current data totals. 42 deaths in prior + 16 deaths in current + 5 deaths reported as deaths in ongoing studies from 1998 SU = 63 total deaths in the combined population of 4837. Preferred terms flagged with * indicate counts which include these additional deaths.

Additional Analyses

The Division asked Ovation to submit a comparative analysis of mortality based on the data from pooled controlled trials. Ovation pooled data from 12 phase II/III epilepsy controlled trials that used a double blind, parallel group, dose, placebo or active control design. Ovation provided a table of the studies included in their analysis and that table is included as an appendix to this review (Table 5). The studies differed in terms of the durations (range 5 days to 52 weeks) and numbers of subjects enrolled (range 18- 457). The analysis included 948 vigabatrin treated subjects, 229 carbamazepine treated subjects, 9 gabapentin treated subjects and 384 placebo subjects. The results of the analysis are provided below (Source: 2/11/08 and 3/14/08 submissions).

Mortality by Treatment Group for Pool of Phase 2-3 Studies					
Treatment Group	Total Number of	Total Number of	Crude	Patient Years	Mortality/100

	Patients[a]	Deaths	Mortality[b]	Exposure	Patient years[c]
Vigabatrin	952	4	0.004	446.004	0.897
Carbamazepine	229	1	0.004	166.084	0.602
Valproate	113	0	0	68.657	0
Gabapentin	9	0	0	1.725	0
Placebo	393	0	0	101.897	0

[a] Includes only patients who received study drug; therefore these numbers may vary from Table 5, which includes all randomized patients.
[b] Crude mortality = number of deaths/total number of subjects
[c] Mortality/100 patient years= number of deaths/patient years exposure x 100

The causes of death for the vigabatrin group were suicide, valvular cardiac failure, myocardial infarction/GI bleed, and possible seizure/pulmonary edema.

Ovation's controlled trial mortality analysis found a higher mortality rate in the vigabatrin treated subjects compared to the active control and placebo subjects. There did not appear to be a clustering of similar causes of death among the vigabatrin subjects. Due to the small number of deaths and the relatively low exposure, this analysis does not provide robust evidence of increased mortality risk with vigabatrin.

Post Marketing Reports
The post marketing reports of deaths from the prior submissions were discussed above.

In the current submission, Ovation summarized deaths in patients identified from foreign post marketing reports received during the period of 3/97 through 6/07. Ovation identified 17 reports that described 18 patient deaths. Twelve of the identified deaths were in patients aged less than 12 years. For these pediatric deaths, the included patients ranged in age from 9 days to 11 years and 3 were males and 4 were females (5 unknown sex). Four reports included insufficient detail to characterize the causes of death. Two patients were found dead in bed (one noted to be taking cisapride). The reported causes of death for the remaining subjects were SSPE, sepsis/pneumonia, congenital heart malformation, underlying metabolic disorder, recurrent pulmonary infections, and respiratory insufficiency/septicemia. For the six deaths in patients 12 years or older, the age range was 12-47 years and 4 patients were male and 2 patients were females. The reported causes of death include suicide (2), malignant hyperthermia, liver damage, bilateral pulmonary embolism, and one patient was found dead in bed.

Discussion
Ovation summarized the deaths occurring during the safety update period and provided a cumulative count of deaths by cause of death (Integrated data) for the epilepsy studies in the development program. I provided a summary of mortality data from earlier submissions that was included in previous Division safety reviews. Ovation's quantitative comparative assessment of mortality was limited by the small number of deaths and the limited exposure. A qualitative assessment of mortality is severely limited in some cases by the lack of clinical detail presented in the death narratives. The causes of death reported by Ovation are generally those expected in a population of patients with seizure disorders. There were deaths due to hepatic failure and these are discussed in more detail in section 7.1.5.6.

7.1.2 Other Serious Adverse Events

Prior Submissions
In previous submissions, the sponsor did not present a comprehensive analysis of serious adverse events (SAEs), but instead presented separate analyses for hospitalizations, cancer diagnoses, status epilepticus events, events leading to disability, life threatening events, overdose events, and congenital anomalies. While these separate presentations included the adverse events that are captured by the regulatory definition of SAEs, the format of these presentations precluded calculation of overall SAE risks. In the following sections, I will summarize the data from prior submissions for hospitalizations, events resulting in disability, and life threatening events. I will not separately present information for overdose events, cancer diagnoses, or congenital malformations as part of the SAE section, but I will cover these events in later sections of this review.

NDA and NDA Amendment (Cutoff date 12/31/95)

For the pooled US epilepsy studies (controlled and uncontrolled), the sponsor reported that 18.7% (83/443) of vigabatrin exposed subjects were hospitalized. The most common reasons for hospitalization were convulsions (5.2%, 23/443), convulsions grand mal (2.7%, 12/443), and confusion and depression (1.1%, 5/443 each). In the pooled primary non-US epilepsy studies, 5.2% (39/765) of vigabatrin subjects were hospitalized. (Source Amendment review, p.25). The sponsor did not identify any events leading to disability or that were life threatening for the primary data group.

In the US controlled epilepsy studies, 6.8% (15/222) of vigabatrin subjects were hospitalized compared to 0.7% (1/135) of placebo subjects (Source: Amendment review, p.25). The most notable difference in risk for AEs leading to hospitalization in these studies was for convulsions/convulsions grand mal. In the US controlled studies 3.6% of vigabatrin subjects were hospitalized for convulsions/convulsions grand mal compared to 0.7% (1/135) of placebo subjects. The AEs leading to hospitalization for vigabatrin subjects are included in the table below.

Table 7.1. AEs that Led to Hospitalizations for US Controlled Epilepsy Trials in Original 1994 NDA Submission Study Patient AEs that led to hospitalization

Subject	AE(s) leading to Hospitalization
Study 71754-3-C-024	
054-003	Pneumonia, Sepsis, Fever
061-004	Convulsion
061-006	Vomiting
Study 71754-3-C-025	
010-111	Convulsions
011-104	Depression
013-008	Convulsions Grand Mal
013-011	Depression
069-003	Convulsions Grand mal, Personality Disorder, Convulsions

071-001	Emotional Lability, Personality Disorder, Psychosis, Suicide Attempt, Therapeutic Response Increased
071-004	Convulsions Grand Mal, Pneumonia, Stupor
071-007 (Placebo)	Convulsions
071-010	Bronchitis, Confusion, Convulsions, Fever
072-006	Convulsions
072-012	Hypertension
073-012	Pneumonia
089-003	Convulsions Grand Mal

Source: Ovation response to Division Questions, 4/15/08, p. 147

For primary non-US controlled trials, the comparisons made between vigabatrin and placebo groups are difficult to interpret because 6 of the 9 studies included in this group used a crossover design and only one of these studies included a washout period prior to crossover, potentially complicating classification of exposure at the time of the event (Source: Amendment review, pp.20-22).

The sponsor reported in the NDA Amendment that 51 vigabatrin exposed subjects from the secondary data group (5.3%, 51/968) were hospitalized. The most common reasons for hospitalization were from the CNS and psychiatric body systems. The sponsor noted that the non-CRF studies did not routinely capture hospitalizations and the only hospitalization reported for the non-CRF group was seizure related (Source: Amendment review, pp. 26-7). The sponsor did not identify any events leading to disability or that were life threatening for these groups.

In the NDA Amendment the sponsor identified 45 vigabatrin treated subjects from compassionate use programs that were hospitalized. The most common reasons for hospitalization for this group were psychosis (n=7), seizure (n=6), and status epilepticus (n=5). The group also included hospitalizations for an allergic skin rash (subject VGST SW01JA), for exfoliative erythematous rash (VGST MUMF-330) and hepatic and renal insufficiency (VGST MUMF 343).

In the NDA Amendment the sponsor identified 284 post marketing reports of patients that were hospitalized. Psychosis was the most commonly reported reason for hospitalization. Eight patients were hospitalized for hepatic injury (Source: Amendment review, pp.27-28).

The sponsor identified 14 eye-related events leading to disability from spontaneous reports, and 9 of these involved visual field loss. After visual events, the next most commonly identified event resulting in disability was behavioral event (event terms of psychosis and aggression) (Source Final Safety Update, p.5).

In the NDA Amendment, the sponsor identified 18 post marketing patients that experienced life threatening adverse events. The majority of these events were seizure related. In addition, the sponsor identified an event of hepatic failure. The patient (report #VGZ-9400-7742) developed fulminant hepatic failure and hepatic coma and was hospitalized. The patient received a liver transplant. The discharge summary for this patient noted that the event was "thought to be drug

induced, secondary to a recent anti-epileptic drug trial with vigabatrin." The patient was also taking gabapentin prior to the event (Source: Amendment review, p.33).

The sponsor reported that a 28 year old female patient (report number VGZ-9500-4387) with a history of elevated liver enzymes temporally related to treatment with carbamazepine and valproate, developed elevated liver enzymes with vigabatrin. A liver biopsy found mild acute and chronic inflammatory cell infiltrate and hepatic bridging necrosis, findings felt to be consistent with drug induced hepatitis. This patient's transaminases reportedly normalized after discontinuation of vigabatrin (Source Amendment review, p.33).

The sponsor also reported that a male pediatric patient (report number VGZ-9500-3964) was treated with vigabatrin for almost 1 year and developed elevated transaminases, prolonged PT and PTT, and coma. The sponsor stated that the patient did not die but admitted that follow up data was not available (Source Amendment review, p.34).

The sponsor identified 3 reports of feeding disorders in patients (7 months, 10 months, unknown) treated for infantile spasms. These patients stopped feeding within 24 hours of the first dose of vigabatrin, and two of the infants were given tube feedings. The reported noted that feeding improved in all three cases after vigabatrin was stopped (Source Amendment review, p.34).

Safety Update (1/1/96-3/15/97)

In the Safety update, the sponsor reported that the integrated (through 3/15/97) hospitalization risk for US epilepsy studies was 20.2% (285/1,409) compared to 9.2% (185/1,975) for non-US primary epilepsy studies. The most common reasons for hospitalizations for both groups were convulsions (US 3.5%, 49/1,409; non-US 2.2%, 44/1,975) and convulsions grand mal (US 4%, 56/1,409; non-US 1.4%, 27/1,975) (Source Final Safety Update Review, p.5).

For the combined data from controlled epilepsy trials presented in the safety update, the sponsor reported that 7.5% of vigabatrin and 2.2% of placebo exposed subjects were hospitalized. When examining the reasons for hospitalization, the most glaring disparity between vigabatrin and placebo was for convulsions. The sponsor reported that 3% (29/969) of vigabatrin subjects but only 0.4% (2/491) of placebo subjects were hospitalized for convulsions (Source Final Safety Update Review, p.5).

The sponsor identified a subject from an ongoing clinical trial that experienced an adverse event that led to disability. This subject experienced decreased vision that was diagnosed as macular degeneration (Source: Final Safety Update, p.5).

In the Safety Update, the sponsor presented all identified life threatening events from all sources. For the combined data the sponsor identified 47 vigabatrin exposed individuals with life threatening events. The most commonly reported life threatening events were increase in seizure frequency (n=12) and suicide attempt (n=9).

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Ovation presented the SAEs pooled from 13 of the 15 safety update studies. The SAEs from the remaining 2 Current submission studies (0098 and 4021) were presented separately due to data quality issues (inconsistent capture of subject numbers or date of birth- 12/28/07 submission, p.77). The 13 studies included in the pooled SAE analyses included 1,299 subjects.

Ovation provided table 4.1.5.4 (p.7323) that summarized the SAEs for the pooled Safety Update population. Ovation reported that 44% (570/1,299) of subjects in the pooled analysis experienced one or more SAEs. The complete list of SAEs is included as an appendix to this review. In the following table, I present the SAEs reported by at least 1% of the Safety Update population.

SAEs Occurring in at Least 1% of Vigabatrin Exposed Subjects, Current Submission

SAE	% (n)
Visual field defect	26% (335)
Convulsion	2.8% (36)
Hemianopia	2.5% (32)
Status epilepticus	1.9% (24)

In response to a Division request, Ovation re-examined their database and identified 12 additional subjects with SAEs that were not included in the above analysis. The SAEs reported for these subjects were VFD (n=9), seizure (n=2), and abnormal behavior, dysarthria, convulsion, and cognitive disorder (Source 5/1/08 submission, pp.138-9).

In addition to identifying the common SAEs, I reviewed table 4.1.5.4 to identify less frequent, but potentially concerning SAEs. I summarize those findings below.

Four subjects had SAEs of rash, 2 had rash maculopapular, 1 had leukocytoclastic vasculitis, and 1 had Stevens Johnson syndrome. The narratives for the SAEs coded as Rash and one of the narratives for an SAE coded as rash maculopapuar described events that did not appear to be SAEs (subject was not hospitalized, event was not described as life threatening, etc.). When asked why these events were classified as SAEs, Ovation reported that the events were coded as SAEs by the previous sponsor and had no further explanation. The subject with an SAE of Stevens Johnson syndrome was also taking lamotrigine and carbamazepine at the time of the event and the narrative suggested that the patient experienced another occurrence suspicious for Stevens Johnson syndrome 3 months after discontinuing vigabatrin, factors suggesting that vigabatrin was not causally related to the event. Narratives for the remaining rash maculopapular SAE and the leukocytoclastic vasculitis SAE are provided below and narratives for the rest of the skin related SAEs are included in an appendix to this review.

Rash maculopapular

Subject 0201/1386-0002 This 14-year old female Caucasian with a history of complex partial seizures was hospitalized for increased seizure frequency. The subject was also noted to have a bilateral extremity erythematous

rash with crusts and excoriation that was described as moderate intensity. The subject was discontinued from the study. The narrative provides no diagnosis for the rash and does not indicate how the rash was treated. The rash was decreased when the subject was discharged from the hospital.

Leucocytoclastic vaculitis

Subject 0223/1480-0005 This 57 year old Caucasian female with a history of simple partial seizures, complex partial seizures and partial generalized seizures experienced leukocytoclastic vasculitis and shortness of breath while on vigabatrin. Subject was on vigabatrin for 23 days prior to the events. On ——— the subject noted a rash (described as bilateral petechia of the lower extremities) on the back of her legs (more severe on the left leg) which worsened the next day. Subject also complained of shortness of breath and wheezing. She took two of her husband's nitroglycerin tablets to relieve the shortness of breath. The outcome of the events was not provided but the subject was hospitalized due to the events. The physical and neurological exams were unremarkable. Lab and x-ray results were not provided. A dermatologist diagnosed leukocytoclastic vasculitis as 'commonly seen' in drug-type reactions. The intensity of the reaction was considered moderate, with a duration of four days. The event resolved. Vigabatrin was discontinued on 28Feb1996 due to the events. Medical history included renal failure, arthritis, left hip fracture 1995, hysterectomy due to carcinoma and fibroids with chemotherapy treatment, carpal tunnel syndrome of the right hand and release, poor memory and drug allergy to Feldene. Concomitant medications included Dilantin, Tegretol, Tylenol, Aleve, Didronel, aspirin, Premarin, Nitrostat and calcium carbonate.

b(6)

Two subjects had SAEs of acute renal failure, and 1 subject had SAEs of glomerulonephritis and proteinuria. One of the renal failure SAEs was attributed to dehydration and the subject's renal function improved with rehydration. The second renal failure SAE occurred in a 13 year old male during hospitalization for encephalitis and the subject's renal function improved with continued vigabatrin treatment. One subject experienced SAEs of proteinuria and glomerulonephritis. The narrative did not provide a clear diagnosis or etiology for these events. I provide excerpts from the narrative summary for the subject with proteinuria and glomerulonephritis below and for the 2 renal failure SAEs in an appendix to this review.

Proteinuria/Glomerulonephritis

Subject 1A/269 ——— This Caucasian male born on ——— was enrolled on 23Apr99 weighing 10.4 kilograms. The subject was assigned to the low-dose group and began vigabatrin on ——— for infantile spasms. Vigabatrin was dosed at 1500 mg/day until decreased to 500 mg/day on ———

b(6)

On ——— he experienced an SAE (seriousness criteria unknown) described as decreased blood albumin lasting 1 day. He recovered from the SAE with no sequelae and the relationship to study drug was judged as unlikely. There were no related AEs.

On ———, he experienced an SAE (seriousness criteria unknown) described as proteinuria lasting 1 day. He recovered from the SAE with no sequelae and the relationship to study drug was judged as not related. He had 3 related AEs including proteinuria of unknown intensity on ——— continuing to study completion. Treatment was 'Other' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He also had mild kidney biopsy on ——— Treatment was 'None', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He had mild hypoalbuminemia on ——— continuing to study completion. Treatment was 'Other' and the investigator assessed the AE as not reasonably attributable to vigabatrin.

On——— he experienced an SAE described as focal glomerulonephritis continuing to study completion. The relationship to study drug was judged as not related. He had 5 related AEs including moderate nephrotic syndrome on ——— continuing to study completion. Treatment was 'Hospitalization' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He also had mild hypertension for less than 1 week on ——— Treatment was 'Other', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He had moderate peripheral edema for 1 week on ——— Treatment was

'Hospitalization', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He had moderate nephrogenic anemia on ___ continuing to study completion. Treatment was 'Other', and the investigator assessed the AE as not reasonably attributable to vigabatrin. He had moderate anemia for 2 weeks on ___ . Treatment was 'Other', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. Although there were 2 adverse events resulting in hospitalization (nephrotic syndrome and peripheral edema), these were not reported as an SAE by the investigator. b(6)

Concomitant AEDs included phenobarbital, prednisolone, methylprednisolone, furosemide, and clorazepate. Other concomitant medications included albumin iv, amoxicillin, aspirin, captopril, cefotaxime, Epogen, general anesthesia, albumin iv 25%, Lasix iv, sedation iv, Kayexalate, Mylicon, Pedialyte, Pepcid, prednisone, Solu-Medrol, calcium carbonate, Tranxene, Tylenol, Xylocaine, and Zithromax.

Two subjects had anemia SAEs and one subject had an SAE of decreased platelet count. One anemia SAE was attributed to epistaxis but the narrative and CRF included few details for this event. The narrative for the other anemia event did not provide sufficient information to characterize the event. The narrative for the decreased platelet count SAE attributed the event to vigabatrin. I provide the 2 anemia narratives and the decreased platelet count narrative below.

Anemia

0101/Subject 13300001 This 26 year old female with a history of partial complex seizures and anemia requiring iron replacement had an AE of anemia while being treated with vigabatrin. The subject discontinued and the narrative reported that the CRF documented the outcome of the anemia AE was study drug discontinued but other "notes" document that the subject voluntarily withdrew from the study. Tegretol was listed as the concomitant medication. The narrative did not provide any additional relevant details. To look for additional information about this event, I reviewed the subject's CRF. Interestingly, this subject's baseline medical history sheet included several AEs that were handwritten while anemia and post seizure headache entries were typed. Similarly, the "notes" that report the patient requested to drop from the study (ex. CRF page 105) were typed while most other CRF entries are handwritten. The CRF noted that the week 0 visit (beginning of titration) was 4/95. The labs from 3/95 (baseline) included a hemoglobin of 12.1mg/dL with a WBC of 9,400/mm3 and a platelet count of 241,000/mm3. The following table summarizes hematology related labs for this subject from study visits.

Date	Hemoglobin (g/dL)	WBC (/mm3)	PLT (/mm3)
6/95	11.2	4,500	250
11/95	10.3	10,100	228
6/96	11.4	6,100	210

CRF page 90 reports that the date of last vigabatrin dose received was 4/24/96. The lab result sheet from 11/95 included a handwritten request for a repeat CBC, in addition to iron and total iron binding capacity tests but results for these tests were not included in the CRF.

Subject 4020/00150039 This 17 year old male with a history of epilepsy was enrolled in Study 4020 and randomized on 8/25/99. The subject began vigabatrin 3000 mg daily treatment on an unknown date in Jul97 (this study of VFD included patients with previous vigabatrin exposure). The subject voluntarily withdrew from the study and was lost to follow-up. His last study visit was on 04Dec00, and at that time vigabatrin treatment was ongoing. The subject experienced a serious adverse event of anemia (acute anemia due to epistaxis) of unspecified severity on an unknown date in Nov00. The clinical investigator assessed the event as unrelated to vigabatrin treatment. The subject was treated with blood transfusion auxiliary products and recovered from the event. The CRF did not include a history of bleeding diathesis or any laboratory results for this subject.

Additional medical history was not provided. Concomitant antiepileptic medications at the time of the event included Lamictal. The narrative reported no additional concomitant medications but the CRF noted the subject was taking "depakine".

Decreased Platelet Count

Subject 0242/15430003 This 22 year old female subject with a history of seizures and headaches discontinued from a trial after 18 months of treatment with vigabatrin due to decreased platelet count. In a previous trial (0223) this subject had two platelet counts of 160 and 166 (Hgb 12.7 and 12.8, and WBC count 4.4 and 5.2). Platelets in December of 1997 were 128,000, Jan 23, 1998 they were 98,000 and Jan 30, 1998 they were 16,000. Work up included a bone scan with biopsy, CT scan, and HIV testing which were all negative. The patient was observed and then discharged home 2 days later. Two days afterward she was re-admitted for 4 days and was started on prednisolone. Doses ranged from 20 mg/d to 80 mg/d ultimately stabilizing at 40 mg/d which is her current dose. Study drug was stopped. The intensity of this event was considered severe by the investigator and the investigator felt the causality to be definitely related to study drug. The subject was lost to follow up. Concomitant medications included advil, neurontin, vitamin E, and oral contraceptive (Genora). I reviewed the CRF provided for this subject and it did not contain any lab results. I then proceeded to the study report for this study and found a listing of lab results for this subject. I summarize some of the hematology lab results from the study report in the table below.

Date	PLT (/mm3)	Hemoglobin (g/dL)	WBC (/mm3)
8/22/96 (Baseline)	170	12.8	5
11/19/95	228	12.9	5.8
2/12/97	159	12.9	4.2
9/4/97	97	12.9	6.7
12/11/97	123	13.1	7
2/26/98	76	13.6	15.5
4/7/98	182	15	8.6

The lab results in the study report did not correlate with the results provided in the narrative.

Three subjects had SAEs of respiratory failure and one of respiratory arrest. These respiratory SAEs all occurred in infantile spasms patients. The narratives for these events provided too few clinical details to allow assessment of potential causes of these events. I provide those narratives below.

Respiratory arrest

b(6)

Subject 1A/112 This Caucasian female born on was enrolled on at Site 1 weighing kilograms. The subject was assigned to the low-dose group and began vigabatrin on for infantile spasms. Vigabatrin was dosed at 250 mg/day, increasing to 375 mg/day on 30 Oct96, to 625 mg bid on 08Jan98, and finally decreased to 500 mg bid on 11Mar98.

On , the subject experienced an SAE described as respiratory arrest, ending on the same day. Non-drug therapy was administered (details not provided), outcome was listed as recovered with no sequelae, and the relationship to study drug was judged as not related. Seriousness criteria for the SAE was not specified. However an adverse event of mild drug hypersensitivity was also reported on 2 occasions on ; one of these events was life-threatening (but not reported as an SAE). Both events continued to study completion. The investigator assessed the events as not reasonably attributed to vigabatrin. Treatment was 'Other,' but no details were provided.

Concomitant AEDs included clonazepam and topiramate. Other reported concomitant medications included albuterol, Auralgan otic, baby lax, Bactroban, Cefzil, Decadron, Donatussin, Murine eye drops, Mylanta, Phenergan, Poly-DM, Tylenol, and Ventolin.

Subject 1A-209 This Caucasian male born on was enrolled on weighing ilograms. The subject was assigned to the low-dose group and began vigabatrin on 27Sep96 for infantile spasms. Vigabatrin was dosed at 250 mg/day, increased to 1250 mg/day on 25Oct96, to 1750 mg/day on 23Nov96, to 2500 mg/day on 03Feb97, and finally decreased to 2000 mg/day on 21Nov97. This subject experienced several SAEs during the study including pneumonia, ear infection, hydrocephalus, gastrointestinal disorder,

On ——— he experienced an SAE lasting 2 days while hospitalized described as cardio-respiratory. The outcome was recovered with no sequelae and the relationship to study drug was assessed as not related. He had 2 temporally related AEs including severe cardiorespiratory arrest for 2 weeks on ——— Treatment was 'Hospitalization', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He also had severe ventriculoperitoneal shunt malfunction for 2 weeks on ——— Treatment was 'Hospitalization', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. Although the 2 adverse events resulted in hospitalization, they were not reported as SAEs by the investigator. b(6)

On ——— , he experienced an SAE described as respiratory arrest, ending the same day, and was hospitalized. The outcome was recovered with no sequelae and the relationship to study drug was assessed as not related. There were no related AEs.

Subject 1A-658 This male (Race = 'Other') born on ——— was enrolled on ——— weighing ——— kilograms. The subject was assigned to the high-dose group and began vigabatrin on ——— for infantile spasms. Vigabatrin was dosed at 750 mg/day, decreasing to 500 mg/day on ——— and finally to 250 mg/day on ———

On ——— he experienced an SAE described as respiratory arrest lasting 1 day and was hospitalized. He recovered with no sequelae and the relationship to study drug was assessed as not related. He also had moderate convulsion for 1 week on ——— with seriousness listed as 'Life-Threatening', but treatment was 'None'. The outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributed to vigabatrin.

Concomitant AEDs included phenobarbital and lorazepam. There were no other concomitant medications reported.

Respiratory Failure

Subject 1A/103 This 2 year and 8- month old Caucasian male, weight ——— kilograms, with a history of infantile spasms, complex partial seizures, partial seizures with generalization, tonic seizures and myoclonic seizures experienced respiratory failure. The subject had been on vigabatrin for approximately two years when the respiratory failure occurred. Vigabatrin dose was 1500mg/day at the time of the event. The subject was admitted for respiratory insufficiency secondary to tonsillar enlargement and a tonsillectomy and adenoidectomy. The investigator assessed the event of respiratory failure as not related to vigabatrin. Severity was not provided; no action was taken. The outcome was "other." Concomitant medications included Topamax 62.5mg TID. The subject terminated from the study because he was "spasm free" with last dose of drug on ———

Ovation reported SAEs of drug hypersensitivity, hypersensitivity, and tongue edema. The narrative for the drug hypersensitivity event mentions an "itchy rash", along with swelling of the lips and tongue, findings suspicious for angioedema. The narrative for the tongue edema event provided insufficient clinical details to evaluate the event. The hypersensitivity event was not described in detail but the narrative reported that the patient was rechallenged with vigabatrin without recurrence. I provide the narratives for the drug hypersensitivity event below and for the hypersensitivity and tongue edema events in an appendix to this review. b(6)

Drug Hypersensitivity

Subject R003/0405-011 This 32 year old Caucasian female with a history of simple partial, complex partial and secondary generalized seizures experienced drug hypersensitivity, diagnosed as allergic reaction with lips, tongue and gums swelling and a generalized itchy rash, while on vigabatrin 1000 mg/day. The subject's tongue swelled after the first dose of study medication (evening of ——— and treatment consisted of Benadryl 100 mg. After the second dose (morning of ———, the subject experienced lips and gum swelling and a generalized red itchy rash and she was treated with another dose of Benadryl 100 mg. Later that same day ——— she was given one dose of Reactine 20 mg. Study drug was discontinued and the subject was withdrawn from the study due to this event. On ——— her symptoms were resolved somewhat and she was given Solu-Medrol 125 mg IV, Benadryl 50 mg IV and prednisone 50 mg daily (for two days). The drug hypersensitivity symptoms gradually resolved

(unknown date in ———) without sequelae. The investigator assessed that the drug hypersensitivity was related to study medication and was moderate in intensity. Seriousness criteria were assessed as medically important. Medical history included numerous drug allergies, depression, feelings of anxiety, suicidal thoughts, fractured right wrist and left ankle 1991, right temporal lobectomy, use of glasses or contact lenses, nonsmoker, no alcohol use. Concomitant medications included valproic acid, Neurontin, clobazam, and lorazepam.

Ovation identified psychiatric SAEs of hallucination, hallucination auditory, hallucination visual, and suicide attempt. The description of the hallucination SAE is included in the narrative describing the rash SAE (subject 0118/1272-0002), in an appendix to this review. I provide summaries for the hallucination auditory, hallucination visual, and suicide attempt SAEs below.

Hallucination visual

Subject R003/0405-001 This 50 year old Caucasian female with a history of simple partial, complex partial, and secondary generalized seizures experienced visual hallucinations and restless legs syndrome while on vigabatrin 1000 mg/day. The subject also experienced affective disorder (diagnosed as severe mood disorder/depression with symptoms of labile mood, sleep disturbance and emotional change). These three events occurred 23Dec2000, which was 11 days after the first dose of study medication. The subject was withdrawn from the study 31Dec2000 due to the affective disorder, visual hallucinations, and restless legs syndrome. The events resolved without sequelae on 11Jan2001 without countermeasures. The investigator judged that the visual hallucination and restless legs syndrome were related to study medication and were moderate in intensity. Seriousness criteria was assessed as medically important for these three symptoms. Concomitant medications included phenytoin, oxcarbamazepine, Apo-Salvent, Atrovent, Cefprozil, and Flovent.

Hallucination auditory

Subject 0201/1387-0002 This 73 pound, 8 year old, Caucasian female with a history of complex partial seizures experienced depression on two occasions, suicidal ideation, auditory hallucination and headache. The patient entered a previous double-blind vigabatrin epilepsy clinical study on 13Jul1995 and received placebo until 5Oct1995. The patient entered this study on 5Oct1995 and received vigabatrin (15 mL BID; 20, 40, 60 or 80 mg/mL) during the 4 week double-blind dose adjustment phase and then entered the open-label phase of the study on 7Nov1995 at which time the subject was receiving 15 mL BID (60 mg/mL = 1.8 gm/day). On 01Nov1995, the subject experienced symptoms of depression and suicidal thoughts. Three weeks later, the subject experienced auditory hallucinations. Length of time on study drug in relation to event onset could not be determined due to the study being blinded at the time of the events.

Lab results included carbamazepine level (08Dec1995) of 6.0, and valproic acid level (08Dec1995) of 62.

b(6)

On ——— , the subject was admitted to the hospital for a psychological evaluation.

The subject reported to her mother that she had wanted to hurt herself and her mother, and heard voices. The subject was maintained on her usual dose of divalproex and carbamazepine; her vigabatrin was decreased to 600 mg BID (10ml BID; 60mg/ml), and she responded well to the decrease of vigabatrin with no seizure activity noted. The subject was discharged from the hospital on ——— The subject underwent individual and family therapy. The event of auditory hallucination resolved 3 weeks after onset and the events of depression and suicidal ideation resolved 6 weeks after onset. The investigator assessed that the depression, suicidal ideation and auditory hallucinations were moderate in intensity and definitely related to study medication. Treatment information was not provided. Concomitant medications included Advil 1-2 tablets PRN, hydrocortisone cream 0.05% PRN, Depakote 250 mg BID, Depakote 375 mg QHS, and Tegretol 100 mg TID.

On 20Sep1996, the subject experienced depression and headache while on vigabatrin TID a (total of 25 mL (10-5-10) per day at 60 mg/mL). Length of time on study drug in relationship onset could not be determined due to the study being blinded at the time of the initial events. The subject was hospitalized for observation and treatment. Treatment received was ibuprofen, paracetamol and Tylenol 3. The events did not resolve and the investigator

deemed that no follow-up was necessary. However, the events were still under treatment. The investigator assessed the events of depression and headache as moderate in intensity and unlikely related to study drug. An alternative etiology provided was stress at home and school. Concomitant medications at the time of the depression and headache included ibuprofen, Advil 1-2 tablets PRN, hydrocortisone cream 0.05% BID, Depakote 125 mg BID, and Depakote 250 mg QHS.

Medical history included oligodendroglioma at age six associated with mild memory problems, learning difficulties, sleepiness, tiredness and headaches. The subject rolled over into the 098 study.

Suicide attempt

Subject 0223/1669-0001 This 49 year old Caucasian male with a history of simple partial seizures and complex partial seizures experienced depression and suicide attempt while on vigabatrin. Subject was on vigabatrin for 18 days prior to the events. On 17Jun1996 the subject became depressed due to family conflicts. On 18Jun1996, the subject appeared to be more severely depressed and was not able to go to work. On ——— the subject attempted suicide, incurred no physical harm to self and was hospitalized in the evening for suicidal tendency and observation. Date of last dose of study medication was on 18Jun1996. Subject was hospitalized for 10 days and discharged on ——— Subject was instructed to follow-up with a psychiatrist, continue medications, limit stress, limit time in the sunshine and eat a regular diet. The investigator assessed the events as possibly related to study medication and severe in intensity. The subject was discontinued from the study due to the events and the events resolved. Medical history included depression, hypertension, kidney stones, red and green color deficiency and left lobectomy 1990. Subject experienced gingival hyperplasia with Dilantin. Concomitant medications included Dilantin, Neurontin, Phenobarbital, Dynacin, Metoprolol, allopurinol, Toprol XL and Cozaar.

b(6)

One subject had an SAE coded as psychotic disorder but Ovation explained that this event was miscoded. The subject (4020/0021-0064) actually experienced an SAE of hemianopia heteronymous with "psychogenic AE" listed as an alternative etiology (Source 3/14/08 submission).

One subject had SAEs of hepatic failure and hepatic necrosis and these events were discussed above with the deaths (narrative is included in an appendix to this review).

SAEs in Studies 0098 and 4021

As noted above, Ovation presented these SAEs separately from the pooled safety data in the current submission due to data quality issues (inconsistent capture of subject numbers or date of birth- 12/28/07 submission, p.77). In these 2 studies there were 151 subjects experiencing 1 or more SAEs. The SAEs reported by at least 5 subjects were visual field defect (n=38), convulsion (n=27), status epilepticus (n=14), chest pain (n=8), and pneumonia (n=7).

In response to a Division request, Ovation re-examined their database and identified 16 additional subjects from study 0098 with 17 SAEs not included in the above analysis. Ovation provided 16 narratives describing these 17 SAEs. The SAEs reported for these subjects were VFD (n=6), increased seizure frequency, basal cell carcinoma, basal call carcinoma recurrence, acute cholecystitis, COPD exacerbation, psychosis, hysterectomy for menometrorrhagia, degenerative arthritis of the ankle, MVA with L3 fracture, left carotid cavernous fistula following surgery for pituitary adenoma, and ACL rupture following fall (Source 5/1/08 submission, pp.163-213).

I reviewed table 2.1 (pp. 11197-11241) to identify less frequently occurring but potentially concerning SAEs from studies 0098 and 4021. The list included 3 subjects with suicide attempts, 2 subjects with psychotic disorder, 1 subject with a rash (that resolved with discontinuation of lamotrigine), and 1 subject with ITP/anemia. I provide summaries for these events below. There were no SAEs of acute hepatic failure, acute renal failure, pancreatitis, aplastic anemia, Stevens Johnson syndrome, Toxic epidermal necrolysis, or hypersensitivity reported for these studies.

Suicide attempt

Subject 1216-0009 This 55 year old Caucasian male with a history of complex partial seizures and partial generalized seizures was hospitalized due to a suicide attempt by cutting wrists, ataxia, mental slowing, dysarthria and depression while on vigabatrin. Subject was on vigabatrin for four years prior to the events. Family noted subject, who lives in a group home, to be dysarthric, ataxic, and intermittently confused. Blood level testing, on an unspecified date, suggested probable overdose due to increased phenytoin and phenobarbital levels. On 29Aug1997, the subject, in a somewhat confused state of mind and depressed about his inability to function more independently cut his wrists. (Two months prior to this event, the subject suffered a leg fracture. The subject subsequently had to go to rehabilitation due to the fracture and was upset with going to rehabilitation). Subject was hospitalized —— and evaluated by psychiatry. They felt his suicide attempt was not well-thought out and subject's depression was no longer present. Also, they thought that the toxicity from his drugs may have played a role in his suicide attempt and they did not feel that he needed any supervision for suicidal risk. Phenytoin level was 17 and phenobarbital level was 40 on an unspecified date. It was also thought that his intermittent adverse events might be due to Mysoline (primidone) and an attempt was made to reduce his dose to 250 mg BID. Following this reduction the subject had several seizures and the Mysoline was increased back to TID. Vigabatrin therapy continued unchanged. After stabilization, subject was discharged to a chronic care facility and the events were considered resolved. The investigator considered the event of suicide attempt by cutting wrists as not related to vigabatrin but possibly related to the subject being upset over rehabilitation or the possibility of toxicity from phenytoin or primidone. Subject has no history of depression or psychiatric disorders. Medical history included tonsillectomy, constipation, rectal polyps and hemorrhoids, acne, ankle fracture and right-sided partial seizures since age 17. Concomitant medications included phenytoin and Mysoline.

b(6)

Subject 1316-0009 (AVENTIS-050523-0000857) This 23 year old male subject with a history of epilepsy experienced a suicide attempt (jumped from bridge), sustained an open compound tibia and fibula fracture of right leg, and L2 vertebrae compression fracture (due to the injury accident) —— while on vigabatrin 3 gm/day. The subject was on vigabatrin for one year and six months. He was out with a friend, became depressed about his epilepsy condition and under the influence of alcohol, jumped off a bridge approximately 17 feet high. The subject was brought to the emergency room and was found to have an open fracture of the right lower extremity and a nonoperative L2 compression fracture. He underwent a right tibia/fibula I&D (incision and drainage), external fixation after reduction for a right grade 2 open tibia/fibula fracture which was well tolerated. Treatment medications included morphine, heparin, clindamycin, levofloxacin, and Vicodin. Vigabatrin therapy remained unchanged. A psychiatry consult evaluated that this subject was not at risk for further suicide attempts and that this current episode was not a suicide attempt. Psychiatry also felt that this subject needed no further psychiatric care but did need to participate in an alcohol rehabilitation program. The subject recovered in 12 days —— The investigator assessed the events as not related to study medication, but rather associated with depression due to the subject's epilepsy condition. Medical history was not provided. Concomitant medication included lamotrigine, lorazepam, clonazepam, and ethanol.

Subject 1204-0008 (AVENTIS-050523-0000832) This 26 year old female with a history of simple and complex partial seizures experienced increase in seizures and was hospitalized on —— while on vigabatrin 3 gm/day. The subject was taken off Paxil and prescribed Prozac (dates not provided). The investigator assessed that the increase in seizures was not related to the vigabatrin, and an alternative etiology was Paxil usage, which was exacerbating her seizures. On ——, the subject was hospitalized for the event of worsening depression. The depression continued to worsen and on —— the subject overdosed on 75.5 mg of lorazepam and alcohol. According to the subject's mother, the subject ingested 151 0.5- milligram tablets in an apparent suicidal gesture and

was admitted to the medical floor. On ——— the subject left the hospital on her own; however she was located by the police on the same day and was subsequently admitted to the psychiatric floor. Admission plans included individual psychotherapy, medication management and a more structured educational program regarding interactions. The subject recovered and was discharged to her apartment with follow- up care provided by her neurologist and psychiatrist. The investigator assessed that the worsening major depression and suicidal gesture were not related to vigabatrin but instead associated with the subject's underlying history of depression, job loss and seizures. Vigabatrin ultimately was discontinued on 15Aug1997 since Topamax was an exclusionary concomitant medication.

Psychotic disorder

Subject 1250-0006 (AVENTIS-050523-0001211) This 38 year old female with a history of complex partial seizures with rare secondary generalization experienced psychosis and bipolar affective disorder while on vigabatrin. Subject was on vigabatrin ranging from 2 grams to 6 grams/day for 3 years and 21 days prior to the events. The subject was on vigabatrin 6 grams/day at the time of the event. The subject had no prior psychiatric history, but began exhibiting bizarre and manic behavior. On ——— the subject, while in church, began lifting her dress in front of the congregation and caused a commotion. The next evening, she rode her bicycle to her mother's apartment complex, took off all her clothes and ran around screaming and yelling about God and sex. Police and paramedics arrived. The subject was combative, incoherent and had to be physically restrained. She was taken to the Emergency Room and a complete medical work up was performed. The subject experienced a seizure and after her post- ictal state subsided, she continued to exhibit pronounced manic symptoms. She spoke rapidly and incoherently. Subject remained agitated and was kept in four point restraints. Urine toxicology screen was negative. Phenytoin serum levels were within normal limits upon hospital admission. Subject denied suicidal or homicidal ideations or thoughts of impending doom. On ——— subject was discharged from the hospital with a discharge diagnosis of bipolar affective disorder with psychosis. Prozac and Depakote were added to her medication regime. Vigabatrin dosing was continued at 6 grams/day unchanged. The event was considered to be resolved. The investigator assessed the events as not related to vigabatrin but rather to an idiopathic cause since the subject had been on vigabatrin for slightly more than 3 years at the time of event onset. Medical history included hypertension. Concomitant medication included phenytoin, hydrochlorothiazide, and enalapril.

b(6)

Subject 1265-0004 (AVENTIS-050523-0001487, AVENTIS-050523- 0002241)
This 32 year old male was hospitalized due to psychotic thoughts and post ictal psychotic disorder. Subject was on vigabatrin for at least three years five months prior to the event of psychotic thoughts. Subject presented to the emergency room stating that he was "not being able to get thoughts out of my head, feel like I want to hurt young people, feel like devils are working against the left side of my head". Subject had experienced these thoughts off and on for a several months. The subject described the feeling on the left side of his head as a pressure that was not painful, but felt sometimes as if the pressure was strong enough to push through his left eye and he expressed that sometimes he wanted to take his left eye out. Vital signs and neurological exam were normal. Mental status examination revealed; subject was pleasant, calm and cooperative. Good eye contact and impulse control. Speech was normal rate, tone and volume; however, he appeared to have difficulty expressing himself. Mood was worried. Affect was restricted. Thought processes were circumstantial and tangential. No paranoia. Denied auditory and visual hallucinations. Subject appeared delusional about the evil force in his head. Denied suicidal thoughts but did confirm homicidal thoughts toward kids but was rather vague and had no plan. The subject did express that he was angry sometimes with the way that kids treated their parents or upset that they were using drugs and felt that he would like to show them how to live a better way. Subject was able to spell the word "WORLD" forward and backward. Subject was oriented to person, place and time. Subject was able to name presidents back to Ford. Memory was 3/3 at zero minutes, 3/3 at five minutes. Intelligence was average. Judgment and insight were poor. Upon admission to the hospital unit, the subject was pleasant and cooperative and did not appear to be responding to any internal stimuli. Study drug remained unchanged due to the event. The event resolved without sequelae. He had a history of depression, without prior hospitalizations, and was treated with fluoxetine for the first time a few months ago. The investigator assessed the psychotic thoughts as not related to study drug and indicated fluoxetine as suspect.

Six months later, the subject was hospitalized for post ictal psychotic disorder related to temporal lobe epilepsy. Subject was on vigabatrin for at least four years prior to the event. Action taken was not provided. The event resolved without sequelae and the subject was discharged five days later. The investigator assessed the event as not related. An alternative etiology provided was underlying seizure. Relevant medical history included left temporal lobectomy 1988, motor vehicle accident 1985. Concomitant medications included carbamazepine, fluoxetine, olanzapine, naproxen and ibuprofen.

Rash

Subject 1202-0006 (AVENTIS-050523-0000941) This 48 year old female with a history of complex partial seizures with secondary generalization experienced an acute extensive rash on face and arms — while on vigabatrin 5 gm/day. The subject was on study medication for three years and thirteen days. The site examined the subject and felt that the rash appeared typical for cutaneous reaction to lamotrigine. Due to the subject's social status and fearing that the discontinuance of lamotrigine would worsen the subject's poor seizure control, the subject was prophylactically admitted to the hospital. The rash started one day prior to the hospital admission. The subject was loaded with phenytoin and put on seizure monitoring. The seizures were well controlled with the addition of phenytoin (serum phenytoin 06Dec: 13.7; serum phenytoin 07Dec: 17.3). The rash was treated with oral Benadryl (diphenhydramine) and lamotrigine taper. The event abated and the subject was discharged — with a diagnosis of skin rash secondary to lamotrigine. Vigabatrin continued unchanged. The investigator assessed the event as not related to vigabratin but rather to lamotrigine. Medical history included mental retardation and chronic static encephalopathy. Concomitant medications included lamotrigine, diazepam, Docusate, sorbitol, multivitamin, Dyazide and Lescol.

b(6)

ITP/Anemia

Subject 1234-0016 (AVENTIS-050523-0000652, AVENTIS-050523- 0000753, AVENTIS-050523-0000769, AVENTIS-050523-0000902) This 45 year old female with a history of complex partial and simple partial seizures experienced hypotension (50/40 mmHg), anemia and idiopathic thrombocytopenia (platelet count 6,000 uL) and was admitted to the hospital through the emergency room on — after two years and three months on vigabatrin therapy. Treatment included packed RBCs and platelets. The vigabatrin dose was 4.5 gm/day. The events were resolving. The investigator assessed these events as unlikely related to vigabatrin therapy; an alternative explanation was stated as undefined underlying disease.

Pediatric Subpopulation (non IS, age 3-<16)

Ovation reported that 141 pediatric subjects from the Overall Safety Population experienced SAEs (32.4%, 141/435; note-total does not include pediatric subjects from trials 0098 and 4021 because the SAEs from these trials were presented separately- see above; Source 12/28/07 submission, p.144). The percentage of pediatric subjects with SAEs (32%) was slightly lower than the percentage reported for the Overall population (44%) in the current submission. The SAEs reported for at least 1% of pediatric subjects were visual field defect (20.2%, 88/435), convulsion (3.5%, 15/435), hemianopia (3%, 13/435), and status epilepticus (1.8%, 8/435). Less frequently reported SAEs of special interest included 3 pediatric subjects with depression, 1 with suicidal ideation, 1 with hallucination, 1 with hallucination auditory, 1 subject with a rash, 1 with rash maculopapular, 1 with Stevens Johnson syndrome and 1 with acute renal failure. There were no SAEs of suicide, suicide attempt, acute hepatic failure, pancreatitis, aplastic anemia, or hypersensitivity reported for the pediatric subjects in the included studies.

IS Subpopulation

Ovation reported that 34% (75/223) of IS subjects in the Overall Safety Population experienced one or more SAEs (Source 12/28/07 Submission, p.166). The SAEs reported by at least 1% of subjects in the IS subpopulation were status epilepticus (4.9%, n=11), pneumonia (4.5%, n=10),

pyrexia (2.7%, n=6), convulsion (2.2%, n=5), bronchospasm (1.8%, n=4), viral infection (1.8%, n=4), and gastroesophageal reflux disease (1.4%, n=3), dehydration (1.4%, n=3), vomiting (1.4%, n=3), respiratory arrest (1.4%, n=3), lobar pneumonia (1.4%, n=3) and infantile spasms (1.4%, n=3).

SAEs Integrated Data

Ovation provided SAE risks by submission and combined for the development program studies. Those risks are included in the table below. The "Prior" column of the table includes information from US, primary non-US, and secondary studies through the 1998 Safety Update (3/1/07 submission, p.194). The "Current" column of the table includes information from the studies in this submission except for studies 0098 and 4021, which were reported separately (3/1/07 submission, p.193). The following table includes the SAEs that were reported for more than one subject.

SAEs Reported by More than One Subject, Integrated Data

Event Category Adverse Event	Prior Data (N=3440) % (n)	Current Data (N=1297) % (n)	Combined (N=4737) % (n)
Any SAE	10.7% (369)	43.7% (567)	19.8% (936)
Blood and Lymphatic Disorders			
Anemia	0.03% (1)	0.15% (2)	0.06% (3)
DIC	0.03% (1)	0.08% (1)	0.04% (2)
Cardiac Disorders			
Myocardial Infarction	0.06% (2)	0.08% (1)	0.06% (3)
Cardiac arrest	0.06% (2)	0	0.04% (2)
Ventricular Tachycardia	0.06% (2)	0	0.04% (2)
Congenital, Familial, and Genetic Disorders			
Tuberous sclerosis	0	0.15% (2)	0.04% (2)
Eye Disorders			
Scotoma	0.03% (1)	0.23% (3)	0.08% (4)
Visual disturbance	0	0.15% (2)	0.04% (2)
Gastrointestinal Disorders			
Vomiting	0.15% (5)	0.62% (8)	0.27% (13)
Abdominal pain	0.09% (3)	0.23% (3)	0.13% (6)
Diarrhea	0.06% (2)	0.23% (3)	0.08% (4)
Gastroesophageal reflux disease	0.03% (1)	0.23% (3)	0.08% (4)
Dyspepsia	0	0.23% (3)	0.06% (3)
Colitis ulcerative	0.06% (2)	0	0.04% (2)
Pancreatitis	0.06% (2)	0	0.04% (2)
Tooth disorder	0	0.15% (2)	0.04% (2)
General Disorders and Administration Site Conditions			
Pyrexia	0.29% (10)	0.85% (11)	0.44% (21)
Chest pain	0.15% (5)	0.08% (1)	0.13% (6)
Fatigue	0.03% (1)	0.39% (5)	0.13% (6)
Death	0	0.31% (4)	0.08% (4)

Drug interaction	0.12% (4)	0	0.08% (4)
Asthenia	0.09% (3)	0	0.06% (3)
Cyst	0.03% (1)	0.15% (2)	0.06% (3)
Unevaluable event	0	0.23% (3)	0.06% (3)
Drowning	0.06% (2)	0	0.04% (2)
Hepatobiliary Disorders			
Cholecystitis	0.12% (4)	0.08% (1)	0.11% (5)
Cholelithiasis	0.03% (1)	0.08% (1)	0.04% (2)
Infections and Infestations			
Pneumonia	0.35% (12)	0.93% (12)	0.51% (24)
Bronchitis	0.06% (2)	0.46% (6)	0.17% (8)
Urinary tract infection	0.15% (5)	0.15% (2)	0.15% (7)
Gastroenteritis	0.06% (2)	0.31% (4)	0.13% (6)
Influenza	0.06% (2)	0.31% (4)	0.13% (6)
Upper Respiratory tract infection	0	0.46% (6)	0.13% (6)
Viral infection	0.03% (1)	0.39% (5)	0.13% (6)
Cellulitis	0.12% (4)	0.08% (1)	0.11% (5)
Infection	0.06% (2)	0.23% (3)	0.11% (5)
Osteomyelitis	0.09% (3)	0.08% (1)	0.08% (4)
Otitis media	0.03% (1)	0.23% (3)	0.08% (4)
Sinusitis	0.06% (2)	0.15% (2)	0.08% (4)
Appendicitis	0.06% (2)	0.08% (1)	0.06% (3)
Lobar pneumonia	0	0.23% (3)	0.06% (3)
Pneumonia viral	0.03% (1)	0.15% (2)	0.06% (3)
Sepsis	0.06% (2)	0.08% (1)	0.06% (3)
Bronchitis acute	0.06% (2)	0	0.04% (2)
Candidiasis	0	0.15% (2)	0.04% (2)
Endocarditis	0.03% (1)	0.08% (1)	0.04% (2)
Gastroenteritis viral	0.03% (1)	0.08% (1)	0.04% (2)
Pharyngitis	0.03% (1)	0.08% (1)	0.04% (2)
Postoperative infection	0	0.15% (2)	0.04% (2)
Pyelonephritis	0.06% (2)	0	0.04% (2)
Respiratory syncytial virus	0	0.15% (2)	0.04% (2)
Injury, Poisoning, and Procedural Complications			
Injury	0.03% (1)	0.62% (8)	0.19% (9)
Overdose	0.15% (5)	0.15% (2)	0.15% (7)
Fall	0.17% (6)	0	0.13% (6)
Ankle fracture	0.12% (4)	0	0.08% (4)
Hip fracture	0.12% (4)	0	0.08% (4)
Joint dislocation	0.06% (2)	0.15% (2)	0.08% (4)
Accidental overdose	0.03% (1)	0.08% (1)	0.04% (2)
Cervical vertebral fracture	0.06% (2)	0	0.04% (2)
Facial bones fracture	0.06% (2)	0	0.04% (2)
Laceration	0.06% (2)	0	0.04% (2)
Lower limb fracture	0.06% (2)	0	0.04% (2)
Near drowning	0.03% (1)	0.08% (1)	0.04% (2)
Road traffic accident	0.03% (1)	0.08% (1)	0.04% (2)
Snake bite	0.06% (2)	0	0.04% (2)
Thermal burn	0.03% (1)	0.08% (1)	0.04% (2)
Tibia fracture	0.06% (2)	0	0.04% (2)

Wrist fracture	0	0.15% (2)	0.04% (2)
Investigations			
Electroencephalogram	0.03% (1)	0.08% (1)	0.04% (2)
Metabolism and Nutrition Disorders			
Dehydration	0.03% (1)	0.23% (3)	0.08% (4)
Hyponatremia	0.09% (3)	0	0.06% (3)
Anorexia	0	0.15% (2)	0.04% (4)
Diabetes mellitus inadequate control	0.06% (2)	0	0.04% (2)
Musculoskeletal and Connective Tissue Disorders			
Back pain	0.12% (4)	0.15% (2)	0.13% (6)
Osteoarthritis	0.09% (3)	0.15% (2)	0.11% (5)
Intervertebral disc protrusion	0.09% (3)	0	0.06% (3)
Arthralgia	0	0.15% (2)	0.04% (2)
Spinal osteoarthritis	0.06% (2)	0	0.04 (2)
Neoplasms Benign, Malignant, and Unspecified (incl Cysts and Polyps)			
Basal cell carcinoma	0.09% (3)	0	0.06% (3)
Breast cancer	0.06% (2)	0	0.04% (2)
Lung neoplasm malignant	0.06% (2)	0	0.04% (2)
Meningioma	0.03% (1)	0.08% (1)	0.04% (2)
Neoplasm malignant	0.06% (2)	0	0.04% (2)
Uterine leiomyoma	0.06% (2)	0	0.04% (2)
Nervous System Disorders			
Visual field defect	0.06% (2)	24.83% (322)	6.84% (324)
Convulsion	2.79% (96)	2.78% (36)	2.79% (132)
Status epilepticus	1.54% (53)	1.85% (24)	1.63% (77)
Hemianopia homonomous	0	1.46% (19)	0.4% (19)
Grand mal convulsion	0.38% (13)	0.23% (3)	0.34% (16)
Complex partial seizures	0.35% (12)	0.23% (3)	0.32% (15)
Hemianopia	0	1.16% (15)	0.32% (15)
Headache	0.12% (4)	0.77% (10)	0.3% (14)
Postictal state	0.35% (12)	0	0.25% (12)
Dizziness	0.09% (3)	0.62% (8)	0.23% (11)
Somnolence	0.15% (5)	0.39% (5)	0.21% (10)
Epilepsy	0.06% (2)	0.54% (7)	0.19% (9)
Partial seizures	0.09% (3)	0.39% (5)	0.17% (8)
Coordination abnormal	0.06% (2)	0.31% (4)	0.13% (6)
Tremor	0.09% (3)	0.23% (3)	0.13% (6)
Cerebrovascular accident	0.15% (5)	0	0.11% (5)
Lethargy	0.09% (3)	0.15% (2)	0.11% (5)
Hemiparesis	0.09% (3)	0.08% (1)	0.08% (4)
Simple partial seizures	0.09% (3)	0.08% (1)	0.08% (4)
Amnesia	0.06% (2)	0.08% (1)	0.06% (3)
Depressed level of consciousness	0.03% (1)	0.15% (2)	0.06% (3)
Disturbance in attention	0	0.23% (3)	0.06% (3)
Infantile spasms	0	0.23% (3)	0.06% (3)
Cerebral hemorrhage	0.06% (2)	0	0.04% (2)
Coma	0	0.15% (2)	0.04% (2)
Dyskinesia	0	0.15% (2)	0.04% (2)

Encephalopathy	0.06% (2)	0	0.04% (2)
Febrile convulsion	0	0.15% (2)	0.04% (2)
Hydrocephalus	0	0.15% (2)	0.04% (2)
Intracranial pressure increased	0.03% (1)	0.08% (1)	0.04% (2)
Memory impairment	0.06% (2)	0	0.04% (2)
Migraine	0.03% (1)	0.08% (1)	0.04% (2)
Partial seizures with secondary generalization	0.03% (1)	0.08% (1)	0.04% (2)
Syncope	2 (0.06%)	0	0.4% (2)
Psychiatric disorders			
Depression	0.32% (11)	0.77% (10)	0.44% (21)
Confusional state	0.38% (13)	0.54% (7)	0.42% (20)
Psychotic disorder	0.38% (13)	0.08% (1)	0.3% (14)
Aggression	0.29% (10)	0.23% (3)	0.27% (13)
Suicidal ideation	0.32% (11)	0.08% (1)	0.25% (12)
Suicide attempt	0.26% (9)	0.08% (1)	0.21% (10)
Abnormal behavior	0.12% (4)	0.23% (3)	0.15% (7)
Anxiety	0.12% (4)	0.23% (3)	0.15% (7)
Agitation	0.09% (3)	0.23% (3)	0.13% (6)
Acute psychosis	0.12% (4)	0	0.08% (4)
Disorientation	0.09% (3)	0.08% (1)	0.08% (4)
Irritability	0.09% (3)	0.08% (1)	0.08% (4)
Affect liability	0.03% (1)	0.15% (2)	0.06% (3)
Conversion disorder	0.03% (1)	0.15% (2)	0.06% (3)
Delusion	0.09% (3)	0	0.06% (3)
Hallucination, auditory	0.06% (2)	0.08% (1)	0.06% (3)
Mental status changes	0.06% (2)	0.08% (1)	0.06% (3)
Alcoholism	0.06% (2)	0	0.04% (2)
Delirium	0.03% (1)	0.08% (1)	0.04% (2)
Depression suicidal	0.06% (2)	0	0.04% (2)
Hallucination	0.03% (1)	0.08% (1)	0.04% (2)
Hostility	0	0.15% (2)	0.04% (2)
Insomnia	0	0.15% (2)	0.04% (2)
Mood disorder due to general medical condition	0.06% (2)	0	0.04% (2)
Paranoia	0.03% (1)	0.08% (1)	0.04% (2)
Personality disorder	0.06% (2)	0	0.04% (2)
Sleep disorder	0.03% (1)	0.08% (1)	0.04% (2)
Renal and Urinary Disorders			
Renal failure acute	0	0.15% (2)	0.04% (2)
Reproductive System and Breast Disorders			
Ovarian cyst	0.06% (2)	0	0.04% (2)
Respiratory, Thoracic, and Mediastinal Disorders			
Pneumonia aspiration	0.29% (10)	0.15% (2)	0.25% (12)
Dyspnea	0.12% (4)	0.15% (2)	0.13% (6)
Hypoxia	0.12% (4)	0.08% (1)	0.11% (5)
Respiratory arrest	0.06% (2)	0.23% (3)	0.11% (5)
Aspiration	0.09% (3)	0.08% (1)	0.08% (4)
Bronchospasm	0	0.31% (4)	0.08% (4)
Asthma	0.09% (3)	0	0.06% (3)

Respiratory distress	0.03% (1)	0.15% (2)	0.06% (3)
Respiratory failure	0.06% (2)	0.08% (1)	0.06% (3)
Acute respiratory distress syndrome	0.06% (2)	0	0.04% (2)
Apnea	0.03% (1)	0.08% (1)	0.04% (2)
Pneumothorax	0.06% (2)	0	0.04% (2)
Skin and Subcutaneous Tissue Disorders			
Rash	0	0.31% (4)	0.08% (4)
Rash maculopapular	0	0.15% (2)	0.04% (2)
Surgical and Medical Procedures			
Brain lobectomy	0.09% (3)	0.15% (2)	0.11% (5)
Hospitalization	0	0.15% (2)	0.04% (2)
Surgery	0	0.15% (2)	0.04% (4)
Vascular Disorders			
Deep vein thrombosis	0.06% (2)	0	0.04% (2)
Hematoma	0.06% (2)	0	0.04% (2)
Hypertension	0.03% (1)	0.08% (1)	0.04% (2)

Additional Analyses

The Division asked Ovation to submit a pooled comparative analysis of SAEs using the same 12 controlled trials that they used for the comparative mortality analysis (see above). In this pooled analysis, the SAE incidence was 31.2/100 PY (139/446 PY) for vigabatrin compared to 12.7/100 PY (21/166 PY) for carbamazepine, 14.7/100 PY (10/68 PY) for valproate, 0/100 PY (0/1.7PY) for gabapentin, and 49.5/100 PY (50/101 PY) for placebo. I reviewed the results of this analysis and identified the SAEs occurring in at least 5 vigabatrin subjects. I list those events below (gabapentin not shown since there were no SAEs).

SAEs by Treatment Group for Pool of Phase 2-3 Studies

Serious Adverse Event	Vigabatrin 446 PY (n=952) Rate/100 PY (n)	Carbamazepine 166 PY (n=229) Rate/100 PY (n)	Valproate 68 PY (n=113) Rate/100 PY (n)	Placebo 101 PY (n=393) Rate/100 PY (n)
Convulsion	5.6 (25)	1.2 (2)	5.9 (4)	7.9 (8)
Status epilepticus	2.9 (13)	0	1.5 (1)	2.0 (2)
Headache	2.2 (10)	0.6 (1)	0	5.9 (6)
Depression	2.2 (10)	2.4 (4)	0	2.0 (2)
Confusional State	1.8 (8)	0	0	0
Dizziness	1.6 (7)	0	0	2.0 (2)
Bronchitis	1.3 (6)	0.6 (1)	0	0
Upper Resp Tract Infect	1.3 (6)	0	0	6.9 (7)
Pneumonia	1.3 (6)	0	0	0
Injury	1.3 (6)	0	0	1.0 (1)
Fatigue	1.1 (5)	0	0	0

Source 3/14/08 Submission, Table 14.2; Person years from p.83.

In this pooled analysis, SAEs of status epilepticus, depression, confusional state, pneumonia, and fatigue occurred more frequently among vigabatrin subjects than placebo subjects.

Post Marketing Reports

Current Submission

Ovation provided a summary of serious AEs reported during the post marketing period for 3/15/97 through 6/30/07. Ovation identified 190 reports with 317 serious adverse events for the 10 year period. Post marketing report events were considered serious if reported as such, or if the event resulted in death. The highest percentage of SAE reports were for the Nervous System disorders (135 reports, 7.5% of total) and Eye disorders (23 reports, 1.3% of the total). The most common SAEs reported were visual field defect (107 events) and convulsions (7 events). In the following table, I list the post marketing SAEs with 3 or more event reports.

MedDRA SOC **MedDRA Preferred Term**	**Patients**	**Events**
Any SAE	190	317
Nervous System Disorders	135	151
Visual field defect	103	107
Convulsion	7	7
Somnolence	4	4
Tunnel vision	4	4
Brain edema	3	3
Encephalopathy	3	3
Status Epilepticus	3	3
Eye disorders	23	30
Visual disturbance	8	8
Strabismus	4	4
Optic atrophy	3	3
General Disorders and Administration Site Conditions	17	19
Death	3	3
Developmental delay	3	3
Condition aggravated	2	3
Injury, Poisoning, and Procedural Complications	14	14
Drug exposure during pregnancy	9	9
Congenital, Familial, and Genetic Disorders	12	36
Dysmorphism	4	4
Multiple congenital abnormalities	3	3
Dentofacial anomaly	2	3
Investigations	12	12
Nuclear magnetic resonance imaging brain abnormal	7	7
Psychiatric disorders	10	16
Surgical and Medical Procedures	6	6
Abortion induced	6	6
Musculoskeletal and Connective Tissue Disorders	4	4
Gastrointestinal Disorders	3	3
Infections and Infestations	3	3
Metabolism and Nutritional Disorders	3	3
Respiratory, Thoracic, and Mediastinal Disordes	3	5
Skin and Subcutaneous Tissue Disorders	2	4

Source Amendment Submission 12/28/07, Post Marketing Reports Section, Table 1.6a, pp. 147-155.

There were no SAE post marketing reports of anemia, liver failure, or hepatitis. Ovation identified one SAE of angioedema, one of rash, and one of rash maculopapular.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Previous Submissions
NDA and NDA Amendment
Forty-five percent (198/443) of vigabatrin exposed subjects discontinued prematurely from US epilepsy studies. Almost 23% (101/443) of enrolled vigabatrin subjects discontinued for lack of efficacy while 17.2% (76/443) discontinued for adverse events. In primary non-US epilepsy studies 29.2% (223/765) of vigabatrin exposed subjects discontinued prematurely. For this group, lack of efficacy (14.2%, 109/765) and adverse event (9.9%, 76/765) were the most commonly recorded reasons for discontinuation. The sponsor acknowledged that 2% (15/765) of the vigabatrin subjects enrolled in these studies discontinued for unknown reasons (Source: Amendment review, pp.20-21, and attachment table C-18).

In US controlled epilepsy studies, 14.4% (32/222) of vigabatrin subjects discontinued prematurely compared to 3.7% (5/135) of placebo subjects. The most common reason for withdrawal in these trials was adverse event with 10.8% (24/222) of vigabatrin subjects discontinuing for AEs compared to 2.2% (3/135) of placebo subjects. In non-US primary controlled epilepsy trials, 19.4% (65/335) of vigabatrin subjects discontinued prematurely. In those trials, 8.4% (28/335) of vigabatrin subjects discontinued for AEs compared to 2.5% (7/284) of placebo patients. As previously noted comparisons from these trials should be interpreted cautiously because 6 of the nine studies used a crossover design and only one of these used a washout period prior to crossover (Source: Amendment review, pp.20-23, attachment table C-18).

Safety Update (1/1/96-3/15/97)
For the epilepsy studies in the Safety Update, the sponsor reported that 42% (708/1,667) of enrollees withdrew prior to completion of the studies. The most common reasons for discontinuation were loss of efficacy (18%, 304/1,667) and adverse event (14%, 225/1,667). (Source Final Safety Update Review, p.4).

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Ovation reported that 66% (1,416/2,146) of the subjects in the included Overall Safety Population studies discontinued due to the following reasons: lack of efficacy 16.1% (n=345), administrative reasons 12.2% (n=261), other 11.8% (n=254), adverse event 9.3% (n=199), lost to follow up 9.1% (n=196), voluntarily withdrew 3.4% (n=74), protocol violation 3.2% (n=69), unknown 0.5% (n=10), death 0.2% (n=4), withdrawn by investigator 0.1% (n=2), and failed to meet entry criteria 0.1% (n=2) (Table 7, p.36). The subject disposition data that appear in table 7 come from the CRF termination pages. Subsequent presentations of discontinuations due to AEs were based on outcome information included in CRF AE pages. This distinction is important because inconsistencies between these two sources of information led to differences in the number of subjects identified as discontinuing due to AEs when comparing disposition table 7 with subsequent presentations of discontinuations due to AEs.

7.1.3.2 Adverse events associated with dropouts

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)
As noted above, 17.2% (76/443) of vigabatrin subjects in US epilepsy studies discontinued for adverse events. For vigabatrin subjects who discontinued for AEs in these studies, the most commonly reported AEs leading to discontinuation were drowsiness (n=12), seizures (convulsions + convulsions grand mal, n=9), depression (n=9), agitation (n=9), fatigue, headache, amnesia (n=7 each), paranoid reaction (n=6) and thinking abnormal (n=5). In primary non-US epilepsy studies, 9.9% (76/765) of vigabatrin exposed subjects discontinued for AEs. The most commonly reported AEs leading to discontinuation from the primary non-US epilepsy studies were seizures (convulsions +convulsions grand mal, n=14), depression (n=13), drowsiness, fatigue, insomnia (n=6, each), dizziness, headache, and aggressive reaction (n=5, each) (Source: Amendment Review, p23, attachment table C-18).

In US controlled epilepsy studies 10.8% of vigabatrin and 2.2% of placebo subjects discontinued for AEs (RR=4.9). In non US primary controlled trials, 8.4% of vigabatrin subjects and 2.5% of placebo subjects discontinued for AEs (RR 3.4) (Source: Amendment review, p.23 and attachment table C-18). Given the previously stated caveat about comparisons within non US primary epilepsy trials, 3.3% (11/335) of vigabatrin subjects and no placebo subjects discontinued for depression. No subjects from primary studies discontinued for hepatic injury or hepatic failure related events (Source Amendment review p.23 and attachment table C-18).

Secondary, non-CRF Data
In Secondary epilepsy studies, AEs led to discontinuation of 11.1% (100/900) vigabatrin exposed subjects. The most commonly reported AEs leading to discontinuation were drowsiness (1.3%, n=12), aggressive reactions, (1.2%, n=11), fatigue (1.1%, n=10), psychosis (0.9%, n=8) and agitation (0.9%, n=8). The sponsor did not summarize in tabular format the AEs leading to discontinuation for the non-CRF cohort (Source Amendment review, p.24, and attachment table C-19).

Safety Update (1/1/96-3/15/97)
The sponsor reported that 234 subjects (13%, 234/1,773) discontinued for adverse events from the trials included in the safety update. The sponsor did not provide a separate summary of the discontinuations due to AE's for this group and the remainder of the presentation focused on the discontinuations for the integrated data through the end of this Safety Update period (Source: Final Safety Update Review, p.4).

Current Submission

Overall Safety Population (3/16/97-6/30/07)

In the current submission, the sponsor reported that 7.8% (168/2,146) of vigabatrin subjects discontinued from trials for adverse events. The AEs leading to discontinuation of at least 5

subjects were convulsions (1.4%, 29/2,146), depression (0.7%, 14/2146), visual field defect (0.6%, 12/2,146), coordination abnormal (0.3%, 7/2,146), weight increased (0.3%, 7/2,146), status epilepticus (0.3%, 6/2,146), abnormal behavior (0.2%, 5/2146), and somnolence (0.2%, 5/2,146). Less frequently occurring, but potentially concerning AEs leading to discontinuation included rash (n=4), anemia (n=1), platelet count decreased (n=1), drug hypersensitivity (n=1), hypersensitivity (n=1), depression suicidal (n=1), suicide attempt (n=1), major depression (n=1), hallucination (n=1), hallucination visual (n=1), leukocytoclastic vasculitis, (n=1), Stevens Johnson Syndrome (n=1), renal failure acute (n=1), and hepatic failure (n=1) (Source: 10/10/06 Submission, pp.78-9). Most of these events were also SAEs and I discussed them above. Below, I summarize information from potentially concerning AEs leading to discontinuation that were not previously discussed.

Rash

0101/Subject 13420003 This 42 year old female subject with a history of eczema developed circular patches of burning and itching skin after 6 months of vigabatrin treatment. The rash was treated with cetaphil and mometasone furoate cream and the rash resolved with study drug taper. The subject was withdrawn from the study. The listed concomitant medication was tegretol.

1A/ Subject 280 This 1 year old male with a history of infantile spasms was terminated from a study for a skin rash and was lost to follow up.

Depression Suicidal

0098/Subject 12230014 This 47 year old male subject with a history of seizures, cortical blindness, hypertension, intermittent UTIs, decubitus ulcers, left hemiparesis, intractable headaches, allergies, depression, and suicidal ideation discontinued from the trial after 336 days of vigabatrin for depression and suicidal ideation. The event resolved one day after stopping study medication.

Pediatric Subpopulation (non IS, age 3-<16)

Ovation reported that 12% (53/444) of the pediatric patients included in the Overall Safety Population discontinued for adverse events. The discontinuation due to AE risk among these pediatric subjects was slightly higher than the risk observed in the overall population (8%). The adverse events leading to discontinuation of at least 1% of vigabatrin pediatric subjects were convulsion (4.3%, 19/444), and abnormal behavior (1.1%, 5/444). Other adverse events leading to discontinuation included depression (0.5%, 2/444), major depression (0.2%, 1/444), hallucination (0.2%, 1/444), Stevens Johnson Syndrome (0.2%, 1/444), and rash (0.2%, 1/444). For the pediatric subjects, there were no discontinuations for AEs of suicide, suicide attempt, acute hepatic failure, pancreatitis, aplastic anemia, or hypersensitivity (Source 12/28/07 submission, pp.151-3).

IS Subpopulation

Ovation reported that 7.6% (17/223) of the IS patients included in the Overall Safety Population discontinued for adverse events. The adverse events leading to discontinuation of more than one IS subjects were pneumonia (n=2), infantile spasms (n=2), and convulsions (n=2). Otitis media, sedation, hypertension, fecaloma, blood ALP increased, irritability, rash, pulmonary hemorrhage, gastrointestinal infection, postoperative infection, and somnolence led to discontinuation of one subject each (Source 12/28/07 submission, pp.171).

Integrated Data

Ovation provided discontinuation or AE risks by submission and combined for the development program studies. The following table includes the AEs that led to discontinuation of at least 3 subjects.

AEs that Led to Discontinuation of More than One Subject, Integrated Data

Event Category Adverse Event	Prior Data (N=3440) % (n)	Current Data (N=2148) % (n)	Combined (N=4855) % (n)
Any AE Leading to Discontinuation	14.3% (493)	7.8% (168)	13.6% (661)
Blood and Lymphatic Disorders			
Anemia	0.06% (2)	0.05% (1)	0.06% (3)
Cardiac Disorders			
Palpitations	0.09% (3)	0	0.06% (3)
Ear and Labyrinth Disorders			
Vertigo	0.26% (9)	0	0.19% (9)
Tinnitus	0.09% (3)	0	0.06% (3)
Eye Disorders			
Vision blurred	0.35% (12)	0.14% (3)	0.31% (15)
Diplopia	0.26% (9)	0.09% (2)	0.23% (11)
Visual disturbance	0.06% (2)	0.05% (1)	0.06% (3)
Gastrointestinal Disorders			
Nausea	0.44% (15)	0	0.31% (15)
Constipation	0.23% (8)	0.09% (2)	0.21% (10)
Vomiting	0.23% (8)	0.05% (1)	0.19% (9)
Diarrhea	0.23% (8)	0	0.16% (8)
Abdominal pain	0.17% (6)	0	0.12% (6)
Abdominal pain upper	0.12% (4)	0.05% (1)	0.10% (5)
General Disorders and Administration Site Conditions			
Fatigue	1.10% (38)	0.09% (2)	0.82% (40)
Gait disturbance	0.17% (6)	0	0.12% (6)
Feeling abnormal	0.15% (5)	0	0.10% (5)
Edema peripheral	0.09% (3)	0.09% (2)	0.10% (5)
Asthenia	0.12% (4)	0	0.08% (4)
Pain	0.09% (3)	0.05% (1)	0.08% (4)
Chest pain	0.09% (3)	0	0.06% (3)
Immune System Disorders			
Hypersensitivity	0.06% (2)	0.05% (1)	0.06% (3)
Infections and Infestations			
Pneumonia	0.03% (1)	0.09% (2)	0.06% (3)
Urinary tract infection	0.09% (3)	0	0.06% (3)
Injury, Poisoning, and Procedural Complications			
Investigations			
Weight increased	0.7% (24)	0.33% (7)	0.64% (31)
Metabolism and Nutrition Disorders			
Anorexia	0.12% (4)	0.05% (1)	0.10 (5)
Increased appetite	0.09% (3)	0.05% (1)	0.08% (4)
Musculoskeletal and Connective Tissue Disorders			

Arthralgia	0.17% (6)	0	0.12% (6)
Muscle twitching	0.09% (3)	0	0.06% (3)
Neoplasms Benign, Malignant, and Unspecified (incl Cysts and Polyps)			
Glioma	0.06% (2)	0.05% (1)	0.06% (3)
Nervous System Disorders			
Convulsion	1.13% (39)	1.35% (29)	1.4% (68)
Somnolence	1.10% (38)	0.23% (5)	0.89% (43)
Dizziness	0.81% (28)	0.14% (3)	0.64% (31)
Headache	0.84% (29)	0.05% (1)	0.62% (30)
Status epilepticus	0.58% (20)	0.28% (6)	0.54% (26)
Coordination abnormal	0.41% (14)	0.33% (7)	0.43% (21)
Memory impairment	0.49% (17)	0.09% (2)	0.39% (19)
Tremor	0.44% (15)	0.14% (3)	0.37% (18)
Visual field defect	0.03% (1)	0.56% (12)	0.27% (13)
Disturbance in attention	0.23% (8)	0.14% (3)	0.23% (11)
Lethargy	0.26% (9)	0.09% (2)	0.23% (11)
Balance disorder	0.23% (8)	0	0.16% (8)
Sedation	0.17% (6)	0.09% (2)	0.16% (8)
Parasthesia	0.17% (6)	0.05% (1)	0.14% (7)
Amnesia	0.15% (5)	0.05% (1)	0.12% (6)
Myoclonus	0.17% (6)	0	0.12% (6)
Nystagmus	0.17% (6)	0	0.12% (6)
Dyskinesia	0.12% (4)	0.05% (1)	0.10% (5)
Grand mal convulsion	0.15% (5)	0	0.10% (5)
Hyperkinesia	0.15% (5)	0	0.10% (5)
Partial seizures	0.12% (4)	0.05% (1)	0.10% (5)
Cognitive disorder	0.03% (1)	0.14% (3)	0.08% (4)
Complex partial seizures	0.09% (3)	0.05% (1)	0.08% (4)
Movement disorder	0.09% (3)	0.05% (1)	0.08% (4)
Postictal state	0.12% (4)	0	0.08% (4)
Dysarthria	0.03% (1)	0.09% (2)	0.06% (3)
Psychomotor hyperactivity	0.6% (2)	0.05% (1)	0.06% (3)
Simple partial seizures	0.06% (2)	0.05% (1)	0.06% (3)
Speech disorder	0.06% (2)	0.05% (1)	0.06% (3)
Psychiatric disorders			
Depression	1.66% (57)	0.65% (14)	1.46% (71)
Confusional state	0.78% (27)	0.14% (3)	0.62% (30)
Irritability	0.73% (25)	0.19% (4)	0.60% (29)
Aggression	0.70% (24)	0.19% (4)	0.58% (28)
Abnormal behavior	0.58% (20)	0.23% (5)	0.51% (25)
Insomnia	0.41% (14	0.14% (3)	0.35% (17)
Psychotic disorder	0.39% (17)	0	0.35% (17)
Agitation	0.20% (7)	0.19% (4)	0.23% (11)
Anxiety	0.26% (9)	0.09% (2)	0.23% (11)
Paranoia	0.23% (8)	0.09% (2)	0.21% (10)
Suicidal ideation	0.29% (10)	0	0.21% (10)
Expressive language disorder	0.23% (8)	0	0.16% (8)
Mental disorder	0.20% (7)	0.05% (1)	0.16% (8)
Hallucination	0.17% (6)	0.05% (1)	0.14% (7)
Affect liability	0.15% (5)	0.05% (1)	0.12% (6)
Hallucination, auditory	0.15% (5)	0	0.10% (5)

Mood swings	0.09% (3)	0.09% (2)	0.10% (5)
Suicide attempt	0.12% (4)	0.05% (1)	0.10% (5)
Delusion	0.09% (3)	0.05% (1)	0.08% (4)
Disorientation	0.06% (2)	0.09% (2)	0.08% (4)
Mental status changes	0.06% (2)	0.09% (2)	0.08% (4)
Nervousness	0.12% (4)	0	0.08% (4)
Abnormal dreams	0.09% (3)	0	0.06% (3)
Anger	0.09% (3)	0	0.06% (3)
Conversion disorder	0.03% (1)	0.09% (2)	0.06% (3)
Crying	0.09% (3)	0	0.06% (3)
Dysphemia	0.09% (3)	0	0.06% (3)
Hallucination visual	0.06% (2)	0.05% (1)	0.06% (3)
Panic attack	0.09% (3)	0	0.06% (3)
Sleep disorder	0.09% (3)	0	0.06% (3)
Thinking abnormal	0.09% (3)	0	0.06% (3)
Renal and Urinary Disorders			
Dysuria	0.12% (4)	0	0.08% (4)
Respiratory, Thoracic, and Mediastinal Disorders			
Dyspnea	0.12% (4)	0.09% (2)	0.12% (6)
Skin and Subcutaneous Tissue Disorders			
Rash	0.23% (8)	0.19% (4)	0.25% (12)
Dermatitis allergic	0.12% (4)	0	0.08% (4)
Pruritis generalized	0.09% (3)	0	0.06% (3)
Vascular Disorders			
Hypertension	0.03% (1)	0.09% (1)	0.06% (3)

Source NDA Amendment Table 66, pp. 193-205

Additional Analyses

The Division asked Ovation to submit a pooled comparative analysis of AEs leading to dropout using the same 12 controlled trials that they used for the comparative mortality analysis and SAE analysis (see above). In this pooled analysis, the incidence for any AE leading to dropout was 32.3/100 PY (144/446 PY) for vigabatrin compared to 40.0/100 PY (63/166 PY) for carbamazepine, 20.6/100PY (14/113) for valproate, 58.8/100 PY (1/1.7 PY) for gabapentin, and 13.9/100 PY (14/101) for placebo. I reviewed the results of this analysis and identified the AEs leading to dropout of at least 5 vigabatrin subjects. I list those events below.

Discontinuations for Adverse Events by Treatment Group for Pool of Phase 2-3 Studies

Adverse Event Leading to Dropout	Vigabatrin 446 PY (n=952) Rate/100 PY (n)	Carbamazepine 166 PY (n=229) Rate/100 PY (n)	Valproate 68 PY (n=113) Rate/100 PY (n)	Gabapentin 1.7 PY (n=9) Rate/100 PY (n)	Placebo 101 PY (n=393) Rate/100 PY (n)
Depression	3.2 (15)	1.2 (2)	2.9 (2)	0	1.0 (1)
Headache	3.0 (14)	0.6 (1)	0	0	2.0 (2)
Convulsion	2.4 (11)	0	2.9 (2)	0	2.0 (2)
Fatigue	1.9 (9)	5.4 (9)	1.5 (1)	0	1.0 (1)
Somnolence	1.7 (8)	1.9 (9)	2.9 (2)	0	2.0 (2)
Rash	1.7 (8)	7.2 (12)	0	0	0
Dizziness	1.5 (7)	2.4 (4)	0	0	0
Disturbance	1.5 (7)	1.8 (3)	0	0	0

in Attention					
Agitation	1.5 (7)	0	0	0	0
Confusional state	1.3 (6)	0	0	0	0
Weight increased	1.3 (6)	1.8 (3)	0	0	1.0 (1)
Insomnia	1.3 (6)	0.6 (1)	0	0	3.0 (3)
Irritability	1.1 (5)	1.2 (2)	1.5 (1)	58.8 (1)	0
Status epilepticus	1.1 (5)	0	0	0	0
Lethargy	1.1 (5)	1.8 (3)	1.5 (1)	0	0
Vomiting	1.1 (5)	1.2 (2)	5.9 (4)	0	1.0 (1)

Source 3/14/08 Submission, Table 14.3; Person years data from p.83

In this pooled analysis, AEs of headache, agitation, confusional state, and status epilepticus appeared to lead to dropout more commonly among vigabatrin subjects than control subjects. Depression AEs occurred more frequently among vigabatrin, carbamazepine and valproate subjects than placebo subjects

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

As noted in the Amendment review, for most of the primary data studies, CRFs recorded responses to open ended questions about adverse events. In addition to recording the AE, the CRF AE sheets were designed to also capture information about severity, action taken and opinions about causality. The sponsor took a different approach to collecting adverse events from non US studies. In addition to capturing the AEs recorded on the CRF AE sheets, the sponsor extracted AEs from comment fields, concomitant medication pages, physical and neurological exams, laboratory pages, and letters. AEs from sources other than the CRF AE sheets had no information about severity, action taken or opinions about causality (Amendment review, p.12).

Treatment emergent AEs were defined as those AEs that occurred for the first time or that worsened during the study period, regardless of investigator assessment of causality (Amendment review, p.12).

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Investigators recorded responses to open ended questions about adverse events on adverse event sheets in the CRF. Ovation defined treatment-emergent adverse events as any adverse event that occurred after the subject had taken one or more doses of vigabatrin (adverse events recorded during placebo baseline periods before active dose of vigabatrin were not included). If a medical

condition or adverse event present before the first dose of medication worsened in severity after taking study medication, the worsening of the condition was considered a treatment-emergent adverse event (12/28/07 submission, p.33).

During the course of the review, the Division discovered information in narrative summaries (lab data, clinical details, etc.) that was not present in the CRFs. When asked about this, Ovation explained that for a number of studies included in the current submission, the previous sponsor did not record SAE data in the CRF but instead captured this information in a separate database (GADERS). The studies using this procedure were 0294, 0223, 0221, 0192, 0222, 0101, 0098, 0118, 4103, 0201, and 0242. Ovation stated that the procedure for reporting SAEs required investigators to notify clinical monitors by fax, overnight mail, or telephone call within one working day. The clinical monitor completed an SAE form and forwarded the form to the company for entry into the GADERS database. Clinical monitors were required to provide the SAE form to the study sites. The investigators apparently did not have to sign off on the information included in the SAE form. When asked if there were any data included in GADERS that were not submitted in the Amendment, Ovation re-queried their database and identified 25 SAE reports that had not been submitted. Ovation submitted narratives for 21 of the SAEs (5 VFD defects were mentioned in the text of a study report but no narratives were written). As part of a broader effort, Ovation also identified 4 SAEs from studies that captured SAEs on the CRFs (R003 and 4020). (Source 5/1/08 Submission, pp. 136-9).

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

In their 3/1/07 submission, Ovation provided a table that listed the adverse event investigator verbatim terms and the MedDRA preferred terms to which the verbatim terms were coded. The table included the terms for the Integrated Data (all epilepsy studies) and provided separate columns for events from prior submissions, the current submission, and a column for combined data (prior data plus current data).

The coding of adverse events generally appeared appropriate although there were several notable examples of unhelpful and inappropriate coding. Ovation used preferred terms that were too nonspecific to be useful. In addition, the result of coding in some cases was to split seemingly related events and to lump unrelated events. Lastly there were infrequent occurrences where the coding appeared incorrect.

An example of the use of a nonspecific term was the preferred term of "Pain". Ovation coded a number of events including ankle pain, leg pain, and chest pain. Relying on this preferred term does not provide a useful summary of the subsumed events.

An example of splitting of related events was use of the preferred terms laceration and skin laceration. These preferred terms appeared to subsume many of the same type of events with no obvious reason as to why one preferred term was selected over the other in any particular instance. Another example of splitting was when despite having a preferred term of "Iron Deficiency Anemia", Ovation coded the adverse event of iron deficient microcytic anemia to the

preferred term "Microcytic anemia". Another splitting example was the use of preferred terms Otitis media and Ear infection which appeared to subsume similar events.

An example of lumping unrelated items was the use of the preferred term General symptom. This preferred term included events such as feet swollen/painful, abdomen and back pain, embedded earrings, bad dreams, blurred vision and sleepiness, chills and diarrhea, and ankle pain.

Lastly, there were occasional eamples where the coding of the verbatim term appeared incorrect. The verbatim term microcytic hyperchromic anemia was coded to hypochromic anemia. The verbatim term "Parent reports Pt's head us "hot" but not rest of body; crying unconsol" was coded to "Tympanic Membrane disorder". In another instance, the verbatim term "Split lip requiring stitches when playing basketball" was coded to chapped lips. Two cases of mycosis (funfgal skin infections) were coded to mycosis fungoides (cutaneous T-cell lymphoma).

7.1.5.3 Incidence of common adverse events

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

Primary Data
The NDA Amendment review included a table (Appendix F2) that reported the pooled AE risks from the 2 US controlled epilepsy trials (024,025), a Canadian placebo controlled trial (021), and the first period crossover for selected non US primary trials. Table F2 included AEs that occurred in at least 1% of vigabatrin subjects and were numerically more frequent compared to placebo The sponsor proposed using information from table F2 in labeling (but using a 2% cutoff) to illustrate adverse event risks in controlled trials. I present information from Table F2 below.

Most Frequently Reported Adverse Events in Placebo-Controlled Epilepsy Trials (>=1% of SABRIL Patients and Numerically More Frequent Than Placebo Patients)

Body System/Adverse event	Vigabatrin (n=406)	Placebo (n=311)
Neurologic		
Headache	28.1%	26.0%
Drowsiness	25.9%	15.1%
Dizziness	19.2%	13.5%
Nystagmus	11.6%	5.1%
Tremor	10.8%	7.7%
Amnesia	9.4%	3.5%
Ataxia	8.1%	4.5%
Confusion	6.9%	2.6%
Parasthesia	6.2%	1.9%
Coordination abnormal	5.2%	2.9%
Gait abnormal	4.9%	3.5%
Concentration impaired	4.7%	1.6%
Speech disorder	3.7%	1.0%

Vertigo	3.7%	2.3%
Hypoesthesia	3.2%	2.3%
Hyporeflexia	3.0%	0.3%
Hyperreflexia	1.7%	1.3%
Tinnitus	1.7%	1.3%
Convulsion Grand Mal	1.5%	1.3%
Twitching	1.5%	0.3%
Hearing impaired	1.0%	0
Myopathy	1.0%	0.3%
Neuropathy	1.0%	0
Psychiatric		
Depression/psychotic depression	12.1%	3.5%
Agitation	10.8%	8.0%
Anxiety	7.1%	4.2%
Emotional lability	4.7%	2.9%
Thinking abnormal	4.2%	0.6%
Aggressive Reaction	3.0%	1.6%
Nervousness	3.0%	2.6%
Personality Disorder	1.5%	1.0%
Dreaming abnormal	1.2%	0.3%
Nightmare	1.2%	0.3%
Paranoid reaction	1.2%	0.3%
Euphoria	1.0%	0
Suicide attempt	1.0%	0
Gastrointestinal System		
Nausea	9.1%	8.0%
Diarrhea	6.9%	5.5%
Abdominal Pain	6.2%	4.2%
Constipation	5.9%	3.5%
Vomiting	5.7%	4.8%
Tooth disorder	3.4%	1.6%
Hemorrhoids	1.2%	0
Body as a Whole		
Fatigue	26.1%	15.8%
Asthenia	5.2%	5.1%
Fever	3.7%	2.6%
Chest pain	2.7%	2.6%
Malaise	2.2%	1.3%
Generalized edema (including edema)	2.0%	0.6%
Face edema	1.5%	0.3%
Rigors	1.2%	0
Respiratory System		
Throat Irritation	6.7%	5.8%
Upper Respiratory Tract Infection	5.4%	3.2%
Sinusitis	2.0%	1.9%
Dyspnea	1.5%	0.3%
Infectious Disease		
Infection Viral	14.3%	12.2%
Infection Fungal	1.5%	0.6%
Dermatologic		
Pruritis	1.5%	0.3%
Sweating Increased	1.5%	0.6%

Musculoskeletal System		
Arthralgia	7.4%	4.2%
Back pain	5.9%	4.2%
Arthrosis	2.5%	1.9%
Myalgia	1.7%	1.6%
Metabolic & Nutritional		
Weight Increase	7.9%	3.9%
Appetite Increased	2.7%	2.6%
Reproductive, Female		
Dysmenorrhea	3.9%	1.6%
Menstrual Disorder	2.0%	1.0%
Amenorrhea	1.2%	0.6%
Vaginitis	1.2%	0.3%
Urinary System		
Urinary Tract Infection	3.2%	0.3%
Urinary Disorder	1.2%	0
Urinary Retention	1.0%	0
Cardiovascular		
Peripheral edema (including dependent and leg)	5.7%	1.0%
Ophthalmologic		
Vision abnormal	10.1%	6.1%
Diplopia	7.9%	5.5%
Eye Pain	2.5%	0.6%
Eye Abnormality	1.7%	0.6%
Hematologic		
Purpura	4.4%	3.5%
Anemia/hypochromic anemia	1.5%	0.6%
Lymphadenopathy	1.0%	0.3%
Ear, Nose, and Throat		
Earache	2.0%	1.3%
Immunologic		
Allergy	1.2%	0.3%
Other adverse events reported in >=1% of patients but equally or more frequent in the placebo group include **Neurologic**: convulsions (including condition aggravated), aphasia, hypokinesia, hypertonia. **Psychiatric**: insomnia, depersonalization, apathy. **GI**: dyspepsia, anorexia, abdominal distension. **Body as a Whole**: pain, trauma, injury, hot flushes. **Respiratory**: congestion, coughing, rhinorrhea, bronchitis, epistaxis, rhinitis. **Infectious Disease**: influenza-like symptoms, infection, herpes simplex. **Dermatologic**: rash, acne, alopecia, eczema, erythema, urticaria, furunculosis. **Metabolic and Nutritional**: weight decrease, phosphatase alkaline increased. **Urinary System**: urinary frequency, urinary incontinence. **Hepatic and Biliary**: GGT increased. **Hematologic**: leucopenia. **Ophthalmologic**: conjunctivitis.		

Source Amendment Review, Appendix Table F2

Safety Update (1/1/96-3/15/97)

The controlled epilepsy trials in the safety update used active comparator groups (valproate and carbamazepine). The percentage of subjects reporting AEs was 83% (280/338) for Sabril, 66% (75/113) for valproate and 85% (194/229) for carbamazepine. Notably, valproate was less

frequently associated with CNS and psychiatric AEs than Sabril. Carbamazepine had an increased risk of skin AEs compared to the other treatments. The following table compares the commonly reported adverse events for Sabril, valproate, and carbamazepine.

A comparison of selected adverse events from the newly completed controlled trials included in the final safety update

Event	Sabril®	Valproate	Carbamazepine
Drowsiness	23% (78/338)	16% (18/113)	28% (64/229)
Fatigue	18% (60/338)	13% (15/113)	21% (49/229)
Dizziness	12% (42/338)	6% (7/113)	13% (29/229)
Weight increase	10% (34/338)	10% (11/113)	5% (11/229)

Compared to the data presented in the NDA amendment (Table F1: Incidence of Adverse events by preferred terms for US and Primary Non US placebo controlled epilepsy trials), the percentage of vigabatrin subjects reporting these events had not substantially changed.

For both the US and non-US uncontrolled trials in the Safety Update, the most commonly reported body systems for AE's were CNS, GI, and Psychiatric. Drowsiness, headache, infection viral and fatigue were commonly reported events in these trials. There were no new cases of hepatic failure, renal failure, Stevens Johnson syndrome, aplastic anemia, or rhabdomyolysis (Safety Update Review, pp. 9-10).

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Ovation reported that 77% (1,651/2,146) of subjects in the safety update population experienced one or more adverse events (12/28/07 submission, p.39). The following events were reported by at least 5% of the study subjects: visual field defect (15.7%, 336), Upper respiratory tract infection (10.8%, 232), headache (9.8%, 210), convulsion (8.3%, 178), dizziness (8.3%, 177), somnolence (7.9%, 169), fatigue (7.7%, 165), weight increased (7.5%, 160), nasopharyngitis (7.2%, 154), otitis media (5.9%, 126), pyrexia (5.4%, 116), and insomnia (5.1%, 110) (12/28/07 submission, Table 10, p.41).

I reviewed Appendix 3 table 4.1.3 that included all AEs reported for the safety update population to look for less frequent events of potential concern. There were 18 (0.8%, 18/2146) anemia AEs, 9 (0.4%, 9/2146) neutropenia AEs, and six platelet count decreased AEs (0.3%, 6/2146), but no aplastic anemia or agranulocytosis AEs. There were 17 events (0.8%, 17/2146) coded as hypersensitivity. There were 3 events coded to the term swelling face and 2 events of face edema. There were 12 AEs coded as drug toxicity and 11 (0.5%, 11/2146) coded as adverse drug reaction for which no additional information was available. There were 2 events of acute renal failure, one of hepatic failure and one of hepatic necrosis. There was one event of skin exfoliation and one event of Stevens Johnson Syndrome.

Pediatric Subpopulation (non IS, age 3-<16)
Ovation reported that 76% (337/444) of pediatric patients in the Overall population experienced one or more adverse events. The percentage of pediatric subjects reporting AEs was similar to the percentage of subjects with AEs in the overall population (77%). Ovation provided Table 38, which summarized the AEs reported by at least 5% of pediatric subjects. The AEs in this table were generally similar to and occurred at a similar frequency as the AEs reported for at least 5% of the Overall population. There appeared to be an increased risk for the following three AEs among pediatric subjects: convulsion (peds 15.8%, 70/444, overall 8.3%, 178/2146), Headache (peds 14.4%, 64/444, overall 9.8%, 210/2146), and weight increase (peds 14.2%, 63/444, overall 7.5%, 160/2146). The following AEs were reported by at least 5% of pediatric subjects but not by at least 5% of subjects in the Overall group: influenza (7%, 31/444), viral infection (7%, 31/444), pharyngitis streptococcal (6.5%, 29/444), sinusitis (5.9%, 26/444), abnormal behavior (8.1%, 36/444), aggression (6.5%, 29/444), and vomiting (7.2%, 32/444) Insomnia was the only AE reported by at least 5% of subjects in the overall population but not for the pediatric subpopulation. (Source: 12/28/07 submission, pp.120-1).

IS Subpopulation
Ovation reported that 93% (208/223) of subjects from IS trials experienced one or more AEs. The AE risk was higher in the IS subpopulation than the Overall population or the Pediatric non-IS subjects subpopulation. The following table summarizes the AE risks occurring in at least 5% of the Overall population and for the IS subpopulation.

Adverse Event	IS Subpopulation (n=223) % (n)	Overall population (n=2148) % (n)
Infections and Infestations		
Upper Respiratory tract infection	47.5% (106)	11% (232)
Otitis media	36.3% (81)	5.9% (126)
Viral infection	19.7% (44)	4.3% (93)
Pneumonia	13% (29)	2.1% (44)
Ear infection	10.8% (24)	2.6% (55)
Sinusitis	7.2% (16)	3.7% (80)
Bronchitis	6.3% (14)	2.5% (54)
Candidiasis	5.4% (12)	0.7% (14)
Gastroenteritis viral	5.4% (12)	1.9% (41)
Urinary tract infection	5.4% (12)	2.1% (46)
Nasopharyngitis	3.1% (7)	7% (154)
Nervous System Disorders		
Sedation	17.9% (40)	3.0% (65)
Somnolence	17.0% (38)	7.9% (169)
Lethargy	6.7% (15)	2.2% (48)
Convulsion	6.3% (14)	8.3% (179)
Status epilepticus	5.8% (13)	1.3% (28)
Headache	0.5% (1)	9.8% (210)
Gastrointestinal Disorders		
Vomiting	16.6% (37)	4.9% (105)
Constipation	13% (29)	3.3% (71)
Diarrhea	12.6% (28)	4.7% (101)
General Disorders and Administration Site Conditions		

Pyrexia	24.2% (54)	5.4% (115)
Unevaluable event	5.4% (12)	2% (42)
Fatigue	0	7.7% (165)
Psychiatric disorders		
Irritability	19.7% (44)	9.0% (20)
Insomnia	11.2% (25)	5.8% (13)
Respiratory, Thoracic, and Mediastinal Disorders		
Nasal Congestion	8.5% (19)	1.7% (36)
Cough	5.4% (12)	1.8% 938)
Skin and Subcutaneous Tissue Disorders		
Rash	9.2% (21)	4.4% (95)
Metabolism and Nutritional Disorders		
Decreased appetite	7.6% (17)	1.4% (31)
Investigations		
Weight increased	0.5% (1)	7.5% (160)

Source 12/28/07 Submission, Table 56, pp. 161-162; Table 10, p.41.

The AEs reported by at least 5% generally occurred more frequently among the IS subjects compared to the Overall population subjects. The greatest differences between the IS and Overall populations were for infection related AEs. While the risks for convulsion were similar for the IS (6.3%) and Overall populations (8.3%), the risk for status epilepticus was notably higher among IS subjects (5.8%) compared to the Overall subjects (1.3%).

Integrated Data

Ovation reported that 96% (3,917/4,077) of the vigabatrin treated epilepsy subjects in the Integrated database reported one or more adverse events (12/28/07 submission, p.180). Ovation provided Table 64 which summarized the adverse events occurring in at least 5% of subjects and I reproduce that table below. Please note that the Prior data and Current data populations cannot be summed to arrive at the Combined population size because 733 subjects contributed data to both the prior and current columns, mostly during study 0098 (12/28/07 submission, p.179).

Table 64. Adverse Events Occurring in ≥5% of Vigabatrin-Treated Subjects- Prior, Current and Combined

Event Category Adverse Event	Prior Data (N=2662) % (n)	Current Data (N=2148) % (n)	Combined (N=4077) % (n)
Any Adverse Event	85.1% (2266)	76.9% (1651)	96.1% (3917)
Eye Disorders			
Vision blurred	6.6% (175)	3.7% (80)	6.3% (255)
Diplopia	6.8% (182)	3.2% (69)	6.2% (251)
Gastrointestinal Disorders			
Nausea	8.3% (222)	2.8% (61)	6.9% (283)
Diarrhea	6.5% (173)	4.7% (101)	6.7% (274)
Vomiting	5.4% (143)	4.9% (105)	6.1% (248)
Constipation	5.0% (132)	3.3% (71)	5.0% (203)
General Disorders and Administration Site Conditions			
Fatigue	19.0% (505)	7.7% (165)	16.4% (670)

Pyrexia	4.3% (114)	5.4% (115)	5.6% (229)
Infections and Infestations			
Nasopharyngitis	9.8% (262)	7.2% (154)	10.2% (416)
Upper respiratory tract infection	6.4% (171)	10.8% (232)	9.9% (403)
Influenza	5.9% (158)	4.0% (86)	6.0% (244)
Otitis media	0.9% (24)	5.9% (126)	3.7% (150)
Investigations			
Weight increased	9.6% (255)	7.5% (160)	10.2% (415)
Musculoskeletal and Connective Tissue Disorders			
Back pain	5.3% (141)	2.2% (47)	4.6% (188)
Nervous System Disorders			
Headache	20.1% (534)	9.8% (210)	18.3% (744)
Somnolence	19.8% (528)	7.9% (169)	17.1% (697)
Dizziness	16.7% (445)	8.2% (177)	15.3% (622)
Convulsion	10.2% (272)	8.3% (179)	11.1% (451)
Visual field defect	0.2% (4)	16.3% (349)	8.7% (353)
Tremor	7.8% (208)	3.8% (82)	7.1% (290)
Nystagmus	7.7% (205)	3.8% (81)	7.0% (286)
Memory impairment	7.5% (199)	3.4% (73)	6.7% (272)
Coordination abnormal	6.6% (175)	4.1% (88)	6.5% (263)
Psychiatric Disorders			
Depression	8.8% (234)	4.7% (100)	8.2% (334)
Insomnia	6.0% (160)	5.1% (110)	6.6% (270)
Irritability	6.2% (166)	4.8% (104)	6.6% (270)
Skin and Subcutaneous Tissue Disorders			
Rash	5.0% (133)	4.4% (95)	5.6% (228)

Ovation commented that with the exceptions of visual field defect, upper respiratory tract infection, otitis media, and pyrexia, the proportion of subjects reporting AEs was higher in the prior data compared to the current data (NDA Amendment, p.179). The Division asked Ovation to search for explanations for the differences in AE risk when comparing prior and current data. In a 4/15/08 response, Ovation provided results from analyses looking for explanatory factors. Ovation noted that study 4020, included among the current data, did not uniformly capture AEs. When Ovation excluded the AE risk data from study 4020, the differences between current and prior data were less marked but did not completely resolve. Ovation noted that a higher proportion of person time in the prior data set was at vigabatrin doses of >=4g/day (27.4%) compared to the current data (16.3%). Ovation found that the current data included a higher proportion of pediatric patients compared to the prior data but when the AE risks for adults and children were analyzed separately, the differences between prior and current data persisted. Similarly, after stratifying by study design (controlled vs. uncontrolled), study dosing (fixed dose vs. flexible dose) and country (US studies vs. non US studies) the differences in AE risks in the prior and current data persisted. Based on these results, Ovation felt the reasons for the higher AE risks in the prior data were mostly due to the use of higher vigabatrin doses in prior data studies and underreporting of AE risks in study 4020, which was included with the current data (Source, Ovation response to Division questions, 4/15/08, pp 6-22)

7.1.5.4 Common adverse event tables

Current Submission

In their proposed vigabatrin labeling, Ovation listed the AEs that occurred in at least 5% of vigabatrin subjects in the Integrated database (see combined column in Table 64 above). Ovation also identified depression and convulsion as the adverse events resulting in discontinuation of at least 1% of subjects treated with vigabatrin.

7.1.5.5 Identifying common and drug-related adverse events

Current Submission
In their proposed labeling, to illustrate treatment related adverse events from clinical trials, Ovation used a table of adverse events occurring in at least 5% of vigabatrin treated subjects from the 2 placebo controlled trials submitted in the original NDA (024 and 025). I reproduce that table below.

Table 1. Treatment-Related Adverse Events Occurring in ≥5% of Patients (Studies 024 and 025)

Body System Preferred Term	Vigabatrin [N=222] %	Placebo [N=135] %
General disorders and administration site conditions		
Fatigue	28.4	14.8
Irritability	9.5	5.9
Gait disturbance	5.4	3.0
Nervous system disorders		
Somnolence	24.3	10.4
Dizziness	19.4	13.3
Headache	14.4	11.9
Nystagmus	13.5	8.1
Tremor	10.8	5.9
Coordination abnormal	8.6	1.5
Amnesia	9.0	3.0
Eye Disorders		
Vision blurred	10.8	4.4
Diplopia	5.4	3.7
Investigations		
Weight increased	7.2	3.0
Psychiatric disorders		
Paraesthesia	6.3	1.5
Depression	6.3	3.0
Disorientation	5.4	0.74
Hypoaesthesia	5.0	1.5
Gastrointestinal Disorders		
Nausea	6.8	5.9

The Division asked Ovation to submit a pooled comparative analysis of AEs using the same 12 controlled trials that they used for the comparative mortality analysis, SAE analysis, and AE leading to dropout analysis (see above). In this pooled analysis, the incidence for any AE was 187.3/100PY (873/466 PY) for vigabatrin compared to 116.9/100 PY (194/166 PY) for carbamazepine, 114.7/100 PY (78/68 PY) for valproate, 470.6/100 PY (8/1.7 PY) for gabapentin, and 342.6/100 PY (346/101 PY) for placebo. I reviewed the results of this analysis and identified the AEs occurring in at least 1% (n=11) of vigabatrin subjects and more frequently when compared to placebo. I list those events below.

Adverse Event	Vigabatrin 466 PY (n=952) Rate/100PY (n)	Carbamazepine 166 PY (n=229) Rate/100PY (n)	Valproate 68 PY (n=113) Rate/100PY (n)	Gabapentin 1.7 PY (n=9) Rate/100PY (n)	Placebo 101 PY (n=393) Rate/100PY (n)
Depression	13.3 (62)	4.2 (7)	5.9 (4)	0	12.9 (13)
Memory impairment	12.2 (57)	9.6 (16)	1.5 (1)	0	11.9 (12)
Coordination abnormal	11.4 (53)	4.8 (8)	5.9 (4)	0	9.0 (9)
Confusional state	7.9 (37)	3.0 (5)	0	58.8 (1)	5.9 (6)
Disturbance in attention	7.3 (34)	6.0 (10)	0	58.8 (1)	6.9 (7)
Asthenia	6.9 (32)	4.2 (7)	2.9 (2)	0	5.9 (6)
Aggression	5.8 (27)	2.4 (4)	2.9 (2)	0	4.0 (4)
Vertigo	5.6 (26)	2.4 (4)	2.9 (2)	0	5.0 (5)
Parasthesia	5.2 (24)	2.4 (4)	1.5 (1)	0	5.0 (5)
Agitation	4.9 (23)	0.6 (1)	0	0	4.0 (4)
Bronchitis	4.7 (22)	2.4 (4)	0	0	4.0 (4)
Edema peripheral	4.1 (19)	0.6 (1)	0	0	3.0 (3)
Urinary tract infection	4.1 (19)	3.0 (5)	0	0	4.0 (4)
Myalgia	3.9 (18)	0.6 (1)	0	0	3.0 (3)
Sleep disorder	3.6 (17)	3.6 (6)	1.5 (1)	0	3.0 (3)
Pruritis	2.9 (13)	6.0 (10)	0	0	2.0 (2)
Hyporeflexia	2.6 (12)	0	0	0	1.0(1)
Eye disorder	2.6 (12)	0.6 (1)	0	0	0
Sedation	2.6 (12)	1.2 (2)	0	0	1.0 (1)
Dyspnea	2.4 (11)	0.6 (1)	0	0	2.0 (2)
Speech disorder	2.4 (11)	0	0	0	2.0 (2)

Source 3/14/08 Submission, Table 14.4; Person years data from p.83

The majority of events appearing above are from the Psychiatric disorder and Nervous system disorder event categories. The only suicide attempt (n=1) and completed suicide (n=1) AEs in these studies were reported for vigabatrin subjects. The incidence of convulsions in this analysis was 16.7/100 PY (78/466 PY) for vigabatrin treated subjects compared to 1.8/100 PY (3/166 PY) for carbamazepine subjects, 7.4/100 PY (5/68 PY) for valproate subjects, 0 (0/1.7PY) for gabapentin subjects and 42.6/100 PY (43/101 PY) for placebo subjects. The incidence of status epilepticus was 3.4/100 PY (16/466 PY) for vigabatrin treated subjects compared to 0 (0/166 PY) for carbamazepine subjects, 1.5/100 PY (1/68 PY) for valproate subjects, 0 (0/1.7 PY) for gabapentin subjects and 5/100 PY (5/101 PY) for placebo subjects. Anemia was reported for 6 vigabatin subjects (1.3/100PY, 6/466PY) 4 carbamazepine subjects (1.7/100PY, 4/229PY) and no valproate, gabapentin, or placebo subjects.

7.1.5.6 Additional analyses and explorations

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

Primary Data

Adverse Events by Sex
The NDA Amendment review noted that 76% of females and 68% of males in the primary data cohort reported one or more AEs. Females were more likely than males to report confusion, hypokinesia, tremor, depression, anxiety, emotional lability, and thinking abnormal. Males were more likely than females to report parathesias and aggressive reactions. Without placebo comparator data we cannot determine if the differences in risk by sex observed in these vigabatrin subjects reflect differences in the background risk for these events or are due to a drug sex interaction (Source Amendment Review, p.36).

Adverse Events by Age
The NDA Amendment Review noted that AE reporting among vigabatrin subjects increased with increasing age. Among 2-12 year old subjects the AE risk was 48% (60/125) compared to 95% (53/56) for subjects at least 65 years old. Drowsiness, dizziness, and confusion consistently increased with increasing age. Older patients seemed to be at greater risk for thinking abnormal. The risk for thinking abnormal was 11% among subjects at least 65 years of age (6/56) with the next closest age stratum 0.9% (6/676, age 16-<40). Again, without placebo comparator data we cannot determine if the differences in risk by age observed in these vigabatrin subjects reflect differences in the background risk for these events or are due to a drug age interaction (Source Amendment Review, p.36).

Safety Update (1/1/96-3/15/97)

Adverse Events by Sex
The sponsor identified the following adverse events where the percentage of individuals reporting an event was at least double when comparing vigabatrin treated males and females:

Adverse events by gender in vigabatrin patients

	Males	Females
Aggressive reaction	2.8% (24/861)	0.9% (8/901)
Allopecia	0.6% (5/861)	2.3% (21/901)
Neuropathy	0.9% (8/861)	2.1% (19/901)
Hypoesthesia	1.6% (14/861)	4.2% (38/901)

This analysis suffered from the same limitations noted above with respect to lack of comparator data.

Adverse Events by Age
In the Safety Update, the sponsor's presentation of AE's stratified by age groups used 6 categories for a relatively small number of patients and resulted in few subjects in the youngest and oldest categories, limiting the value of comparisons among strata. In addition, there was no presentation for a similar, unexposed (control) group (Source Final Safety Update Review, p.10).

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Adverse Events by Sex
Ovation reported that the incidence of non-gender specific adverse events were similar for males and females (12/28/07 submission, p.59). I examined appendix 3 Table 4.1.8 to identify any adverse events occurring in at least 1% of male or female subjects and where the risk was at least double when comparing males and females. I provide those results below.

Adverse Events Occurring in >= 1% of Male or Female Subjects and Where the Risk Was at Least Double When Comparing Males and Females

Adverse Event	Risk in Males (n=1,074)	Risk in Females (n=1,061)
Urinary Tract infection	1.4% (15)	2.9% (31)
Affect lability	0.6% (6)	1.4% (15)
Nervousness	0.6% (6)	1.2% (13)
Pain	0.5% (5)	1.5% (16)
Gastroesophageal reflux disease	1.1% (12)	0.3% (3)
Injury	1.7% (18)	0.7% (7)
Anticonvulsant toxicity	1.5% (16)	0.6% (6)
Alopecia	0.6% (6)	2.5% (27)
Rhinorrhea	0.4% (4)	1.4% (15)
Sinus congestion	0.5% (5)	1.1% (12)
Arthralgia	1.2% (13)	2.5% (27)
Lymphadenopathy	0.2% (2)	1.3% (14)
Hypertension	1.4% (15)	0.6% (6)
Hot flush	0.4% (4)	1.0% (11)
Hypersensitivity	0.3% (3)	1.3% (14)

Excludes Reproductive System and Breast Disorders System Organ Class

This analysis suffered from the same limitations noted above with respect to lack of untreated comparator data.

Adverse Events by Age
In their analysis of adverse events by age, Ovation reported that vigabatrin treated subjects in the <2 year old group had the highest adverse event risk (94%, 205/219) in the Overall population followed by the >=65 year old group (86%, 19/22), the 40-<65 year old group (82%, 301/365), the 12-<16 year old group (79%, 140/177), the 16-<40 year old group (77%, 594/771), and the 2-12 year old group (74%, 199/268) (12/28/07 submission, p.57). Since the <2 year old group consists of IS patients, any observed differences from age stratified analyses could be due to

differences in the underlying populations, differences in age, combinations of these factors or other unconsidered factors.

Ovation reported that nasopharyngitis and depression were more commonly reported by adults than children and that children more commonly reported upper respiratory tract infections, pyrexia, abnormal behavior, otitis media, vomiting, influenza, viral infection, aggression, streptococcal pharyngitis and sinusitis.

I examined appendix 3 Table 4.1.7 to identify any common adverse events occurring in at least 5% of all subjects and where the risk was at least double for one age group when compared to the other age groups. I provide those results below.

Adverse Events Occurring in at least 5% of All Subjects, and at least Double for One Age Group when Compared to the Other Age Groups

Event	<2 yrs (n=219)	2-<12 yrs (n=268)	12-<16 yrs (n=177)	16-<40 yrs (n=771)	40-<65 yrs (N=365)	>=65 yrs (n=22)
Visual field defect	0	17% (45)	25% (45)	21% (165)	23% (83)	27% (6)
Headache	<1% (1)	15% (41)	14% (25)	11% (82)	9% (34)	9% (2)
Convulsion	6% (13)	14% (38)	19% (33)	7% (57)	8% (29)	0
Dizziness	0	4% (12)	10% (18)	10% (78)	12% (44)	18% (4)
Somnolence	17% (38)	6% (15)	6% (11)	7% (51)	8% (29)	13% (3)
Upper respiratory tract infection	48% (104)	17% (45)	13% (23)	5% (37)	3% (11)	0
Nasopharyngitis	3% (7)	14% (38)	11% (19)	6% (47)	6% (22)	5% (1)
Otitis media	36% (79)	10% (26)	5% (9)	<1% (6)	<1% (2)	0
Insomnia	11% (24)	1% (3)	2% (4)	5% (38)	6% (22)	5% (1)
Irritability	20% (42)	4% (11)	3% (6)	3% (22)	2% (9)	0
Depression	0	2% (5)	4% (7)	7% (52)	6% (22)	0
Fatigue	0	9% (23)	8% (15)	11% (81)	7% 925)	23% (5)
Pyrexia	24% (53)	11% (30)	5% (9)	1% (10)	1% (5)	5% (1)
Vomiting	16% (36)	9% (23)	5% (9)	3% (24)	1% (5)	5% (1)
Diarrhea	12% (27)	5% (13)	5% (8)	3% (26)	4% (14)	5% (1)
Weight increased	<1% (1)	13% (34)	17% (30)	7% (51)	5% (19)	0
Other events of interest (<5% of all subjects but demonstrating notable risk differences by age)						
Sedation	18% (40)	<1% (2)	1% (2)	2% (13)	1% (4)	0
Decreased appetite	8% (17)	<1% (2)	<1% (1)	1% (8)	<1% (1)	0

Dose Response

In response to a Division request for a dose response analysis, Ovation provided a table of treatment emergent adverse events. Using pooled data from 5 fixed-dose, randomized, placebo-controlled CPS trials, Ovation calculated person time exposure for the different dose groups and assigned adverse events to the dose category at which the event occurred. I reviewed the table to identify AEs occurring in at least 1% of vigabatrin subjects (n=4) and at least twice as frequent when compared to placebo. For any such events, I selected the events where the rate appeared to increase with increasing vigabatrin dose. I present those results below.

Dose Response for Select AEs from 5 Fixed Dose Randomized Placebo CPS Controlled Trials

Event	Vigabatrin Dose (g/day)					Placebo
	>0-2 g/day (34 PY) Rate (n)	2-<3 g/day (17 PY) Rate (n)	3-<4 g/day (62 PY) Rate (n)	4-<5 g/day (15 PY) Rate (n)	>=5 g/day (13 PY) Rate (n)	(141 PY) Rate (n)
Abdominal pain upper	0.06 (2)	0.12 (2)	0.10 (6)	0.07 (1)	0.16 (2)	0.02 (3)
Edema peripheral	0.06 (2)	0.12 (2)	0.11 (7)	0.13 (2)	0.23 (3)	0.01 (1)
Swelling	0	0.06 (1)	0.02 (1)	0	0.23 (3)	0.01 (1)
Weight increase	0.21 (7)	0.42 (7)	0.18 (11)	0.53 (8)	0.39 (5)	0.04 (6)
Back pain	0.15 (5)	0.18 (3)	0.11 (7)	0.33 (5)	0.16 (2)	0.05 (7)
Muscle twitching	0	0.06 (1)	0.03 (2)	0.13 (2)	0.31 (4)	0.01 (2)
Myalgia	0.06 (2)	0	0.06 (4)	0	0.16 (2)	0.02 (3)
Coordination abnormal	0.21 (7)	0.36 (6)	0.19 (12)	0.46 (7)	0.39 (5)	0.05 (7)
Hypoaesthesia	0.06 (2)	0.12 (2)	0.13 (8)	0.26 (4)	0	0.04 (6)
Hyporeflexia	0.06 (2)	0	0.10 (6)	0	0.16 (2)	0.01 (1)
Memory impairment	0.18 (6)	0.18 (3)	0.26 (16)	0.73 (11)	0.39 (5)	0.06 (8)
Abnormal dreams	0.03 (1)	0.12 (2)	0.03 (2)	0.07 (1)	0.16 (2)	0.01 (1)
Confusional state	0.06 (2)	0.18 (3)	0.18 (11)	0.20 (3)	0.47 (6)	0.02 (3)
Expressive language disorder	0.06 (2)	0.18 (3)	0.03 (2)	0.20 (3)	0.31 (4)	0.02 (3)

Source 5/1/08 Submission, Table 1.2

For most of the events listed above, the small number of outcomes precludes drawing firm conclusions about dose response.

Analyses of Specific Events

Depression and Suicide

Ovation provided a summary of safety data related to depression and suicide with vigabatrin (Source 12/28/07 Submission, pp.227-228). The summary included descriptions of results from clinical pharmacology studies, literature reports, adverse event risks in the development program clinical trials, comparisons of risks for vigabatrin and placebo subjects in controlled trials and a summary of spontaneous reports for depression and suicide in patients treated with vigabatrin.

Ovation noted that clinical pharmacology studies of the effects of vigabatrin on psychometric and psychomotor function showed no significant effects on concentration, attention, coordination, memory, or mood. Ovation referenced the 1994 NDA submission that included the results from these studies but did not provide details about these studies in the current amendment submission.

Ovation acknowledged literature reports of behavioral symptoms in patients treated with vigabatrin but said these adverse events were associated with confounding factors such as withdrawal, control of seizures, cerebral lesions, mental retardation, and overdose.

Ovation summarized an expert report presented in the NDA Amendment (5/31/97) that examined the risks for psychiatric AEs using a pool of three controlled trials. Ovation noted that the vigabatrin clinical trials were not specifically designed to study relationships between vigabatrin and psychiatric events. Using data from controlled trials 021, 024, and 025, a psychiatric expert examined the incidence of psychosis (hallucination, paranoid reaction, psychosis, and schizophrenic reaction), depression, agitation, aggression reaction, manic symptoms (manic reaction, euphoria, libido increased, and cyclothymic reaction), suicide attempt, emotional lability, and anxiety (anxiety and nervousness). This analysis found an increased risk for psychotic symptoms (2.5% vs. 0.3%, p=0.028) and depression (12.1% vs. 3.5%, p<0.001) among vigabatrin subjects. The NDA Amendment review of the psychiatric expert report noted that the 49 vigabatrin subjects who experienced depression in these 3 controlled trials had more serious outcomes (6/49 discontinued, 3/49 hospitalized, and 2/49 with psychotic depression) compared to the placebo subjects (0/11) who developed depression (Source NDA Amendment review, p.50). The expert felt that most of the subjects that developed psychosis had mild symptoms and noted that some cases resolved with discontinuation of vigabatrin, some with continuation of vigabatrin and some with neuroleptic treatment.

Ovation reported that during open label studies, agitation and aggression were the most commonly reported psychiatric AEs and that 2 of 38 subjects with a history of schizophrenia had exacerbations of their disease during vigabatrin treatment. In the open label trials, the rate of discontinuation for psychiatric AEs was 6.1% for subjects with a history of psychiatric illness compared to 5.2% for subjects with no such history.

Ovation also summarized psychiatric event data from the 1998 Response to the Approvable letter. In that submission, the sponsor reported that the discontinuation rates for select psychiatric AEs (depression and psychosis, psychomotor slowing, and drowsiness and fatigue) was low. The sponsor reported that 2.5% of subjects in all North American controlled trials discontinued, was hospitalized, or received medical treatment for depression. One and a half percent of subjects in North American trials discontinued, was hospitalized, or received medical treatment for psychosis. The sponsor also noted that 2 vigabatrin and no placebo subjects in North American trials attempted suicide.

There was 1 completed suicide among 4,855 subjects in epilepsy trials included in the Integrated database. In addition, there were 21 Depression SAEs (0.44%) 12 Suicidal ideation (0.25%) SAEs, 10 Suicide attempt (0.21%) SAEs, 2 (0.04%) Depression suicidal SAEs and 1 (0.02%) major depression SAE.

Using the data from 12 pooled controlled studies, one vigabatrin subject died as a result of suicide (0.2/100 PY, 1/446 PY) compared to no comparator subjects (placebo 101 PY, Carbamazepine 166 PY, Valproate 68 PY, Gabapentin 1.7 PY). The table below provides the non fatal depression related SAE risks for the pooled controlled trial data. These data suggest an

increased risk for depression and suicide related SAEs among vigabatrin subjects compared to the comparator subjects in these trials, although the number of SAEs is relatively small.

Depression Related SAEs for Pool of Phase II/III Studies with Vigabatrin

Event	Vigabatrin 446 PY Rate/100 PY	Carbamazepine 166 PY Rate/100 PY	Valproate 68 PY Rate/100 PY	Gabapentin 1.7 PY Rate/100 PY	Placebo 101 PY Rate/100 PY
Depression	2.2 (10)	0.6 (1)	0	0	0
Suicidal ideation	0.4 (2)	0	1.5 (1)	0	0
Suicide attempt	0.2 (1)	0	0	0	0
Depressed mood	0.2 (1)	0	0	0	0

Source 3/14/08 Submission, Table 14.2, pp.37-8

In the Integrated database Ovation reported that 71 subjects (1.5%, 71/4855) discontinued for depression AEs. In addition, Ovation reported that 10 subjects (0.2%) discontinued for suicidal ideation, 5 (0.1%) for suicide attempt, 2 (0.04%) for depressed mood, 2 (0.04%) for depression suicidal, 2 (0.04%) for major depression, and 1 (0.02%) for completed suicide.

The table below provides the discontinuation for AE risks for depression related AEs for the pooled controlled trial data. These data suggest an increased risk for depression AEs leading to discontinuation among vigabatrin subjects compared to the comparator subjects in these trials.

Depression Related AEs Leading to Discontinuation for Pool of Phase II/III Studies with Vigabatrin

Event	Vigabatrin 446 PY Rate/100 PY	Carbamazepine 166 PY Rate/100 PY	Valproate 68 PY Rate/100 PY	Gabapentin 1.7 PY Rate/100 PY	Placebo 101 PY Rate/100 PY
Depression	3.4 (15)	1.2 (2)	2.9 (2)	0	1.0 (1)
Suicidal ideation	0.4 (2)	0	0	0	1.0 (1)
Suicide attempt	0.2 (1)	0	0	0	0
Depressed mood	0.2 (1)	0	0	0	0
Major depression	0.2 (1)	0	0	0	0

Source 3/14/08 Submission, Table 14.3, pp.44-5.

In the Integrated database, 8.2% (334/4077) of subjects reported depression AEs, 1.0% (40/4077) reported depressed mood AEs, 0.6% (23/4077) reported suicidal ideation AEs 0.3% (13/4077) reported suicide attempt AEs, 0.1% (4/4077) reported depression suicidal AEs, and 0.07% (3/4077) reported major depression AEs and 1 subject committed suicide.

The table below provides the depression related AE risks for the pooled phase II/III controlled trial data. These data suggest similar risks for depression AEs for vigabatrin and placebo, and

increased risks for depression AEs among vigabatrin subjects compared to the active comparator subjects in these trials.

Depression Related AEs for Pool of Phase II/III Studies with Vigabatrin

Event	Vigabatrin 446 PY Rate/100 PY	Carbamazepine 166 PY Rate/100 PY	Valproate 68 PY Rate/100 PY	Gabapentin 1.7 PY Rate/100 PY	Placebo 101 PY Rate/100 PY
Depression	13.9 (62)	4.2 (7)	5.9 (4)	0	12.9 (13)
Suicidal ideation	1.1 (5)	0	0	0	1.0 (1)
Suicide attempt	0.2 (1)	0	0	0	0
Depressed mood	3.1 (14)	0.6 (1)	0	0	4.0 (4)
Major depression	0.2 (1)	0	0	0	0

Source 3/14/08 Submission, Table 14.4, pp.67-9.

There did not appear to be a clear dose response for depression related AEs in a pool of 5 randomized placebo controlled trials that included more than one dose of vigabatrin. I provide those results below.

Event	Vigabatrin Dose (g/day)					Placebo
	>0-2 g/day (34 PY) Rate (n)	2-<3 g/day (17 PY) Rate (n)	3-<4 g/day (62 PY) Rate (n)	4-<5 g/day (15 PY) Rate (n)	>=5 g/day (13 PY) Rate (n)	(141 PY) Rate (n)
Depression	0.18 (6)	0.77 (13)	0.26 (16)	0.40 (6)	0.47 (6)	0.05 (7)
Depressed mood	0.06 (2)	0.12 (2)	0.11 (7)	0	0	0.01 (2)
Suicidal ideation	0.03 (1)	0.06 (1)	0	0	0.08 (1)	0
Suicide attempt	0	0	0	0	0.08 (1)	0

Source 5/1/08 Submission, Table 1.2

Peripheral Neuropathy

Ovation summarized data related to peripheral neuropathy in individuals treated with vigabatrin. Ovation explained that as part of the 1997 response to the Approvable letter, the previous sponsor submitted an expert review of neuropathy related adverse events. The sponsor's expert reported that in North American controlled trials and their open label follow up studies, 2.4% (11/457) of vigabatrin subjects developed symptoms and or signs of a distal, large fiber, sensory, polyneuropathy. Manifestations of polyneuropathy included numbness or tingling in the toes or feet, reduced lower limb vibration or positional sensation, and progressive loss of reflexes, starting at the ankles. The sponsor's expert found no relationship between neuropathy and daily vigabatrin dose or cumulative dose. The sponsor reported that for cases with follow up, neuropathy was reversible upon discontinuation of vigabatrin. Ovation noted that the reviewed

studies were not designed to systematically evaluate peripheral neuropathy and did not include nerve conduction studies, quantitative sensory testing or skin or nerve biopsy.

In addition to summarizing the expert review, Ovation provided a review of post marketing reports of neurological events. Ovation reviewed reports received from 3/15/97 through 6/30/07. Ovation provided estimates of postmarketing exposure from 9/22/89 through 9/22/06 including an estimate of 821,969 person years and 1,600,000 patients exposed. Ovation commented that few postmarketing reports described events related to peripheral neuropathy. Ovation reported that the most common adverse event possibly associated with peripheral neuropathy was parasthesia (n=3). Ovation noted that one additional report described peripheral neuropathy. Ovation concluded that postmarketing reports describing peripheral neuropathy were rare; often include few details, in some cases described confounding factors.

Hepatic Injury
In the original NDA review, the medical officer summarized 12 cases of hepatic injury in subjects/patients treated with vigabatrin. The summary did not specify the source of the cases (clinical trials, spontaneous reports, compassionate use, etc.). The summary did note that 7 of the 12 cases resulted in death and that the range of exposure duration prior to these events was 4 days to 6 years (median 8.5 months). In addition, half of the cases occurred in individuals aged 10 years or younger (3 deaths, 2 survived, 1 unknown). The medical officer commented that the clinical laboratory liver function results were unremarkable except for the documented declines in SGPT.

In the 1997 Amendment to the NDA, the sponsor provided an expert review of hepatic injury cases with vigabatrin. The consultant, Dr. Zimmerman, wrote that "Vigabatrin appears to be associated with a very low risk of hepatotoxicity." The consultant recommended informing prescribers that ALT levels may be unreliable for detecting early hepatotoxicity (given that vigabatrin loweres these levels) and that attention to clinical manifestations of liver injury (jaundice, hepatomegaly, nausea) is necessary. The consultant also commented that "...the lack of production of active metabolites (1) leads to the inference that hepatic injury by this drug is unlikely. Nevertheless, the possibility that vigabatrin might produce hepatic injury by another mechanism cannot be excluded.

The consultant reviewed available information for all 21 hepatic serious adverse events and offered an opinion about the relationship to vigabatrin. The cases included 3 deaths and 3 non fatal hepatic AEs from vigabatrin clinical trials. The consultant ruled out vigabatrin as a cause in 2 of the fatal cases (one attributed to metastatic carcinoma and the other to clarithromycin). The consultant could not rule out vigabatrin as a cause of fulminant hepatitis death from a Japanese controlled trial (not part of the integrated safety database). The consultant concluded that 3 non-fatal hepatic SAEs from clinical trials were not related to vigabatrin (one viral, two due to concomitant medications). The consultant's summaries of the fatal clinical trials cases are included below.

Patient 202-06Y-06 (Protocol JGVG-CL-202)
A 34-year-old female from Japan taking vigabatrin 3 g/day for 251 days concomitantly with phenytoin and phenobarbital. The patient experienced fulminant hepatitis and was hospitalized. All medications were stopped abruptly after occurrence of the event. The patient eventually died. Autopsy findings showed fulminant hepatitis. Other drugs include phenytoin and phenobarbital. No way to distinguish between vigabatrin and other anticonvulsants.
Attribution to vigabatrin: Possible.

Patient 31730707 (VGST-MUMF-350)
A 39-year old male from Italy had been taking vigabatrin 3.5 g/day for approximately 6 years concomitantly with phenytoin, primidone, aspirin, clarithromycin, and dipyrone, when he experienced hyperpyrexia probably due to an infection. He was treated at home with aspirin, noraminopyridine, and clarithromycin. Subsequently, the patient was admitted to an intensive care unit where he died 2 days later. Hepatic insufficiency attributed to clarithromycin.
Attribution to vigabatrin: Unlikely.

Patient 30330028 (Protocol 097-306)
A 45-year-old male from Denmark had been taking vigabatrin in doses ranging from 4.5 to 6 g/day for just under 2 years when he died from metastatic brain carcinoma. Over the course of his therapy, this patient suffered increasing neurological symptoms from his cerebral tumor including depression, dementia memory loss, nausea and vomiting, nervousness, sleep disturbances, and dizziness. As his cancer metastasized to his colon and liver, he also suffered from abdominal pain, flu, hiccups and muscle atrophy. Increased liver enzymes, including AST were reported and attributed by the reporting physician to the hepatic tumors.
Attribution to vigabatrin: Unlikely.

The remaining 15 hepatic AEs were identified from spontaneous reports (estimated exposure was 125,000 patients). The consultant concluded that 3 deaths and one transplant case identified from spontaneous reports were probably or possibly related to vigabatrin, but did not feel vigabatrin was a contributing factor in 2 other deaths. For the remaining serious hepatic adverse events, the consultant felt that 8 were probably or possibly related to vigabatrin and one was not. The consultant noted the lack of information about the cases and stated that the duration of treatment argued against vigabatrin as the cause.

I provide the consultant's summaries and comments for the fatal/transplant post marketing cases that the consultant classified as probably/possibly related to vigabatrin.

Patient 94001440
A 34-year-old female from France had been taking vigabatrin 2 g/day for 789 days concomitantly with phenytoin, carbamazepine, and paracetamol when she developed hepatic disease and was hospitalized for the hepatorenal syndrome with necrotizing hepatitis, portalsystemic encephalopathy, and generalized seizures. She was considered a candidate for liver transplant; however, there was a sudden decrease in factor V with acidosis and the patient subsequently died. The reporting physicians assessed the events as being unrelated to vigabatrin therapy but possibly related to carbamazepine or phenytoin. Unable to rule out association with vigabatrin.
Attribution to vigabatrin: Possible.

Patient 94003033
A 10-year-old female from Germany had been taking vigabatrin 1.5g/day for 1 year concomitantly with carbamazepine and clonazepam, when she was hospitalized with a diagnosis of acute liver necrosis and subsequently died. A liver biopsy revealed subacute hepatodystrophy with hepatic necrosis and intrahepatic cholestasis that apparently attributed to a toxic hepatosis which may have been present for a long time. According to the reporting physicians, it was not possible to determine whether the hepatosis was due to an endogenous or exogenous toxin.

Attribution to vigabatrin: Possible.

Patient 94007742
A 26-year-old female from the U.K. had been taking vigabatrin 4 g/day for 137 days concomitantly with valproate and gabapentin when she experienced fulminant hepatic failure and hepatic coma. Subsequently she received a liver transplant. Reporting physicians were not certain whether the event was of post-viral etiology or drug induced. If drug induced, both vigabatrin and gabapentin was suspected. Patient survived.
Attribution to vigabatrin: Possible.

Patient 95001102
An 18-year-old male from France had been taking vigabatrin 5 g/day for 1,192 days when he developed hepatic disease. He had previously taken carbamazepine and primidone but was on vigabatrin alone for 13 months prior to the event. It should be noted that this patient also was potentially exposed to toxic chemicals in the workplace. His hepatic disease presented with gastroenteritis, then icterus, and he was hospitalized. The patient developed signs of hepatic encephalopathy with no fever or rash. He also developed massive acute hepatitis during hospitalization. Bilirubin continued to increase and the patient developed secondary renal impairment. The patient subsequently died due to intracranial hypertension secondary to cerebral edema.
Attribution to vigabatrin: Possible.

Among the 13 cases that the consultant classified as probably or possibly related to vigabatrin, 10 were taking other medications known or reported to cause hepatotoxicity. The consultant felt the reports provided insufficient information to support a definite causal relationship between vigabatrin and hepatotoxicity or to assess demographic risk factors.

When specifically asked what information to provide prescribers, the consultant responded, "Information provided to prescribing physicians should include reference to the reported hepatic adverse events and to the fact that the inhibitory effect of vigabatrin on transaminase levels may preclude the use of transaminase levels to detect hepatotoxicity."

In the current submission, the sponsor reported a death due to hepatic failure from a clinical trial (described above with deaths). That case is confounded by the documented complicated post-operative clinical course (status epilepticus, presumed hypotension requiring pressor therapy, etc.) making it unclear as to whether vigabatrin contributed to hepatic failure in this subject. The sponsor did not identify any additional hepatic related adverse events from clinical trials in the current submission.

Based on the information available in 1997, the Division proposed labeling that referenced the cases of liver injury with vigabatrin and attempted to describe the risk in terms of the exposure and estimated underreporting. Ovation proposes no reference to hepatic injury in labeling. Ovation cites the minimal biotransformation of vigabatrin, use of concomitant medications in many cases, and the long duration of treatment prior to development of liver injury as arguments against a relationship between vigabatrin and hepatotoxicity.

To be able to calculate a reporting rate for hepatic failure resulting in death or transplant, the Division asked Ovation to provide reports for all serious hepatic post marketing cases not included in the expert review. Ovation provided 12 reports. The list included 3 deaths. One death was not likely related to vigabatrin because the patient had stopped vigabatrin 2 months prior and was being treated with phenytoin and carbamazepine at the time of the event. The second death

was a literature report of the clinical trial patient that was taking clarithromycin and was mentioned above. The third report was also literature report but appeared to be a previously unreported case with not obvious alternative explanation. A summary of that case is provided below.

A 3 year old male with a history of pre-term birth (30 weeks), perinatal cerebral hemorrhage, generalized leucomalacia, developmental delay, microcephaly, spastcity, and simple motor seizures beginning at age 14 months was treated with phenobarbital. Vigabatrin was added due to insufficient seizure control. Nine months later, the patient presented with fever, hypovolemia, hypoglycemia, coma, elevated AST (577 U/L), elevated ammonia, elevated BUN and creatinine. The patient was diagnosed with liver failure. The patient developed a severe coagulopathy, a GI bleed, and died. A post mortem liver biopsy revealed massive parenchymal necrosis, periportal fibrosis, central sclerosis of lobules, and no evidence of fatty deposits. The authors stated that that other causes, acute infectious disease, or other toxic events had been excluded. The authors did not provide the details of the evaluation for causes of liver failure in this patient.

I searched PubMed and found no additional published cases of hepatic injury with vigabatrin.

Clinical trial hepatic failure risk
Over the course of development program, the sponsors have reported 4 clinical trial deaths for hepatic related events. Three events are from prior submissions and one event is from the current submission. One death appeared to be due to metastatic cancer and another was likely due to concomitant medication (clarithromycin). The third death occurred in the setting of multiple organ failure that followed a hypotensive episode in a subject who developed status epilepticus. One additional hepatic related death occurred in a Japanese clinical trial that was not part of the integrated database. Thus there were no unexplained liver failure cases resulting in death or transplant in the clinical development program.

From post marketing reports, there were four hepatic related deaths and one transplant. In none of the cases was a likely alternative explanation documented but all were taking multiple medications at the time of the event. If one were to consider the five post marketing reports and the one Japanese study report, there were a total of 6 deaths or transplants with 856,000 person years of vigabatrin use. This yields a risk for liver failure resulting in death or transplant of 7.0/1,000,000PY. Excluding cases with exposure to vigabatrin for more than 1 year prior to developing liver injury leaves 3 cases of death/transplant and a reporting rate of 3.5/1,000,000PYs.

Discussion
According the Dr. Zimmerman, the sponsor's consultant, there was no preclinical evidence of vigabatrin related hepatotoxicity. There did not appear to be an increased risk of transaminase elevations among vigabatrin treated subjects in controlled trials, although vigabatrin does result in *decreases* in transaminases that could possible obscure these test result comparisons. Ovation found no "Hy's Law" cases (transaminase elevations >3x ULN and total bilirubin >2.0mg/dL) in the development program. The clinical trial database included 3 hepatic related deaths. All three cases were confounded (one metastatic cancer, one concomitant chlarithromycin, one in the setting of multiple organ failure following hypotension). There was a case from a Japanese study

that was not part of the sponsor's development program and therefore should not be counted among the clinical trial deaths.

In the post marketing period there have been 6 reports of hepatic injury resulting in death/transplant. The reporting rate for these events exceed the general population background rate we have used in the past to assess these events although this background rate may not accurately reflect the rate in patients with seizure disorder who are exposed to medications that are known to cause liver injury. I do not believe that available data are sufficient to allow the conclusion that vigabatrin causes liver injury but the data do merit close monitoring.

Cognition/Neuropsychiatric Function
Ovation commented that animal studies demonstrated anti-aggression and anti-depression effects of vigabatrin but not anxiolytic, antipsychotic, learning or memory effects.

In adult human healthy volunteers, Ovation reported that vigabatrin had no effect on cognition or other neuropsychiatric function in acute or sub chronic doses. Furthermore, Ovation reported that chronic vigabatrin doses in subjects with epilepsy did not have an effect on psychometric or psychomotor function. Ovation cited clinical pharmacology studies that reportedly did not find differences in learning, memory, reaction time, attention, or concentration when comparing normal volunteers exposed to vigabatrin to volunteers exposed to placebo.

Ovation cited data neuropsychiatric test data collected during vigabatrin clinical trials. In studies 024 and 025 (US controlled epilepsy trials), Ovation reported that comparing vigabatrin and placebo subjects, no differences were observed in verbal and non verbal memory, coordination, adjustment, and general intellect tests.

Ovation noted that study 024 found statistically significant differences in the change from baseline when comparing vigabatrin and placebo subjects for the Profile of Mood States for the following items: depression/dejection, fatigue/inertia, confusion/bewilderment and total mood disturbance. Ovation commented that the differences were due to small improvements in the placebo group. Study 025 did not replicate the findings for the Profile of Mood States but instead found a significant, dose dependent decrease in the Digit Cancellation Test score.

Ovation reported that they had little data available for examining the effects of vigabatrin on cognition and neuropsychological functions in children. Ovation noted that neurocognitive data from studies 071754PR0118, 071754PR0192, and 071754PR0221, and 071754PR0294 were not analyzed because of the small sample sizes. In addition neurocognitive data from study 071754PR0201, the open label follow up study for studies 071754PR0118, 071754PR0192 were not analyzed. Ovation reported that an independent study found that for 6 children (mean age, 5.5 years) with partial epilepsy treated with vigabatrin the DQ, a global measure of mental development, remained unchanged at the end of the follow-up period

Ovation reported results from developmental tests administered to IS patients during vigabatrin clinical trials. In study W019, Ovation noted that at baseline 3/40 subjects were noted as normal, 33/40 suspect and 4/40 untestable using the Denver Test of Psychomotor Development. At end

study, 23% were rated normal and 60% suspect. In study FR03, Ovation reported improvement in the Developmental Quotient in all subjects (statistical test not performed due to missing data). Ovation also reported results from longitudinal neuropsychological evaluations of a group of 7 children (mean age, 5.5 years) with infantile spasms due to tuberous sclerosis who were treated with vigabatrin. The development quotient was assessed at onset of initiation of vigabatrin and at the end of the follow-up (a mean of approximately 3 years). At baseline all children demonstrated moderate to severe mental retardation; five with autistic behavior. After disappearance of spasms, DQ increased by approximately 10 points in 6 of the subjects (p=0.03). In 4 subjects, the DQ rose by 20 points; one subject showed an increase by 30 points and another one increased by 40 points. One subject remained with severe mental retardation and autistic behavior. Ovation interpreted these results as suggesting that vigabatrin does not adversely affect mental function.

Ovation felt that the information presented supported that vigabatrin had little effect on neuropsychological function in adults and children with epilepsy. Ovation's conclusions are not consistent with the findings from phase II/III controlled trials where vigabatrin was associated with an increased risk for a number of CNS AEs including somnolence, sedation, coordination abnormalities and confusional state.

Edema related events
In the Integrated Database, Ovation identified 3% (124/4077) patients with AE of edema peripheral, 0.4% (16/4077) with edema, 0.1% (5/4077) with generalized edema, 0.1% (5/4077) with localized edema, 0.1% (4/4077) with facial edema, <0.1% (3/4077) with pitting edema <0.1% (3/4077) with gravitational edema. None of these events were SAEs, and only 5 edema peripheral events and 2 edema events led to d/c.

In the group of 12 phase II/III controlled trials there were slight increases in risk among vigabatrin subjects compared to control subjects for edema peripheral (vigabatrin 4.3/100PY, 19/446PY; placebo 3/100PY, 3/101PY), edema (vigabatrin 1.1/100PY, 5/446PY; placebo 0/101PY) generalized edema (vigabatrin 0.7/100PY, 3/446PY; placebo 0/101PY) One placebo and no vigabatrin subject had an AE of pitting edema. In these studies, none of the edema related AEs were SAEs. One vigabatrin (0.2/100PY, 1/446PY) and no placebo subjects (0/101PY) discontinued for an edema related AE (Source 3/15/08 Submission).

Dose response analyses of controlled trials data suggested an increasing risk of edema peripheral and generalized edema with increasing vigabatrin dose but not other edema related adverse events. The analysis is limited by the small number of edema related events. The results are provided below.

Dose Response for Edema AEs from 5 Fixed Dose Randomized Placebo CPS Controlled Trials

Event	Vigabatrin Dose (g/day)					Placebo
	>0-2 g/day (34 PY) Rate (n)	2-<3 g/day (17 PY) Rate (n)	3-<4 g/day (62 PY) Rate (n)	4-<5 g/day (15 PY) Rate (n)	>=5 g/day (13 PY) Rate (n)	(141 PY) Rate (n)
Edema peripheral	0.06 (2)	0.12 (2)	0.11 (7)	0.13 (2)	0.23 (3)	0.01 (1)

Generalized edema	0	0	0.03 (2)	0.07 (1)	0.08 (1)	0
Edema	0.03 (1)	0	0.02 (1)	0	0	0
Pitting edema	0	0	0	0	0	0.01(1)

Source 5/1/08 Submission, Table 1.2

The Division requested additional data to further explore the risk of edema AEs among vigabatrin subjects. We were specifically interested in events related to peripheral/generalized edema, face edema, and pulmonary edema. Ovation provided a data set that included adverse event information and lab data information for vigabatrin subjects that experienced an AE included in the Standardized MedDRA query (SMQ) of hemodynamic edema, effusions, and fluid overload and the SMQ of angioedema. Ovation identified 281 subjects with 361 AEs that met the SMQ search criteria. A number of these AEs did not appear to describe events related to the Division's intended analysis. I excluded events describing localized/focal edema (ex. brain edema, joint effusion, nasal edema, etc.) and events not directly related to the purpose of the analysis (wheezing, hypersensitivity). After exclusion of these events, there were 215 subjects with 273 edema related AEs. I list the edema AE preferred terms below.

Included Edema Event Preferred Terms from the Integrated Database

Included Edema Preferred Terms	N
Eyelid edema	2
Face edema	2
Fluid retention	25
Generalized edema	5
Gravitational edema	5
Edema	21
Edema peripheral	163
Periorbital edema	2
Pitting edema	4
Pulmonary edema	5
Swelling	30
Swelling Face	9

For the 215 subjects in this analysis, 140 were female, 72 were male and sex was not reported for 3 subjects. The average age of subjects with an edema AE was 38.2 years (median 38.5 years) and the range of ages was from 0.6 years to 72 years (age missing for 9 subjects). The median time to onset for the subjects' first edema AE was 77 days (mean 260 days, range 0-4456 days).

Two of the included 273 edema related AEs were SAEs (both pulmonary edema events). For these 2 subjects, (0101/13490007, 71754-W-002/078-051) pulmonary edema was the only edema related AE reported. Eight subjects discontinued for edema related AEs. The edema AEs leading to discontinuation were edema peripheral (n=4), edema (n=2), gravitational edema and pulmonary edema.

Of the 215 subjects with an edema AE, 50 also had a weight gain AE. Twenty three of these weight gain AEs were reported within 30 days of the edema AE. Fifteen weight gain AEs were

reported more than 30 days prior to the edema event and 9 were reported more than 30 days after the edema event was reported (relationship not known for 3 events).

Of the 215 subjects with an edema AE, 19 also had a cardiovascular AE. Six of these CV AEs (high blood pressure n=3, low blood pressure, pulmonary edema, and cardiac arrest), occurred within 30 days of the edema AE. Five CV AEs (isolated PVC, heart racing, heart palpitations, hypotension, hypertension) occurred more than 30 days before the edema AE and 5 occurred more than 30 days after (palpitations n=2, ventricular tachycardia, acute MI, poor blood circulation) (relationship not known for 3 events).

Of the 215 subjects with an edema AE, 12 also had a renal AE. Two of these renal AEs (passing urine less, incontinence), occurred within 30 days of the edema AE. Five renal AEs (difficulty in micturation, urinary problems, increased frequency of urination, difficulty initiating urination, and decreased albumin) occurred more than 30 days before the edema AE and 5 occurred more than 30 days after (excessive urination, increased nocturia, difficulties in micturition, dimished bladder strength, and urgency but voiding small amount).

Three of the 215 subjects with an edema AE also had an AE of proteinuria. Proteiuria was reported 5 days before the edema AE in 1 subject and 32 days after the edema AE in the second subject (relationship not know for the third subject).

Of the 215 subjects with edema AEs, 104 had a total of 114 serum albumin results within 30 days of the AE. Seven of the 114 serum albumin results were <3.5g/dL.

Of the 215 subjects with edema AEs, 109 had a total of 119 serum creatinine results within 30 days of the AE. Sixteen results were above 1.0mg/dL with the highest reported creatinine being 1.2mg/dL. Only one subject with an edema AE experienced an increase in creatinine from baseline of >0.3mg/dL. Subject 1A/269, a subject with a history of nephrotic syndrome, experienced edema, proteinuria, hypertension, and worsening nephritic syndrome. This subject's creatinine rose from 0.2mg/dL at baseline to 1.0mg/dL.

None of the subjects with an edema related AE also had a hepatic AE.

The data provided by Ovation identifies a number of subjects that developed edema during treatment with vigabatrin. These events were infrequently classified as SAEs and were not common causes of discontinuation from trials. These edema events in these subjects did not appear to be related to cardiovascular, renal or hepatic adverse events. Lab data did not suggest that these subjects were experiencing hypoalbuminemia, proteinuria, or increases in creatinine, although the lab data was incomplete.

SUDEP

In their proposed labeling, Ovation updated their SUDEP rate for vigabatrin using the data from the Integrated safety population. Ovation did not discuss SUDEP in their Amendment safety presentation. Ovation's updated SUDEP rate for vigabatrin (1.9/1,000 person years,

18/7091PYs) was similar to the rates presented in their previous submissions and continues to be in the range of SUDEP rates observed during the development programs for other AEDs.

Status Epilepticus
In their proposed labeling, Ovation provided risks for status epilepticus in 3 placebo controlled epilepsy trials and in the Integrated population. Ovation reports a risk of status epilepticus of 2.3% (5/222) among vigabatrin subjects and 2.2% (3/135) for placebo subjects in the pooled controlled trials. For the Integrated safety database, Ovation reports that the risk for status epilepticus was 2.6% (105/4077). Ovation did not discuss status epilepticus in their Amendment safety presentation.

7.1.6 Less Common Adverse Events

Included in an appendix to this review is a table that presents adverse events occurring at rates between 1/100 and 1/1000, and adverse events estimated to occur at rates less than 1/1000 for the overall safety population.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Prior Submissions

NDA and NDA Amendment

Primary Data
The analyses of lab data from US studies was presented in the original NDA and was not repeated in the NDA amendment. The sponsor reported that laboratory data from US studies were obtained at pre and post dose visits. The majority of subjects had liver transaminases tests, BUN, creatinine, electrolytes, and hematological (hemoglobin, hematocrit, WBC, differential, and platelets) tests. The NDA included comparisons of lab results by treatment from controlled studies as well as results for all vigabatrin treated subjects. The protocols for the US studies stated that clinically significant abnormal lab results would be followed up. The protocol did not require rechallenges for abnormal lab results and any unscheduled lab test results were not included in the lab data analyses. Studies 024 and 025 used central labs to analyze samples while studies 005 and 006 used local labs (Response to Division questions, 4/15/08, pp.85-6).

The majority of subjects in the NDA amendment presentation had liver transaminases tests, BUN, creatinine, electrolytes, and hematological (hemoglobin, hematocrit, WBC, differential, and platelets) tests. A smaller subset of subjects had urinalysis testing, coagulation testing, and AED blood levels. The sponsor noted that the laboratory site normal ranges were available for only 32 of the 87 protocols included in their analyses and for those protocols without laboratory site normal ranges, sponsor defined normal ranges were used to identify outliers (NDA

Amendment Sb-V2-P263). The protocols for the non-US primary studies did not require that clinically significant abnormal lab results to be followed up. The protocol did not require rechallenges for abnormal lab results and any unscheduled lab test results were not included in the lab data analyses. Ovation reported that the protocols did not mention if central or local labs were used to analyze samples (Response to Division questions, 4/15/08, p.86).

Safety Update (1/1/96-3/15/97)
The Safety Update did not include laboratory result analyses.

Current Submission

Overall Safety Population (3/16/97-6/30/07)

The studies summarized in the current submission required laboratory testing including liver transaminases tests, BUN, creatinine, electrolytes, and hematological (hemoglobin, hematocrit, WBC, differential, and platelets) tests. Ovation reported that none of the protocols for the studies in the current submission specifically addressed whether patients were followed until any abnormal results normalized or if patients were rechallenged following abnormal test results. Except for IS study 1A which used local labs, all studies that collected labs used central labs to analyze the samples. Unscheduled labs results were not used in the safety data analyses (Response to Division questions, 4/15/08, pp.86-7).

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)
In the NDA, the sponsor presented comparative lab data for subjects participating in the US controlled epilepsy trials (024, 025). The NDA amendment presented pooled data from the study dosing periods for vigabatrin treated subjects from non-US, CRF supported studies (non US primary data and the Secondary data) (Source NDA Amendment review, p.36).

Current Submission
Ovation did not provide lab data analyses for the Overall population in their NDA amendment. Ovation did provide summaries of select lab data for the adult partial epilepsy subpopulation, the pediatric non-IS subpopulation and the IS subpopulation. For the adult partial epilepsy subpopulation, Ovation provided results taken directly from the study reports for studies 0101 (controlled adjunctive therapy), 0222 (controlled monotherapy), 0223 (controlled monotherapy), and 0242 (long term study) (Source: NDA Amendment 12/28/07 submission, p.111). For the pediatric non-IS subpopulation, Ovation summarized select lab results from controlled CPS studies 0118, 0221, and 0192, and from long term CPS studies 0201 and 0294 (Source: NDA Amendment 12/28/07 submission, pp.156-7). Ovation presented limited laboratory analyses for IS subjects from study 1A (Source: NDA Amendment 12/28/07 submission, p.172).

7.1.7.3 Standard analyses and explorations of laboratory data

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

Primary Data
The lab data for the US studies was presented in the original NDA and consisted of mean change analyses, outlier analyses, and review of lab related AEs. The NDA amendment included pooled analyses of lab data for the combined primary non-US studies and secondary studies. The sponsor did not provide comparative analyses from controlled trials in the NDA amendment. The sponsor's NDA amendment lab analyses consisted of outlier risk calculations for vigabatrin exposed subjects and presentation of lab related AEs. The sponsor did not provide mean change from baseline analyses in the NDA amendment because they said they lacked site normal ranges across protocols (Source: NDA Amendment, p. 286).

The following table lists the outlier criteria used for the primary studies (NDA and NDA amendment).

Lab Outlier Criteria for US and Primary Non US Studies

Analyte	Low Outlier	High Outlier
SGOT (U/L)	N/A	>=150 and increase 50
SGPT (U/L)	N/A	>=165 and increase 50
Alkaline phosphatase (U/L)	N/A	>=390 and increase 75
Total protein (g/dL)	<= 4.5 and decrease 1	>=10 and increase 2
Albumin (g/dL)	<=2.5 and decrease 0.5	>=5 and increase 1.5
Total bilirubin (mg/dL)	N/A	>=2 and increase 0.5
LDH (U/L)	N/A	>=750 and increase 75
GGTP (U/L)	N/A	>=300 and increase 100
Creatinine (mg/dL)	N/A	>=2 and increase 0.5
BUN (mg/dL)	N/A	>=30 and increase 10
RBC ($x10^6$/L)	<=3.5 and decrease 0.5	N/A
Hemoglobin (g/dL)	Males <=11.5 and decrease 1.1 Females <=9.5 and decrease 1.1	N/A
Hematocrit (%)	Males <=37 and decrease 5 Females <=32 and decrease 5	N/A
Platelet count ($x10^3$/L)	<=75 and decrease 20	>=700 and increase 100
WBC ($x10^3$/L)	<=2.8 and decrease 0.5	>=16 and increase 5
Neutrophils ($x10^3$/L)	<=1.2 and decrease 0.2	N/A
Lymphocytes ($x10^3$/L)	<=0.8 and decrease 0.2	>=5 and increase 3
Eosinophils ($x10^3$/L)	N/A	>=0.57 and increase 0.4
Sodium (meq/L)	<=126 and decrease 5	>=156 and increase 4
Potassium (meq/L)	<=3 and decrease 0.9	>=6 and increase 0.5
Chloride (meq/L)	<=90 and decrease 10	>=118 and increase 10
Calcium (mg/dL)	<=8.2 and decrease 0.7	>=12 and increase 0.8
Phosphorus (mg/dL)	<=1.7 and decrease 1.8	>=5.5 and increase 1.8
Glucose (mg/dL)	<=50 and decrease 20	>=175 and increase 89
Cholesterol (mg/dL)	N/A	>=600 and increase 100
Amylase (U/L)	N/A	>=220 and increase 50

Uric acid (mg/dL)	N/A	Males >=10.5 and increase 2 Females >=8.5 and increase 2

Source NDA amendment Table B-39.

7.1.7.3.1 Analyses focused on measures of central tendency

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

The NDA reviewer did not discuss analyses of lab data that focused on measures of central tendency. In the NDA amendment, the sponsor presented an analysis of mean change data to further examine changes in hematocrit and hemoglobin among vigabatrin treated subjects compared to placebo. The sponsor looked for a dose response using data from the 2 US controlled studies. The sponsor reported finding a dose response in their analyses and commented that the trends achieved statistical significance in the dataset for US controlled trial 71754-3-C-025 (Source: NDA Amendment, p.286). I present the results for the pooled US controlled trials dose response analysis below.

Hematocrit and Hemoglobin Change from Baseline to End of Study by Dose, Us Controlled Epilepsy Studies

		US Controlled Epilepsy Studies (024, 025)				
Parameter		Placebo	1g VGB	3g VGB	6g VGB	All VGB
Hematocrit	Change from baseline	0.53	0.58	-0.24	-1.39	-0.29
Hemoglobin	Change from baseline	0.02	-0.12	-0.44	-0.91	-0.46

Source: 5/31/97 Submission, table B-47

The sponsor also presented in the NDA amendment results from mean change lab analyses that demonstrated that vigabatrin was associated with reduction of transaminases in US trials and the sponsor identified a dose response for this finding. Those results are summarized below.

Mean Change from Baseline for AST and ALT, Studies 024 and 025

Parameter	Placebo (n=135)	VGB 1g/d (n=45)	VGB 3g/d (n=135)	VGB 6g/d (n=41)	All VGB (n=221)
AST	-0.18 ±4.34	-1.51 ±5.53	-3.65 ± 6.05	-3.88 ± 4.35	-3.26 ± 5.71
ALT	-0.07 ± 8.12	-11.82 ± 9.30	-16.23 ± 10.10	-19.12 ±12.88	-15.87± 10.72

Source: 5/31/97 Submission, table B-42, p.SB-V2-P273.

Current Submission

Adult Subpopulation

Ovation provided selected mean change results (those with statistically significant differences) from 3 of the 4 studies that comprise the adult subpopulation database (0101, 0222, and 0223).

Those results are summarized below. For the remaining adult study, 0242, Ovation reported that the observed mean changes for labs were small and not clinically significant and that one subject had an SAE of thrombocytopenia and one had an SAE of renal failure (both cases described above with SAEs).

Select Lab Test Mean Change from Baseline Results from Adult Vigabatrin Studies

Laboratory test	Treatment	Mean Change ± SD
Study 0101		
SGPT (ALT) (U/L)	Vigabatrin (n=110)	-13.87 ± 1.64
	Placebo (n=56)	0.17 ± 2.30
Creatinine (mg/dL)	Vigabatrin (n=110)	-0.04 ± 0.01
	Placebo (n=56)	0.00 ± 0.01
RBC (/mm^3)		
Females	Vigabatrin (n=59)	-0.18 ± 0.03
	Placebo (n=23)	0.06 ± 0.05
Males	Vigabatrin (n=47)	-0.11 ± 0.04
	Placebo (n=30)	0.06
Hemoglobin (g/dL)		
Females	Vigabatrin (n=59)	-0.44 ± 0.09
	Placebo (n=23)	-0.07 ± 0.15
Males	Vigabatrin (n=47)	-0.27 ± 0.11
	Placebo (n=30)	0.02 ± 0.14
Study 0222		
SGPT (ALT) (U/L)	Vigabatrin (n=7)	-25.29 ± 14.10
	Gabapentin (n=8)	0.88 ± 10.79
Creatinine (mg/dL)	Vigabatrin (n=7)	-0.09 ± 0.11
	Gabapentin (n=8)	0.05 ± 0.08
Sodium (mEq/L)	Vigabatrin (n=7)	2.57 ± 3.26
	Gabapentin (n=8)	-1.88 ± 3.98
Study 0223		
SGPT (ALT) (U/L)	Vigabatrin 1g/day (n=17)	-13.76 ± 13.09
	Vigabatrin 3g/day (n=15)	-17.47 ± 12.42
	Vigabatrin 4g/day (n=17)	-16.59 ± 13.01
	Vigabatrin 6g/day (n=18)	-15.56 ± 10.11

Source: 12/28/07 Submission, pp.111-112.

The information provided by Ovation for study 0101 is consistent with previously submitted data demonstrating declines in ALT, hemoglobin, and RBCs in vigabatrin treated subjects.

I reviewed all lab mean change results listed in the study reports for the adult vigabatrin studies in the current submission. While the hematocrit mean change comparison between vigabatrin and placebo in study 0101 had a p value>.05, the difference was in the same direction as for hemoglobin with larger mean declines among vigabatrin subjects. I provide those results below.

Hematocrit Mean Change from Baseline Results from Study 0101

Laboratory test	Treatment	Mean Change ± SD
Study 0101		
Hematocrit (%)		

Females	Vigabatrin (n=59)	-1.70 ± 0.42
	Placebo (n=23)	-0.98 ± 0.67
Males	Vigabatrin (n=47)	-1.99 ± 0.44
	Placebo (n=30)	-1.28 ± 0.56

Source: Study report for 0101

Subjects in study 0223 experienced declines in hemoglobin and hematocrit but there did not appear to be a clear dose response relationship in this study. I provide those results below.

Hemoglobin and Hematocrit Mean Change from Baseline Results from Study 0223

Study 0223		
Hemoglobin (g/dL)	Vigabatrin 1g/day (n=17)	-0.14 ± 0.67
	Vigabatrin 3g/day (n=18)	-0.01 ± 0.80
	Vigabatrin 4g/day (n=17)	-0.10 ± 0.77
	Vigabatrin 6g/day (n=18)	-0.09 ± 0.71
Hematocrit (%)	Vigabatrin 1g/day (n=17)	-0.58 ± 2.50
	Vigabatrin 3g/day (n=18)	-0.54 ± 2.21
	Vigabatrin 4g/day (n=17)	-0.34 ± 2.71
	Vigabatrin 6g/day (n=18)	-0.43 ± 2.76

Source: Study report for 0223

Mean change from baseline for alkaline phosphatase did not appear to be consistent across studies. In study 0101, the mean change from baseline for alkaline phosphatase among vigabatrin subjects was -0.76 compared to 5.24 for placebo but in study 0222, the mean change from baseline for alkaline phosphatase was similar for vigabatrin subjects (4.29) and placebo subjects (5.24). In study 0223 the mean change from baseline for alkaline phosphatase for the vigabatrin 1g/day group was -44.29, for the 3g/day group was -19.13, for the 4g/day group was -18.88 and for the 6g/day group was -7.83.

Pediatric non-IS Subpopulation
Ovation provided selected mean change results (those with statistically significant differences) from the 3 controlled studies that comprise the pediatric non-IS subpopulation database (0118, 0221, 0192). Those results are summarized below. For the long term studies 0201 and 0294, Ovation only reported that the mean changes from baseline for all parameters were not clinically relevant (12/28/07 Submission, p.157).

Mean Change from Baseline Results from Pediatric non-IS Controlled Trials (0118, 0221, and 0192)

Laboratory test	Treatment	Mean Change ± SD
Study 0118		
SGPT (ALT) (U/L)	Vigabatrin (n=90)	-22.19 ± 18.14
	Placebo (n=27)	-3.12 ± 5.57
SGOT (AST) (U/L)	Vigabatrin (n=90)	-10.13 ± 13.88
	Placebo (n=27)	0.54 ± 5.60
RBC (x $10^3/\mu L$)	Vigabatrin (n=87)	-0.22 ± 0.29
	Placebo (n=29)	0.13 ± 0.61
Hemoglobin (g/dL)	Vigabatrin (n=87)	-0.35 ± 0.74
	Placebo (n=29)	0.56 ± 1.57

Hematocrit (%)	Vigabatrin (n=87)	-1.04 ± 2.34
Study 0221		
SGPT (ALT) (U/L)	Vigabatrin (n=40)	-12.40 ± 7.40
	Placebo (n=40)	1.90 ± 8.12
SGOT (AST) (U/L)	Vigabatrin (n=40)	-5.59 ± 7.67
	Placebo (n=40)	0.97 ± 9.35
Alkaline phosphatase (U/L)	Vigabatrin (n=40)	15.03 ± 68.79
	Placebo (n=40)	-11.46 ± 31.02
Creatinine (mg/dL)	Vigabatrin (n=40)	-0.07 ± 0.07
	Placebo (n=40)	0.01 ± 0.08
Hemoglobin (g/dL)	Vigabatrin (n=39)	-0.39 ± 0.65
	Placebo (n=40)	0.19 ± 0.71
Hematocrit (%)	Vigabatrin (n=39)	-1.13 ± 2.26
	Placebo (n=40)	0.62 ± 2.35
Platelets (x $10^3/\mu L$)	Vigabatrin (n=38)	16.72 ± 39.96
	Placebo (n=40)	-15.83 ± 82.57
Study 0192		
SGPT (ALT) (U/L)	Vigabatrin (n=20)	-11.45 ± 10.71
	Placebo (n=21)	-3.33 ± 4.03

Source: 12/28/07 Submission, pp.156-7.

As the table above illustrates, the changes in transaminases, and hemoglobin seen in the adult population were also observed in the pediatric non-IS population.

I reviewed all lab mean change results listed in the original study reports for the pediatric non-IS vigabatrin studies. Study 0118 randomized subjects to three different vigabatrin doses (20mg/kg/day, 60mg/kg/day, and 100mg/kg/day) and therefore provides information about dose response. The study 0118 lab results suggest dose response for transaminase decline and hemoglobin, hematocrit and RBC declines. I provide those results below.

Transaminase, Hemoglobin, Hematocrit, and RBC Mean Change from Baseline Results from Study 0118

Study 0118		
SGPT (ALT) (U/L)	Placebo (n=27)	-3.12 ± 5.57
	Vigabatrin 20mg/kg/day (n=29)	-13.52 ± 8.30
	Vigabatrin 60mg/kg/day (n=29)	-22.19 ± 18.14
	Vigabatrin 100mg/kg/day (n=32)	-19.53 ± 11.48
SGOT (AST) (U/L)	Placebo (n=27)	0.54 ± 5.60
	Vigabatrin 20mg/kg/day (n=29)	-5.41 ± 11.59
	Vigabatrin 60mg/kg/day (n=29)	-6.93 ± 9.19
	Vigabatrin 100mg/kg/day (n=32)	-10.13 ± 13.88
Hemoglobin (g/dL)	Placebo (n=29)	0.56 ± 1.57
	Vigabatrin 20mg/kg/day (n=28)	0.02 ± 0.59
	Vigabatrin 60mg/kg/day (n=31)	-0.20 ± 0.72
	Vigabatrin 100mg/kg/day (n=28)	-0.35 ± 0.74
Hematocrit (%)	Placebo (n=29)	1.84 ± 5.20
	Vigabatrin 20mg/kg/day (n=28)	-0.41 ± 2.01
	Vigabatrin 60mg/kg/day (n=31)	-0.30 ± 2.20
	Vigabatrin 100mg/kg/day (n=28)	-1.04 ± 2.34

RBC (x $10^3/\mu L$)	Placebo (n=29)	0.13 ± 0.61
	Vigabatrin 20mg/kg/day (n=28)	-0.10 ± 0.20
	Vigabatrin 60mg/kg/day (n=31)	-0.15 ± 0.22
	Vigabatrin 100mg/kg/day (n=28)	-0.22 ± 0.29

Source Study report for 0118, Table 34.

In study 0192, the mean change from baseline for alkaline phosphatase among vigabatrin subjects was 20.18 compare to -2.50 for placebo. Similarly, in study 0221, the mean change from baseline for alkaline phosphatase for vigabatrin subjects was 15.03 compared to -2.50 for placebo. The remaining mean change lab results from study 0192 and from study 0221 were unremarkable.

The mean changes from baseline lab results from long term open label studies 0201 and 0204 were generally in the same direction as the changes observed in vigabatrin subjects in the controlled trials.

IS subpopulation
Ovation did not provide mean change analyses for the lab data from study 1A in the Current submission. The Division requested mean change analyses for study 1A. Ovation noted that lab values were not collected during the blinded phase of the trial, when subjects were randomized to low or high dose vigabatrin. Lab data are available only for the open label phase of the trial, which allowed flexible dosing. When Ovation presented the results from the open label phase, the results were grouped by high dose and low dose, reflecting the original randomization, and for all subjects combined. Since the classification by dose does not necessarily reflect the dosing that the subject received at the time of the lab test, I present the combined data below.

Subjects in study 1A experienced declines in AST and ALT. At month 1, the mean change from baseline for AST was -10.2 and for ALT was -17.7. There did not appear to be marked additional decline during months 3-30 (Source 5/16/08 Response to Questions, pp.23-25).

At month 1, subjects in study 1A experienced a mean decline in hematocrit of -0.65 and hemoglobin of -0.33. For the remaining months of the study the surviving subjects experienced mean increases and deceases in hematocrit and hemoglobin compared to baseline (Source 5/16/08 Response to Questions, pp.41-44). For platelets, study subjects consistently experienced mean decreases for all study months with the largest mean decline compared to baseline at month 24 (-56.7 x10^3, n=39) (Source 5/16/08 Response to Questions, pp.52-53).

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

Primary Data

The following table summarizes select lab outlier risks for the US epilepsy controlled trials in the original NDA.

Select Lab Outlier Results, US Controlled Epilepsy Studies 024, 025

Analyte	Vigabatrin	Placebo
High SGOT	0.4% (1/222)	0.7% (1/135)
Low Sodium	4% (8/221)	4% (5/135)
Low Calcium	20% (45/221)	30% (40/135)
Low glucose	4% (8/221)	4% (5/135)
High Amylase	5.2% (3/58)	3.8% (2/53)
Low Hematocrit	13% (28/221)	6% (8/135)
Low Hemoglobin	0.9% (2/221)	(0/135)
Low WBC	10% (23/221)	5% (7/135)
Low neutrophils	7% (16/221)	4% (6/135)
Low lymphocytes	15.4% (68/442)	6.7% (9/135)

No vigabatrin or placebo subjects in US epilepsy controlled trials had lab results that met outlier criteria for SGPT, bilirubin, alkaline phosphatase, BUN, or creatinine (Source Amendment Review, pp.38-41, NDA Amendment p.Sb-V2-P286).

Safety Update (1/1/96-3/15/97)

The safety update review included reviews of responses to Division questions that were part of the Approvable letter. One of the Division's questions asked the sponsor to characterize transaminase test low outliers. In response, the sponsor noted that in the North American controlled trials, 94% (263/280) of subjects had a 60-100% maximum decrease in their ALT compared to baseline. Furthermore, 4% (11/280) had an ALT result of 0. In the placebo subjects from these trials, 78% had a 0%-40% maximum decrease in their ALT compared to baseline. In the vigabatrin subjects, the decrease in ALT appeared to be dose related. In looking at the time course, the sponsor noted that 94% had their first abnormal ALT (defined as a 20% drop from baseline) during the first 3 weeks of therapy. The sponsor noted that 47% reached their maximum decrease within 4-8 weeks of staring vigabatrin. AST was also decreased in vigabatrin exposed subjects but less so than the ALT. The sponsor reported that 93% of subjects in the North American controlled trials had a 0-60% maximum decrease in their AST from baseline with 54% experiencing maximum decreases in the 20-40% range. No vigabatrin exposed subjects had an AST result of 0. The drop in AST also appeared to be dose related. The time to onset for the first abnormal AST was 4-8 weeks after starting vigabatrin and 40% reached their maximum decrease during this period of time (Source Safety Update review, p.20).

In addition to requests about transaminase results, the Division requested additional information regarding anemia related events in vigabatrin subjects. The sponsor confirmed the finding of an excess of anemia adverse events (4) and clinically significant outliers for anemia (12) in the vigabatrin treated group (5.7%; 16/280) compared to the placebo group (1.6%, 3/188) in the North American controlled trials. The sponsor reported that none of the 16 vigabatrin subjects with an anemia adverse event or outlier result required hospitalization, transfusion, or discontinuation from the study for this event. The Division requested information about the work up of these events and the sponsor reported that no other relevant lab tests (Coombs, ferritin, reticulocyte count etc.) were reported for these patients. For the 4 patients with anemia recorded

as an adverse event, the sponsor noted that they had underlying medical conditions associated with anemia (PUD, ulcerative colitis) or a history of anemia. They stated that 3 of these individuals were treated (2 with iron, 1 with folate) and improved (Source Safety Update review, p.20).

Current Submission

Adult Subpopulation

I reviewed the lab outlier analyses in the study reports for controlled trials 0101, 0222, and 0223. None of these studies included low transaminase outlier criteria. For the lab test outliers examined in these studies, the frequency of outliers was low and there was little difference in risk between vigabatrin and control groups or among different vigabatrin dose groups. In study 0101, 1 vigabatrin (0.5%, 1/190) and no placebo (0/100) subjects had a low outlier for RBC, hematocrit, and hemoglobin (Source Study report 0101, p.113). In study 0222, 1 vigabatrin (10%, 1/10) subject had a low hemoglobin outlier compared to no gabapentin subjects (0/10) and 2 vigabatrin subjects (20%, 1/10) had low hematocrit outliers compared to no gabapentin subjects (Source Study report 0222, p.88). The results from study 0223 were similar to the results for the other Adult epilepsy studies. I provide the low outlier results for hemoglobin and hematocrit from study 0223 in the table below.

Treatment	Outlier at any time % (n)
Low Hemoglobin (females <=9.5g/dL, males <=11.5g/dL)	
Vigabatrin 1g/day	0/17
Vigabatrin 3g/day	0/18
Vigabatrin 4g/day	5.3% (1/19)
Vigabatrin 6g/dL	4.8% (1/21)
Low Hematocrit (females <=32%, males <=37%)	
Vigabatrin 1g/day	5.3% (1/17)
Vigabatrin 3g/day	0/18
Vigabatrin 4g/day	5.3% (1/19)
Vigabatrin 6g/dL	9.5% (2/21)

Source: Study report for 0223, pp.111-112

Pediatric non IS Subpopulation

I reviewed the lab outlier analyses in the study reports for controlled trials 0118, 0221, and 0192. None of these studies included low transaminase outlier criteria. In study 0118, the risks for low hemoglobin and hematocrit outliers were similar across the three vigabatrin dose levels and for placebo (Source Study report 0118, pp.138-9). In study 0221, 9.3% (4/43) of vigabatrin subjects and 2.3% (1/43) of placebo subjects had a low hemoglobin outlier while 33% (14/43) of vigabatrin subjects and 14% (6/43) of placebo subjects experienced low hematocrit outliers (Source Study report 0221, p. 110). In study 0192, no vigabatrin or placebo subjects experienced low hemoglobin outliers and 18% (5/28) of vigabatrin subjects and 11% (3/27) of placebo subjects experienced low hematocrit outliers (Source Study report 0192, p.94).

IS Subpopulation

The study report for 1A noted that of the 145 subjects with normal hemoglobin at baseline, 18 (12.4%) had a low outlier result after 1 month of vigabatrin treatment and of the 147 subjects

with a normal hematocrit at baseline, 8 (5.4%) had a low result after 1 month of vigabatrin treatment (source Study report 1A, p.368).

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

The NDA review noted that there were no reports of deaths or withdrawal for hematology test results (NDA review p.76). The NDA amendment review identified one primary non US study subject that discontinued for a hypochromic anemia that improved with iron replacement (NDA amendment review, p.41).

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Ovation provided a table summarizing the lab related SAEs. Ovation identified 2 SAEs of renal failure acute, 2 of anemia and one of DIC (Amendment Submission, Table 20, p.80). In addition, there was one subject that died from acute hepatic failure that was not included in the table. These events were discussed above with the SAEs. Ovation reported that one subject discontinued for low platelets (discussed above with SAEs) and one for increased ALP (Amendment Submission, Table 4.1.6.1, p.7340).

Given the findings of mean decreases and increased risk for low outliers in hemoglobin and hematocrit in subjects treated with vigabatrin, the Division asked Ovation to look for clinically important anemia events. Specifically, the Division asked Ovation to identify all study subjects with a hemoglobin result below 8g/dL and or a hematocrit result below 24%.

Ovation identified 8 cases of treatment emergent anemia meeting the search criteria, but 4 of the cases did not appear to be actual anemia events. Subject 057-013 had a hematocrit result of 13% at the time her hemoglobin was 12.5g/dL and Ovation noted that all of her other hematological test results were normal. Subject 25405 had a hemoglobin of 7g/dL at the time her hematocrit was 53%. This subject's remaining hematocrit values during the study were above 47%. Subjects 013-007 and 089-013 had low hemoglobin and hematocrit results but repeat testing within 3 days were normal, suggesting that the abnormal results were spurious.

Two subjects with lab results that met the anemia search criteria had apparent explanations for their results. Subject 26324 had a history of microcytic anemia and had a hemoglobin of 8.4g/dL with a hematocrit of 31% at baseline. The subject's lowest recorded hemoglobin was 7.8g/dL (Hct 27%). Subject 0269, a 26 month old with IS, developed renal disease (glomerulonephritis) and required treatment with erythropoietin and transfusions. This subject's lowest recorded hemoglobin was 5.6g/dL (Hct 18.3%) and he remained anemic throughout the study.

Ovation provided no clear explanatory factors for the treatment emergent anemia in the remaining 2 cases. Subject 0308, a 13 month old male with IS, had a baseline hemoglobin of 11.7g/dL (Hct 35.2%). During the study, his hemoglobin dropped to 7.9g/dL (Hct 24.5%) and Ovation commented that this occurred when the subject stopped taking iron supplements. The subject's hemoglobin improved to 11.2g/dL (Hct 33.8%) by the end of the study, but Ovation was not able to determine if the subject received treatment for the anemia. Subject 0174, a 5 month old with IS had a baseline hemoglobin of 13.1g/dL (Hct 40.1%). By visit 4, the subject's hemoglobin had declined to 5.3g/dL (Hct 13.1%). The subject withdrew from the study for lack of efficacy and Ovation did not provide follow up information. Anemia was not reported as an adverse event for this subject. (Source 5/16/08 Submission, pp. 6-8).

7.1.7.4 Additional analyses and explorations

7.1.7.5 Special assessments

Hepatic Injury
The Division asked Ovation to identify the number of vigabatrin clinical trial subjects with evidence of hepatic injury as defined by elevation of AST or ALT to 3 X ULN AND elevation of total bilirubin to 2 X ULN. Ovation identified 64 studies that captured at least one baseline and one on treatment transaminase result and total bilirubin result. Ovation manually reviewed lab result data listings for the studies included in prior submissions, for which electronic data sets do not exist, and queried lab result electronic datasets for the studies included in the current submission. Ovation reported that no vigabatrin subjects in the development program studies had elevation of AST or ALT to 3 X ULN AND elevation of total bilirubin to 2 X ULN (Source 5/2/08 Submission).

The Division also asked Ovation to provide an analysis of pooled controlled trial data that summarized the risk for transaminase and total bilirubin high outliers for vigabatrin and comparator treatments. The results of that analysis are provided in the following table (Source 5/2/08 submission).

Table 3. Liver Function Data

	Vigabatrin (N=952) n / N (%)[a]	Carbamazepine (N=229) n(%)[a]	Valproate (N=113) n(%)[a]	Gabapentin (N=9) n(%)[a]	Placebo (N=393) n(%)[a]	Total (N=1696) n(%)[a]
ALT (SGPT) (U/L)[a]						
>1.5x ULN	4 / 892 (0.45)	4 / 226 (1.77)	2 / 110 (1.82)	1 / 7 (14.29)	1 / 354 (0.28)	12 / 1589 (0.76)
>3x ULN	1 / 892 (0.11)	1 / 226 (0.44)	1 / 110 (0.91)	0 / 7 (0.00)	0 / 354 (0.00)	3 / 1589 (0.19)
>5x ULN	0 / 892 (0.00)	0 / 226 (0.00)	0 / 110 (0.00)	0 / 7 (0.00)	0 / 354 (0.00)	0 / 1589 (0.00)
>10x ULN	0 / 892 (0.00)	0 / 226 (0.00)	0 / 110 (0.00)	0 / 7 (0.00)	0 / 354 (0.00)	0 / 1589 (0.00)
>20x ULN	0 / 892 (0.00)	0 / 226 (0.00)	0 / 110 (0.00)	0 / 7 (0.00)	0 / 354 (0.00)	0 / 1589 (0.00)
AST (SGOT) (U/L)[a]						
>1.5x ULN	2 / 778 (0.26)	3 / 226 (1.33)	1 / 111 (0.90)	0 / 9 (0.00)	0 / 343 (0.00)	6 / 1577 (0.38)
>3x ULN	2 / 778 (0.26)	0 / 226 (0.00)	1 / 111 (0.90)	0 / 9 (0.00)	0 / 343 (0.00)	3 / 1577 (0.19)
>5x ULN	1 / 778 (0.13)	0 / 226 (0.00)	0 / 111 (0.00)	0 / 9 (0.00)	0 / 343 (0.00)	1 / 1577 (0.06)
>10x ULN	0 / 778 (0.00)	0 / 226 (0.00)	0 / 111 (0.00)	0 / 9 (0.00)	0 / 343 (0.00)	0 / 1577 (0.00)
>20x ULN	0 / 778 (0.00)	0 / 226 (0.00)	0 / 111 (0.00)	0 / 9 (0.00)	0 / 343 (0.00)	0 / 1577 (0.00)
Total Bilirubin (mg/dL)[b]						
>1.5x ULN	1 / 927 (0.11)	0 / 223 (0.00)	0 / 112 (0.00)	0 / 6 (0.00)	0 / 374 (0.00)	1 / 1642 (0.06)
>2x ULN	0 / 927 (0.00)	0 / 223 (0.00)	0 / 112 (0.00)	0 / 6 (0.00)	0 / 374 (0.00)	0 / 1642 (0.00)
Either AST or ALT > 3x ULN with Total Bilirubin > 1.5x ULN	0 / 916 (0.00)	0 / 229 (0.00)	0 / 113 (0.00)	0 / 6 (0.00)	0 / 367 (0.00)	0 / 1631 (0.00)

n= number of subjects with specified abnormality / N=number of subjects normal (i.e. ≤ ULN) at baseline. Percentages are calculated based on the number of subjects normal at baseline.
[a] ULN=Upper limit of normal, defined as 40 U/L.
[b] ULN=Upper limit of normal, defined as 1.2 mg/dL.

These results suggest that transaminase and total bilirubin high outlier results were uncommon among the subjects enrolled in the pool of vigabatrin controlled trials. One must interpret the transaminase elevation outlier results in light of the evidence presented above that suggests vigabatrin causes dose dependent declines in transaminase results.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

The NDA review did not document the extent of vital sign testing in the vigabatrin studies. The NDA review included a summary of outlier risks for systolic and diastolic blood pressure, pulse, and weight observed in the US epilepsy controlled trials 024 and 025. The NDA amendment review noted that the sponsor provided a summary of vital sign mean changes from study 025 but included no summary of vital sign data from non US studies (NDA Amendment review, pp.44-45).

Safety Update (1/1/96-3/15/97)
The Safety update did not provide a summary of vital sign data.

Current Submission

Overall Safety Population (3/16/97-6/30/07)

The studies included in the current NDA amendment submission collected vital signs including pulse, systolic and diastolic blood pressure, respiration, and in some cases weight.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)
In the NDA review, comparative vital sign data were presented for subjects participating in the US controlled epilepsy trials (024, 025). In the NDA Amendment the sponsor provided a dose response analysis for vital signs in study 025, but no comparative vital sign analyses for non US studies.

Current Submission
In the current NDA Amendment submission, Ovation provided comparative vital sign data from individual controlled trials. The results from each controlled trial were presented separately and no pooled analyses were performed.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)
The NDA Amendment review included a table that summarized mean change from baseline results for vitals signs from US controlled epilepsy study 025. Aside from small mean increases in respiration that appeared to show evidence of dose response, there did not appear to be a relationship between vigabatrin and vital sign changes. I provide a summary of the vital sign results below.

Parameter/ Treatment	N	Mean change from Baseline	P value*
Pulse (bpm)			
Placebo	45	-1.8	.1692
Vigabatrin 1g/day	45	0.4	
Vigabatrin 3g/day	43	1.7	
Vigabatrin 6g/day	41	1.2	
Respirations (rpm)			
Placebo	45	-0.7	.0182

Vigabatrin 1g/day	45	0.1	
Vigabatrin 3g/day	43	0.4	
Vigabatrin 6g/day	41	0.6	
Systolic BP (mmHg)			
Placebo	45	-5.1	.1284
Vigabatrin 1g/day	45	1.0	
Vigabatrin 3g/day	43	3.4	
Vigabatrin 6g/day	41	0.0	
Diastolic BP (mmHg)			
Placebo	45	-1.4	.1284
Vigabatrin 1g/day	45	1.3	
Vigabatrin 3g/day	43	0.7	
Vigabatrin 6g/day	41	-1.3	

*Linear trend test across 4 treatment groups from an analysis of covariance model adjusting for baseline
Source NDA Amendment, Appendix A, Table 6, p. Sa-V1-P297

Current Submission
For the Adult and Pediatric non IS subpopulations, Ovation commented only that weight gain has been observed in studies and that there were no clinically relevant effects of vigabatrin on vital signs in the adult studies. Ovation provided no comment about vital sign data from study 1A.

Adult Subpopulation
I reviewed the study reports for controlled trials 0101, 0222, and 0223 to look for evidence of vigabatrin related changes in vital sign parameters. I found no analysis of vital sign data in study 0101. For study 0222, the investigators provided a mean change from baseline to final visit analysis. Vigabatrin subjects experienced larger drops in mean diastolic and systolic blood pressure and larger mean increases in weight compared to gabapentin subjects. I provide those results below.

Vital sign parameter	Treatment	Mean change from baseline to final
Diastolic Blood Pressure (mmHg)	Vigabatrin (n=9)	-10.00
	Gabapentin (n=9)	-2.67
Systolic Blood pressure (mmHg)	Vigabatrin (n=9)	-10.00
	Gabapentin (n=9)	-7.11
Heart Rate (bpm)	Vigabatrin (n=9)	-0.67
	Gabapentin (n=9)	-1.11
Weight (lbs)	Vigabatrin (n=8)	5.63
	Gabapentin (n=9)	-1.00

Source Study report 0222, pp.1764-1766.

Mean change from baseline to final vital sign results for systolic blood pressure, diastolic blood pressure and pulse did not appear to demonstrate dose response in study 0223. For weight, subjects exposed to vigabatrin 1g/day gained an average of 2.5 pounds compared to 3.2 pounds for the 3g/day group, 3.2 pounds for the 4g/day group and 3.8 pounds for the 6g/day group (Source Study report 0223, p.1359).

Pediatric non-IS Subpopulation
For the pediatric non-IS controlled studies 0118, 0221, and 0192 the investigators stratified the mean vital sign changes from baseline into 3 age categories (3-<6yrs, >=6-<12 yrs, and >=12 yrs), resulting in few subjects in each category. For diastolic BP, systolic BP, heart rate and respirations there did not appear to be any consistent differences between vigabatrin and placebo (stratified by age) in any of these 3 studies. There did appear to be evidence of vigabatrin associated weight gain. In study 0118 (treatment phase up to 14 weeks), in the youngest age group (3-<6yrs old) there was little difference in mean weight change when comparing the different vigabatrin doses to placebo but for the older age groups, vigabatrin subjects gained more weight than placebo subjects and there was a suggestion of a dose response in the oldest age group (>=12 yrs). I provide those weight results below.

Mean Weight change (lbs) from baseline to Visit 9, by Age group, study 0118

Age Group	Placebo (n)	Vigabatrin 20mg/kg/day	Vigabatrin 60mg/kg/day	Vigabatrin 100mg/kg/day
3-<6 years	2.3 (7)	1.8 (5)	4.0 (1)	2.3 (8)
>=6-<12 yrs	1.5 (14)	4.1 (7)	6.0 (12)	5.5 (11)
>=12 yrs	-1.9 (10)	7.3 (17)	9.1 (18)	9.7 (11)

Source Study report 0118, Table 16.2, p.3421

In study 0221 (treatement phase up to 17 weeks), there was little difference between the vigabatrin and placebo groups for the two youngest age strata (3-<6 yrs, >=6yrs-1<12 yrs) for mean weight change. For the >=12 yrs age group the mean change in weight from baseline to maintenance visit was 3.1 pounds for vigabatrin (n=20) and 1.5 pounds for placebo (n=14) (Source Study report 0221, p.2788). In study 0192, there was little difference between vigabatrin and placebo subjects in the 3-<6 yrs age category for mean weight change. In the >=6-<12yrs category, vigabatrin subjects (n=10) gained 2.5 pounds compared to 1.1 pounds for placebo subjects (n=14). In the >=12 yrs age category, vigabatrin subjects (n=15) gained an average of 3.3 pounds compared to 1.2 pounds for placebo subjects (n=12) (Source Study report 0192, p.98).

IS Subpopulation
Since neither the Amendment submission nor the study report included vital sign analyses for study 1A, the Division asked Ovation to provide this information. Ovation provided their response in a 4/23/08 submission. In the first 2 weeks of study 1A, subjects were randomized to low dose or high dose vigabatrin. After those 2 weeks, subjects continued in the flexible dose open label phase. During the first two weeks, there did not appear to be notable differences when comparing the low and high dose groups for vital signs mean changes from baseline. I provide the vital sign mean changes from baseline at week 2 for the low dose and high dose groups.

Study 1A Vital Sign Mean Changes from Baseline at Week 2, by Dose Group

Vital sign parameter	Treatment	Mean change from baseline to week 2
Diastolic Blood Pressure (mmHg)	Low dose (n=90)	-0.4
	High dose (n=74)	-0.5
Systolic Blood pressure (mmHg)	Low dose (n=102)	-0.6

	High dose (n=94)	2.9
Heart Rate (bpm)	Low dose (n=108)	-0.7
	High dose (n=98)	0.4
Respiratory rate	Low dose (n=86)	-0.6
	High dose (n=80)	0.5

Source Tables 5.2-5.4, 4/23/08 submission

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

The NDA review included a table of vital sign outliers (normal at baseline and then exceeded outlier criteria at some time during treatment) from the US epilepsy controlled trials. I include information from that presentation below.

Vital Sign Parameter	Outlier criteria	Vigabatrin N=221	Placebo N=135
Systolic BP low	< 90mm Hg	1.4% (3)	0.8% (1)
Systolic BP high	>180mm Hg	0	0
Diastolic BP low	<50 mm Hg	0	0
Diastolic BP high	>120mm Hg	0	0
Pulse low	<50 bpm	0.5% (1)	0
Pulse high	>120 bpm	2.7% (6)	3% (4)
Weight decrease	>15%	0	0
Weight increase	>15%	0.5% (1)	0
Weight increase	7-15%	47.3% (62)	15.8% (21)

Source NDA review p.77

The NDA Amendment review did not include vital sign outlier data.

Current Submission
Adult Subpopulation
The study reports for controlled studies 0101, 0222, and 0223 did not provide summaries of subjects with outliers for vital signs.

Pediatric non-IS Subpopulation
The outlier analyses for the Pediatric non IS controlled trials were limited. All three studies used the same criteria to identify end study vital sign outliers. I provide those criteria below.

Vital Sign Parameter	Low Outlier Criteria	High Outlier Criteria
Pulse (bpm)	<50 and a drop >=15 from baseline	>140 and an increase of >=15 from baseline
Systolic BP (mmHg)	<80 and a drop of >=20 from baseline	>140 and an increase of >=20 from baseline
Diastolic BP	<50 and a drop of >=15 from baseline	>90 and an increase of >=15 from baseline

In study 0118, investigators reported that no subjects experienced an end study outlier result (low or high) for heart rate or systolic BP measurement and no subjects experienced a high outlier diastolic BP. One placebo subject and three vigabatrin 20mg/kg/day subjects (but no vigabatrin 60 or 100mg/kg/day subjects) experienced low end study diastolic BP measurements (Source Study report 0118, p.141). In study 0221 no subjects had an end study outlier for pulse (high or low) or low systolic BP or high diastolic BP. One vigabatrin and one placebo subject had an end study outlier for high systolic BP and one vigabatrin and one placebo subject had an end study outlier for low diastolic BP (Source Study report 0221, p.113). The only end study vital sign outliers from study 0192 occurred in placebo subjects (one low SBP, two low DBP) (Source Study Report 0192, p.99).

IS Population (Study 1A)
In their 4/23/08 submission, Ovation provided an outlier vital sign analysis for Study 1A that defined outlier values as those >2 SD from the mean. The Division requested additional vital sign outlier analyses for Study 1A that used specific cutoff values. Those cutoff values are listed below.

Pulse

Age	Low	High
1-12 months	<100	>160
>12 months	<80	>110

Systolic Blood Pressure

Age	Low	High
1-12 months	<70	>110
>12 months	<74	>110

Diastolic Blood Pressure

Age	Low	High
1-12 months	<50	>70
>12 months	<55	>75

Respirations

Age	Low	High
1-12 months	<30	>60
>12 months	<24	>40

Ovation provided the results of their analyses in their 5/16/08 submission. Week 2 results from those analyses are summarized below. Week 2 includes data from subjects receiving randomized low or high dose vigabatrin. The remainder of the study allowed flexible dosing and so they lack comparative value.

Vital Sign Outlier Results, Study 1A, Week 2			
	High Dose	Low Dose	Combined
Pulse (BPM)			

N	82	85	167
Low outlier	1.2% (1)	4.7% (4)	3.0% (5)
High Outlier	2.4% (2)	9.4% (8)	6.0% (10)
Systolic Blood Pressure (mm Hg)			
N	66	81	147
Low outlier	3.0% (2)	8.6% (7)	6.1% (9)
High Outlier	19.7% (13)	12.3% (10)	15.6% (23)
Diastolic Blood Pressure (mm Hg)			
N	37	49	86
Low outlier	24.3% (9)	24.5% (12)	24.4% (21)
High Outlier	16.2% (6)	16.3% (8)	16.3% (14)
Respirations (resp/min)			
N	46	55	101
Low outlier	17.4% (8)	21.8% (12)	19.8% (20)
High Outlier	(0)	4.1% (2)	3.5% (3)

In general, outlier risks were either similar for the two vigabatrin dose groups or higher among the low dose group. There was a slight increase high outlier risk for systolic blood pressure for the vigabatrin high dose group compared to the low dose group.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

Neither the NDA review nor the NDA Amendment review discussed marked vital sign outliers or dropouts for vital sign outliers.

Current Submission
Ovation did not provide an analysis of marked vital sign outliers. For the Integrated population, the only vital sign related SAEs were hypertension (0.04%, 2/4,739). Thirty-one vigabatrin subjects (0.64%, 31/4,855) discontinued from trials included in the Integrated Population for weight increased and one subject (0.02%, 1/4,855) discontinued for weight decreased. One subject from the Integrated Population discontinued for blood pressure increased (0.02%, 1/4,855)

7.1.8.4 Additional analyses and explorations

Given the evidence supporting a relationship between weight gain and vigabatrin, the Division requested additional analyses to clarify this relationship. Using weight data from studies included in the Integrated analysis, Ovation provided summary data about weight gain in vigabatrin treated subjects. After excluding data from IS studies and from infants in non IS studies, and excluding studies that did not include at least one baseline and one post baseline weight measurement, Ovation examined weight gain in 1843 vigabatrin subjects. Ovation reported that 26.3% (484/1843) vigabatrin subjects gained >= 7% weight compared to baseline.

Ovation also provided a comparative analysis. Using data from 9 controlled trials, Ovation found that 17.4% (77/443) of vigabatrin subjects gained >=7% of baseline body weight during treatment compared to 8% (22/275) of placebo subjects, 19% (4/21) of valproate subjects and no (0/8) gabapentin subjects. The mean weight change from baseline was highest for vigabatrin (3.5kg) followed by valproate (2.7kg), and placebo (1.6kg). Gabapentin subjects experienced a mean change in weight of -0.63kg.

Ovation provided analyses that stratified by sex and age to look for differences in weight gain by demographic factors. As demonstrated below, females appeared to have a greater risk of gaining at least 7% of baseline body weight and had a higher mean increase in body weight compared to placebo.

Weight change by sex, from 9 randomized controlled vigabatrin trials

% of Subjects that gained >=7% compared to baseline			
Sex	Vigabatrin	Placebo	RR
Male	17.1% (38/215)	8.5% (11/130)	2.0
Female	17.1% (39/228)	7.6% (11/145)	2.3
Mean weight change from baseline (kg)			
	Vigabatrin	Placebo	Vigabatrin-Placebo
Male	3.0	1.8	1.2
Female	3.9	1.5	2.4

Source 5/23/08 submission, Tables 3.3, 3.4, p.11

Ovation provided weight change analyses that stratified subjects into the following 3 age groups: <18 years, 18-45 years, and 46-64 years. The relative risk for weight gain of >=7% of baseline body weight was highest among the 18-45 year old age group. The mean weight gain relative to placebo was similar in all three age groups. Those results are provided below.

% of Subjects that gained >=7% compared to baseline			
Age group	Vigabatrin	Placebo	RR
<18 years	36.7% (51/139)	19.3% (17/88)	1.9
18-45 years	8.9% (23/258)	3.1% (5/162)	2.9
46-64 years	6.5% (3/46)	0	-
Mean weight change from baseline (kg)			
	Vigabatrin	Placebo	Vigabatrin-Placebo
<18 years	6.0	3.6	2.4
18-45 years	2.4	0.8	1.6
46-64 years	2.0	-0.1	2.1

Source 5/23/08 submission, Tables 3.5, 3.6, and 3.7 pp.11-12

Ovation also attempted to analyze weight change by dose using data pooled from 5 studies. Given the differences in trial durations, and different dosing regimens in each of the included trials, the differences attributed to dose are likely greatly influenced by the different durations of treatment.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Ovation acknowledged that the non-clinical and clinical studies conducted during the vigabatrin development program preceded the recent FDA and ICH guidelines recommending that drugs be evaluated for QT interval prolongation. Ovation summarized cardiovascular-related results from previously submitted studies as well as results from newly completed pre-clinical studies designed to assess the effect of vigabatrin on cardiac repolarization.

Among the preclinical findings cited by Ovation was the lack of effect in raising the electrical stimulation threshold or the ventricular fibrillation threshold in perfused rabbit heart preparations, transient dose dependent elevation in blood pressure in rats when vigabatrin was injected into the nucleus tract solitarius, and slight increase in blood pressure in intravenously injected rats. Ovation also reported no increases in blood pressure, heart rate, interventricular pressure, dP/dt, cardiac output, calculated peripheral resistance, stroke volume or atrial pressures following intravenous or subacute oral administration in dogs. In addition, Ovation reported that a long term toxicity study in dogs that included ECGs found "no drug effect throughout the one year dosing period."

In 2006, Ovation hired ChanTest Inc. to conduct studies of vigabatrin's effect on the hERG channel current. Vigabatrin was exposed to cells at 100 and 300μg/mL concentrations (highest dose corresponds to approximately 4 times the maximum plasma concentration). Vigabatrin did not significantly inhibit hERG currents (0.4% and 0.8%) while terfenadine, the positive control, inhibited hERG currents by 75%.

In follow up tests in isolated rabbit Purkinje fibers there was no significant difference in when comparing the effect of vigabatrin and vehicle on action potential duration. The positive control, sotalol, caused significant prolongation of action potential duration.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

In a report included in the October 10, 2006 NDA Amendment submission, Ovation reviewed the vigabatrin cardiovascular safety data. Ovation summarized cardiovascular safety data from the previously conducted clinical trials. The summaries did not provide details about the number of ECGs conducted, or mention if the ECGs were recorded at the time of estimated peak or trough drug or metabolite levels. Examples of the types of information in these summaries are that there were no significant changes observed or that ECG data were not collected or that no adverse events of QT prolongation or torsades were observed. There were no quantitative assessments of intervals provided in these summaries.

Ovation referenced an evaluation of cardiovascular safety data that was performed by a consultant cardiologist, Craig Pratt MD and was submitted as part of the 1997 NDA Amendment. Dr. Pratt reviewed selected abnormal ECGs from studies 097-005 and 097-006 (the reported QT intervals and heart rate data for subjects who reported cardiovascular AEs or had changes in ECGs). In addition, Dr. Pratt reviewed all cardiovascular deaths and AEs that had occurred on vigabatrin. Ovation reported that this review included a total of 2,516 vigabatrin and 1,219 placebo subjects from US and non US studies, as well as vigabatrin spontaneous cardiovascular reports through 31 December 1995." Ovation reported that Dr. Pratt found no meaningful effects of vigabatrin on PR, QRS, or QT intervals and no signal of cardiovascular AEs related to vigabatrin (Source 10/10/06 Amendment Submission, Analysis of Vigabatrin Effect on QTc, p.10).

Ovation also referenced cardiovascular safety data from clinical trials that was presented in the Safety Update for 3/15/97 through 6/17/05. Ovation noted that there were 21 cardiovascular AEs reported in this Safety Update including heart rate increased, hypertension, hypotension, orthostatic hypotension, tachycardia, bradycardia, and palpitations. Four study subjects withdrew from clinical trials for cardiovascular AEs. The cardiovascular AEs leading to discontinuation were hypertension (n=2), infarction NOS, and AV block second degree. Ovation did not summarize all serious cardiovascular AEs or all cardiovascular AEs resulting in death. Ovation did note that there were 3 fatal events coded to the term myocardial infarction. Ovation provided narratives for these events. One death occurred in a 54 year old male with no history of cardiovascular disease. This subject's was found dead in bed and a post mortem examination was not performed. The two remaining deaths occurred in subjects with histories of cardiovascular disease and the narratives provided no information to support the reported cause of death (Source 10/10/06 Amendment Submission, Analysis of Vigabatrin Effect on QTc, pp.10-12).

Ovation referenced a second source of cardiovascular risk data, postmarketing reports collected by Aventis. Ovation identified cardiovascular 6 postmarketing reports during the period of 3/97 through 6/05. The events reported were AV block complete, cardiac failure, cardiomyopathy, palpitations, pulmonary valve stenosis, and tachycardia.

In their report on vigabatrin's effect on QTc, Ovation reanalyzed ECG data from a controlled trial (005) and its open label extension (006). These trials were conducted between 1982 and 1983. Study 005 was an add-on trial with a flexible dose design allowing titration to the maximum tolerated dose. Ovation's new analyses used heart rate, PR, QRS, and QT interval data contained in electronic files. The ECG intervals were not re-measured using current standards and the original ECGs are not available for review or re-measurement (p.22). These analyses were based on data for 76 subjects from study 005 and 71 subjects from study 006. The analyses provided the mean change from baseline among vigabatrin treated subjects and there were no control data for comparison.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Study 005
Ovation presented analyses of the mean change from baseline at week 3 and week 15 in study 005. Week 3 was the week of maximum tolerated dose and week 15 was the end of the maintenance period. In addition to slight declines in heart rate, Ovation found increases from baseline in mean QT, QTcB, and QTcF that were greater at week 3 than at week 15. The results for their ECG interval data analyses from study 005 are presented in the following table.

Mean Change from Baseline for Heart Rate, PR interval, QRS interval, QT interval, QTcB, and QTcF, Study 005

ECG Parameter	Week 3 Change from Baseline	Week 15 Change from Baseline
Heart rate (bpm)	-0.6 (n=72)	-2.7 (n=72)
PR (ms)	0.3 (n=72)	2.2 (N=72)
QRS (ms)	0.1 (n=72)	3.0 (n=72)
QT	11.6 (n=69)*	8.6 (n=71)
QTcB	10.2 (n=69)*	1.7 (n=71)
QTcF	10.7 (n=69)*	4.1 (n=71)

Data from Appendices 1-7
*These change from baseline statistics include data for a subject with a recorded QT of 870msec which Ovation feels is likely an error but this hypothesis cannot be evaluated because the ECGs from this study are not available.

In addition to the mean change analyses presented above, Ovation also presented results that were stratified by sex. This study included 76 males and 14 females. Ovation reported finding a difference in mean heart rate change from baseline by sex. At week 15, among males the mean heart rate change from baseline was -3.4 bpm compared to an increase of 0.8 bpm for females. Females had smaller mean increases from baseline for QTcB and QTcF compared to males at week 3 and longer increases at week 15. Given the small number of female subjects in this trial, and limitations related to methodology, any conclusions based on these results are questionable. The results are provided below.

Mean Change from Baseline by Sex for Heart Rate, PR interval, QRS interval, QT interval, QTcB, and QTcF, Study 005

ECG Parameter	Sex	Week 3 Change from Baseline	Week 15 Change from Baseline
Heart rate (bpm)	Male	-0.1 (n=60)	-3.4 (n=60)
	Female	-2.9 (n=12)	0.8 (n=12)
PR (ms)	Male	-0.3 (n=60)	3.7 (N=60)
	Female	3.3 (n=12)	-5.0 (n=12)
QRS (ms)	Male	0.0 (n=60)	3.4 (n=60)
	Female	0.8 (n=12)	0.8 (n=12)
QT	Male	11.9 (n=58)*	8.8 (n=60)
	Female	10.0 (n=11)	7.6 (n=11)
QTcB	Male	12.0 (n=58)*	-0.5 (n=60)
	Female	1.2 (n=11)	14.0 (n=11)
QTcF	Male	11.9 (n=58)*	2.7 (n=60)
	Female	4.2 (n=11)	11.8 (n=11)

Data from Appendices 8-21
*These change from baseline statistics include data for a subject with a recorded QT of 870msec which Ovation feels is likely an error but this hypothesis cannot be evaluated because the ECGs from this study are not available.

Ovation felt that the ECG results from these studies did not show clinically important changes in any conduction interval.

Extension 006
Ovation presented mean ECG interval changes from baseline data from the open label extension 006. These analyses included results from months 3, 6, 9, 12, 18, 24, 30, and 36. The study included 52 subjects at month 3, but by month 36 the study size had dropped to 24 subjects. The mean heart rate change from baseline was negative in each month that was analyzed (range -0.6bpm at month 3 to -4.8bpm at month 30). For each of the 8 months analyzed, the mean QTcB change from baseline was negative (range -0.8 at month 36 to -12.9 at month 18). The range of mean QTcF changes from baseline was -9.1 at month 18, to 3.2 at month 6 (Source Appendices 1-7).

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Study 005
Using cutoffs of increase from baseline of >30ms and >60ms, Ovation identified the percentage of vigabatrin treated subjects with increases in QT, QTcB, and QTcF. Those results are provided below.

Study 005: Percentage of subjects with increases of >30msec and >60msec from baseline for QT, QTcB, and QTcF

ECG Parameter	>30ms increase	>60ms increase
Week 3		
QT	13% (n=9)	1.4% (n=1)
QTcB	18.8% (n=13)	4.3% (n=3)
QTcF	15.9% (n=11)	1.4% (n=1)
Week 15		
QT	18.3% (n=13)	5.6% (n=4)
QTcB	18.3% (n=13)	5.6% (n=4)
QTcF	15.5% (n=11)	2.8% (n=2)

Source Appendices 1-7

Ovation also identified the percentage of subjects with absolute QT, QTcB, and QTcF intervals that exceeded 450ms, 480ms, and 500ms. Those results are provided below.

Outliers, Absolute values for QT interval, QTcB, and QTcF

ECG Parameter	>450ms	>480ms	>500ms
Week 3			
QT	1.3% (1)	1.3% (1)	1.3% (1)
QTcB	2.7% (2)	1.3% (1)	1.3% (1)
QTcF	1.3% (1)	1.3% (1)	1.3% (1)
Week 15			
QT	0	0	0
QTcB	3.9% (3)	2.6% (2)	0
QTcF	2.6% (2)	0	0

Extension 006
In study 006, the percentage of subjects with increases in QTcB of more than 30ms ranged from 9.1% (3/33, month 18) to 24.5% (12/49, month 3). The percentage of subjects with increases in QTcB of more than 60ms ranged from 0% (months 12, 18, 30, and 36) to 10.3% (3/29, month 24). The percentage of subjects with increases in QTcF of more than 30ms ranged from 4.3% (1/23, month 36) to 20.4% (10/49, month 3). The percentage of subjects with increases in QTcF of more than 60ms ranged from 0% (months 12, 18, 30, and 36) to 8.2% (4/49, month 3) (Appendices 6 and 7).

In study 006, 4 subjects experienced an absolute QTcB >480ms (all at month 3) and 3 subjects experienced an absolute QTcB>500msec (all at month 3). Three subjects experienced a QTcF >480msec (2 at month 3 and 1 at month 6) and no subjects had an absolute QTcF>500ms (Appendices 6 and 7).

Given the methodological limitations of the data analyses and without comparator data it is difficult to interpret the significance of the outlier risks from studies 005 and 006.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

No vigabatrin subjects from the Overall population or the Integrated population discontinued from a clinical trial for QT prolongation.

7.1.9.4 Additional analyses and explorations

Post-Marketing Experience
Ovation searched their Oracle AERS post marketing database and the medical literature for cases of cardiovascular AEs associated with vigabatrin. The Ovation post marketing report search used the following preferred terms: cardiac death, sudden cardiac death, sudden death, syncope, coronary artery reocclusion, acute pulmonary edema, pulmonary congestion, and pulmonary edema. Ovation stated that their search strategy would also capture torsades de pointes, ventricular tachycardia, and ventricular fibrillation.

Ovation reported that they identified 41 events with one or more of the listed search terms. Ovation excluded 5 reports from further consideration because 2 were clinical trial reports, 2 described congenital heart defects, and one described elevated CPK levels in a febrile child. For the remaining 36 reports, Ovation provided tables that included demographic data and brief narrative summaries of the events.

Ovation identified nine reports as having insufficient information to allow analysis. The event terms for these reports were cardiomyopathy (2), bradycardia (2), arrhythmia, palpitation, creatine phosphokinase increased, CK increased, and cyanosis/irregular heartbeat. Ovation felt that another five reports suggested etiologies other than vigabatrin for the reported events. The AE terms for these reports were cardiorespiratory failure, tachycardia, cardiac arrest, syncope

and palpitations. One of these events occurred prior to vigabatrin treatment and the alternative etiologies identified for the remaining events were pneumonia/sepsis, obstructive apnea, fulminant hepatic failure, and hypoglycemia. Ovation's assessment of these reports appeared reasonable.

Ovation felt that 13 reports had complicating factors for the described events. There appeared to be overlap for some of the events included in this category and the category described above (identified etiologies other than vigabatrin). The cardiac adverse events included in this group were bradycardia (n=3), sudden death (n=2), palpitation (n=2), palpitation/sick sinus syndrome, tachycardia, syncope, cardiac failure, third degree heart block, and first degree AV block. Ovation identified the following complicating factors: improbable temporal relationship (symptoms predated treatment), overdose, allergic reaction, cerebral hemorrhage, acute liver failure, concomitant carbamazepine, seizure, event continued after vigabatrin discontinued and normal ECG at the time of the event.

Ovation felt that the remaining 9 cardiovascular events did not have clear alternative etiologies or complicating factors. These events were tachycardia (n=2), sudden death (n=2), sudden death unexplained, faint, bradycardia, angina, arrhythmia/PACs.

Ovation felt that most reports had either documented alternative etiologies or complicating factors. For events without those explanations, Ovation felt there was limited information and that the sudden deaths might represent background cases of SUDEP. Ovation noted that there were no cases of torsades de pointes, ventricular tachycardia, or ventricular fibrillation.

7.1.10 Immunogenicity

7.1.11 Human Carcinogenicity

The NDA Amendment did not include a discussion of human carcinogenicity with vigabatrin. The Division requested analyses comparing the number of treatment emergent cancers in the vigabatrin development program to the expected number of cancers based on SEER data. In their 4/23/08 response to a Division request, Ovation provided a listing of 86 subjects/patients with malignancies. Ovation included 2 patients from Japanese studies, 4 from compassionate use programs, and 6 from spontaneous reports. The remaining 74 subjects were from clinical trials included in the Integrated database. Ovation calculated expected numbers of cancers based on the sex and age distribution and the duration of treatment of the clinical trial population. Ovation reported excesses of breast cancer, brain cancers and pancreatic cancers among vigabatrin treated patients. Ovation did not discuss these findings.

The Division asked Ovation for their interpretation of these findings. In a submission dated 5/7/08, Ovation noted that in their 4/23/08 submission they included not only treatment emergent cancer diagnoses but also included prevalent cases. In addition, they included cases that were not confirmed malignancies. Lastly Ovation included cases from outside the development program.

The inclusions of these cases resulted in an erroneously inflated estimate of cancer risk because these cases counted in the numerator of the risk calculations did not contribute exposure data to the denominator. Ovation repeated their analysis using only clinical trial, incident, confirmed cancer diagnoses in the numerator. Using these criteria, Ovation identified 33 subjects with an incident cancer diagnosis in the vigabatrin development program studies. A table of cancer diagnoses is provided below.

Table 1.2. Tumors by Site from the Integrated Safety Database* (N=4855) - Revised

Site	No of Patients	Patient (protocol) numbers
Breast (infiltrating ductal carcinoma right breast, malignant breast tumor, breast cancer, , breast lump removed,)	7	1237-0018(98), 061-002(71754-3-C-028), 26626(097-266LT), 1206-0008(98), 1231-0005(98), 1258-0004(98), 1195-0002(98)
Brain (cerebral tumor, astrocytoma, low grade glioma, left frontal cerebral glioma, neuroblastoma, oligodendroglioma, retinal	10	34031911(097-345), 34031915(097-345), W-108-002(71754-3-W-007), W-101-032(71754-3-W-007), VGB-175(1A), 1193-0004(98), 1204-0019(98), 009-011(097- 005)
Site unspecified and ill defined (excision of an occipital hole tumor)	1	40733203(097-332)
Skin- basal cell (basal cell carcinoma)	5	1255-0001(98),1259-0001(98), 1198-0031(98), 1204-0013(98), 1260-0010(98)
Lung (lung cancer, lung tumor with metastasis, lung neoplasm malignant)	4	1228-0001(98), 1198-0017(98), 21202(097- 306), 1230-0010(98)
Pancreas (pancreatic carcinoma)	1	1237-0012(98)
Cervix (cervical carcinoma, cervix carcinoma)	2	1192-0014(98),1195-0002(98)
Adenocarcinoma	1	VGB-15400001(242)
Angiosarcoma	1	VGB-475(1A)
Colon (colon tumor)	1	30330028(097-306)
Leukemia (chronic myelogenous leukemia)	1	1268-0007(98)
Liver (liver tumor)	1	30330028(097-306)
Ovary (ovarian cancer)	1	068-068(097-335)
Total No. of Patients with Cancer Reports Through the December 2007 Safety Update = 33		
* Excludes patients from Japanese studies, Compassionate Use studies, and spontaneous reports.		

Source 5/7/08 Submission, p.7

Ovation found an increased ratio of observed to expected cancer diagnoses (all malignances) in the vigabatrin development program (O:E 1.45, 95% CI 1.0-2.04). For site specific diagnoses, the biggest increase when comparing observed to expected diagnoses was for brain cancers. The observed to expected ratio for brain cancers was 31.25 (95% CI 14.99-57.47). As Ovation points out, this disparity is likely due to the differences between the vigabatrin clinical trial population (patients with epilepsy) and the general population from which SEER data is derived. Ovation cited publications from Shirts et al, Forsgren et al and Olsen et al and others that found increased risks for brain tumors among patients with intractable or refractory epilepsy. In the publication by Shirts et al, the most relevant of the publications, the investigators described the results of a population based cohort of seizure patients (n=959) in Rochester, MN, between 1935 and 1979.

The investigators found an SMR for all cancers of 1.4. The increase was driven by an increase in primary brain tumors (SMR 22). I provide a table summarizing the results of this study.

TABLE 1.—*SMR for total and site-specific cancer incidence, both sexes*

Site	Observed No. of cancers	Expected No. of cancers	SMR	95% CI
Digestive system	10	15.4	0.8	0.4, 1.4
Respiratory system	9	3.3	2.7	1.2, 5.2
Breast	10	4.9	2.0	0.98, 3.8
Urinary system	6	4.1	1.5	0.5, 3.2
Female genital system	2	3.2	0.6	0.1, 2.3
Male genital system	1	4.0	0.3	0.01, 1.4
Lymphatic–hematopoietic system	7	2.4	2.9	0.97, 5.0
Brain	17	0.7	24.3	14.2, 38.8
Other sites	3	7.7	0.4	0.1, 1.1
Total	65	45.7	1.4	1.1, 1.8

Shirts et al also found a downward trend in the SMR for brain cancer with time since the diagnosis of seizures. The investigators interpreted this finding as supporting that the brain tumors were leading to seizures rather than anticonvulsant medications leading to the development of brain tumors.

In relation to the brain cancers in the vigabatrin development program, a number of subjects had relatively short vigabatrin exposure durations prior to the cancer diagnoses. For the 9 subjects with exposure information, 4 subjects were exposed to vigabatrin for less than 9 months prior to diagnosis (18 days, 4.1 months, 7.5 months and 8.5 months), 2 were exposed for between 1 and 2 years (13.9 months, 23.1 months) and 3 were exposed for over 2 years (28.6 months, 28.7 months and 51 months). The short exposure duration raises questions about whether vigabatrin was causally involved with these events.

In addition to brain cancer, Ovation also found an excess of breast cancer diagnoses in the vigabatrin clinical trial database. Ovation identified 7 breast cancers when 3.33 would have been expected based on SEER data (O:E 2.1, 95% CI 0.85-4.33). This result is similar to result presented above by Shirts et al for their cohort study. Ovation did note that one breast cancer was diagnosed after only 1.9 months of vigabatrin and another after 6.1 months. The duration of vigabatrin treatment for the remaining cases was 32.1 months, 33.8 months and 47.7 months (duration not specified in 2 cases). Ovation noted that vigabatrin has no known interaction with steroidal hormones, and that carcinogenicity studies in vitro and in vivo have been negative. Ovation did not find any reported cases of breast cancer in association with vigabatrin treatment in the worldwide published literature.

7.1.12 Special Safety Studies

Safety studies examining visual field changes in vigabatrin treated patients are reviewed by Dr. Ronald Farkas and data related to IME are being reviewed by Dr. Phillip Sheridan, both of the Division of Neurology Products.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

The NDA reviewer noted that withdrawal seizures were documented in animal models using acute single dosing with vigabatrin. In addition, the reviewer noted that withdrawal seizures, including status epilepticus, were seen during discontinuation of vigabatrin in clinical trials. The reviewer discussed results from 10 clinical trials with follow up that would allow assessment of withdrawal seizures. The incidence of withdrawal seizures ranged from 0-15.7% and the incidence of status epilepticus during withdrawal was 1.3%. (Withdrawal seizures were defined by a twofold or greater increase in weekly seizures compared to the maximum seizure rate noted during baseline or active therapy within 4 weeks after vigabatrin was discontinued or after tapering was begun, or documented status epilepticus not present during baseline and occurring within 4 weeks after vigabatrin was discontinued or after tapering was begun). (Source NDA Review, pp. 98-99). The NDA Amendment did not present analyses of withdrawal phenomena.

Current Submission
In the 12/28/07 Amendment submission, Ovation provided a summary addressing abuse potential of vigabatrin. Ovation concluded that vigabatrin does not have significant activity at abuse related CNS targets. Ovation noted that in pre-clinical studies, vigabatrin did not produce significant reinforcement in a primate self administration study, did not substitute for phenobarbital, partially substituted for muscimol and did not produce suppression of morphine withdrawal. Ovation noted that a controlled human abuse liability study has not been performed. Ovation reported that there are no reports of recreational vigabatrin use or substitution with vigabatrin in methamphetamine or cocaine dependent subjects in abuse treatment trials. Ovation felt that abuse related events were infrequent in vigabatrin treated study subjects and that there is a lack of evidence of diversion. Ovation also felt that post marketing data show no evidence of abuse potential. Ovation did not comment on withdrawal phenomena. The formal FDA review of these data has not been completed at the time of this review.

7.1.14 Human Reproduction and Pregnancy Data

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

In the NDA Amendment, the sponsor identified 139 pregnancies in women exposed to vigabatrin (through 12/31/95). The sponsor reported that 13% (18/139) of the pregnancies resulted in major or minor malformations. The sponsor reported the following major and minor malformations: congenital dislocation of hip (n=2); unspecified musculoskeletal problems; conjoined twins (therapeutic abortion); squint requiring surgery; bilateral cleft palate; agenesis of cardiac septum, microcepahly, pulmonary artery atresia, spina bifida (therapeutic abortion); choanal atresia,

congenital nystagmus, craniosynostosis; ventricular septal defect; congenital diaphragmatic hernia (death within 24 hours of birth); left hemisphere atrophy, decreased right arm motor function, seizures; undescended testicle; club feet; shuddering when handled; facial palsy, tachypnea; eye roving, low hairline, low set ears, poor muscle tone, torticollis; hypospadia, bilateral clinodactyly of the fourth toes, capitonated deep palmar flexion creases, diastasis recti abdominis, multiple facial anomalies, wide internipple distance; and plagiocephaly, orbital asymmetry, hyperextensible interphalangeal joints, fifth finger clinodactyly. The sponsor also reported that 12% (16/139) of the pregnancies ended in spontaneous abortion and 7% (10/139) ended in therapeutic abortion, including the two mentioned above (Source Amendment review, pp 45-46).

Current Submission
Ovation summarized the post marketing adverse event reports in the Aventis Drug Exposure Via Mother database. Ovation first summarized reports through 8/31/2000, followed by reports from 9/1/2000 through 9/1/2006.

Through 8/31/2000, there were 268 reports of pregnancy exposures in the events pregnancy registry plus 6 reports from a UK PEM study. This total includes the 139 pregnancies that were identified in the 5/31/97 NDA Amendment and described above (Source: Response to Division Questions, 4/23/08). Of these reports, 219 included outcome information (127 normal, 53 abnormal). The abnormal outcomes included 23 major malformations, 22 minor malformations, 5 perinatal complications, and 2 developmental disorders. Ovation also identified 21 spontaneous abortions and 18 therapeutic abortions. Ovation reported that for the 23 major malformation reports, 9 mothers were taking 2 concomitant AEDs, 9 were taking 1 concomitant AED and 4 were either taking no concomitant AED or the status of concomitant AEDs was unknown. For the 22 minor malformation reports, 7 mothers were taking at least 2 concomitant AEDs, 9 were taking 1 concomitant AED, and 6 were either taking no concomitant AEDs or the status of concomitant AEDs was unknown (Source NDA Amendment, pp.233-4).

From 9/2000 through 9/2006 the Drug Exposure Via Mother Database received 26 reports of pregnancies with vigabatrin exposure including 19 reports that provided outcomes. These reports include 8 abnormal outcomes with 1 report of major malformations, 5 reports of minor malformations and dysmorphic abnormalities, 2 reports of perinatal complications, and 1 report of developmental disorder. Ovation reported 1 spontaneous abortion and no therapeutic abortions during this interval (Source NDA Amendment, pp.234-5).

7.1.15 Assessment of Effect on Growth

Ovation provided no discussion of the effect of vigabatrin on growth in their current submission. The Division asked Ovation to summarize data that would allow an assessment of growth in vigabatrin treated children.

In their 5/16/08 response to Division questions, Ovation identified pediatric studies that captured height and weight data. Ovation noted that CPS studies 0118, 0192, 0221, and 0294 and IS

studies W019, FR03, and 1A recorded baseline and final height and weight. The protocols for these studies did not specify the methodology for measuring these parameters.
Ovation provided a table summarizing the weight and height changes in the CPS placebo controlled trials (duration 14-17 weeks). Ovation stratified the results by sex and by age (2-<12, 12-16). The results are included in the table below.

Weight and Height Mean Changes from Baseline in the CPS Placebo Controlled Trials

Sex	Vigabatrin		Placebo	
	Weight	Height	Weight	Height
2-<12 year olds				
Male n	42	6	28	7
Mean change from baseline	3.4kg	2.6cm	1.5kg	3cm
Female n	42	6	39	8
Mean change from baseline	4.1kg	2.1cm	2kg	1.1cm
>12-16 year olds				
Male n	80	10	46	12
Mean change from baseline	4.5kg	2.4cm	1.9kg	2.4cm
Female n	87	15	57	14
Mean change from baseline	4.3kg	1.9cm	1.8kg	2.4cm

The data suggest consistently greater mean increases in weight for pediatric CPS subjects exposed to vigabatrin compared to placebo. The increases in height were similar for vigabatrin and placebo subjects although these results are based on very small numbers of treated individuals. In addition, the lack of protocol specified methodology requiring careful height measurement would be expected to lead to notable inaccuracy and decrease the ability to detect drug related differences, if present.

As Ovation noted, the short duration for controlled phases of the IS studies precludes any meaningful comparative analyses of height and weight data. Ovation felt the mean weight gain for the entire treatment period (including open label) was within the range predicted by growth charts. (Source 5/16/08 Submission, pp.8-13).

7.1.16 Overdose Experience

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

In the NDA amendment, the sponsor identified 33 overdose events in 31 individuals. These reports were identified from clinical trials, spontaneous reports and from the medical literature.

For 18 of the overdose events, vigabatrin was the only drug reported as used in the overdose. For those overdosing on vigabatrin only, the symptoms included in more than 1 report were coma/semi comatose (n=5), drowsy/sleepy (n=2), vertigo (n=2) seizure (n=2), and psychosis (n=2). The highest reported overdose was 50g taken by an 18 year old female. This individual

experienced coma and bradycardia and required intubation but the event resolved without sequelae.

Among patients overdosing on multiple drugs, the highest reported vigabatrin dose was 150mg. In addition to overdosing on vigabatrin this patient also ingested 30-50 primidone tablets and 30-50 valproic acid tablets. The sponsor did not include information about the clinical course for this patient but did report that the patient recovered.

Safety Update (1/1/96-3/15/97)
The sponsor updated the vigabatrin overdose experience in the Safety Update. Through the update cutoff there were 38 vigabatrin overdose events in 36 individuals (includes the events noted above). Fifteen events were suicide attempts, 7 were accidental, and the reason for overdose in the remaining 16 events was unknown. No deaths were reported but outcome information was missing for 7 events. The reported symptoms were coma/unconsciousness (12), drowsiness/somnolence (4), apnea/irregular breathing (3), bradycardia (3), vomiting (3), confusion (3), vertigo (2), agitation (2), and increased seizure activity or status epilepticus (2). Ataxia, semi comatose, delirium, concentration impaired, abnormal behavior, speech disorder, auditory hallucinations, psychosis, hypotension, hypothermia, headache, slowed thinking, irritability, tremor, oliguria, pupillary hippus, withdrawn, syncope, dehydration, and pulmonary infiltrates were reported for one patient each (Source Safety Update review, pp.7-8).

Current Submission

Overall Safety Population (3/16/97-6/30/07)
Ovation identified 2 subjects in the Overall Safety Population with SAEs of overdose and one subject with an SAE of accidental overdose. Subject 0201 13870001, a 4 year old female (body weight 15.4 kgs) ingested 6g of vigabatrin (usual daily dose 0.9g/day). She was taken to an emergency department and underwent gastric lavage and was discharged home after 6 hours of observation. The narrative included no information about overdose related symptoms for this subject. Subject 0201 14100003, a 9 year old female (weight 152 pounds) ingested 12g/day for one month (usual daily dose 6g/day) due to the parents misreading the medication bottle. The narrative provided no details about symptoms but stated that the subject recovered and continued in the study. Subject 0201 13970001, a 4 year old female (body weight 15.4 kgs) ingested 30-40 500mg vigabatrin tablets (usual dose 1g/day). She was taken to an emergency department and underwent gastric lavage and was given charcoal. She was hospitalized overnight for observation. She experienced mild ataxia that resolved after several days. She continued in the study. No additional serious spontaneous reports of overdose were included in Ovation's review of postmarketing reports.

Ovation's proposed labeling for overdose identified many of the overdose symptoms listed above. Ovation notes that there is no antidote for vigabatrin, and that measures to remove unabsorbed drug, including emesis or gastric lavage should be used in cases of overdose. Ovation that charcoal does not significantly adsorb vigabatrin and that the effectiveness of hemodialysis in the treatment of vigabatrin overdose is unknown.

7.1.17 Postmarketing Experience

Post marketing events are discussed in the relevant sections above.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

The safety data from the prior submissions included in this review comes from several sources. For prior submissions, including the original NDA (8/29/94), NDA amendment (5/31/97), safety updates (7/31/97, 1/20/98), and response to the approvable letter (4/28/98), information cited in this review comes from the FDA Amendment review (10/28/97), and the FDA Final Safety Update and Response to the Approvable letter review (8/21/98). In addition, Ovation references material from prior submissions when presenting their Integrated Data analyses in the Amendment.

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Ovation's 12/23/05, 10/10/06, and 3/1/07 NDA Amendment submissions included Safety Updates that the Division found incomplete and therefore refused to file. Ovation's 12/28/07 submission is the most recent submission and is the focus of this review. The 12/28/07 submission presents new (not previously reviewed) pooled clinical study data for all indications for the period from 3/16/97 to 6/30/07. Ovation refers to the subjects that provide the new data as the Overall Safety Population. The Overall Safety Population is comprised of the subjects that participated in 5 studies in adults with epilepsy, 5 studies in pediatric subjects with complex partial seizures, 4 studies assessing visual field defects, and one study in infants with infantile spasms (IS) (12/28/07 submission, p.16). Ovation pooled data from 14 of the 15 newly completed clinical studies for the overall safety population analyses (data for subjects from study 4103 were not pooled since only SAEs and not all AEs were collected in this study, SAEs from this study were presented separately, 12/28/07 submission, p.16). In addition to the overall pooled presentation, Ovation also separately presented the safety data from the studies identified above for adult subjects, pediatric (non IS) subjects and IS subjects.

Integrated Data

Section 6 of Ovation's 12/28/07 submission provides an integrated presentation of safety data from the original NDA filing through 3/15/97 (previously submitted data), from 3/16/97 through

6/30/07 (overall safety population data), and an updated integrated summary (previously submitted data + overall safety population data) that is cumulative through 6/30/07.

Clinical Data Sources
Ovation received clinical data for the vigabatrin trials from the previous sponsor in the form of data sets, data listings, case report forms, and study reports. For any data obtained from the previous sponsor that was not in the form of electronic data sets, Ovation hired a CRO to create electronic data sets by extracting the information from case report data listings or CRFs. (Source ISS, pp.32-33). In addition to their Integrated Summary of Safety presentation, Ovation submitted study reports, case report forms and narratives for deaths, SAEs, and AEs leading to withdrawal, and selected datasets for the overall safety population data in their submission.

7.2.1.1 Study type and design/patient enumeration

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

The data in the following table summarizes the exposure by data group and was taken from Table B-8 which was submitted with the NDA amendment (5/97).

Summary of Number of Exposed Subjects in US and Primary non-US Vigabatrin Trials

Data Group	Placebo	Vigabatrin	Other[1]	Total
US Studies	135	537	52	592
Non-US CRF Studies	682	1189	31	1290
Total Primary Data	*817*	*1726*	*83*	*1882*
Non US Secondary Studies	421	968	12	986
Non-CRF Studies[2]	-	-	-	925
Total unique number of patients[3]	-	-	-	***3561***

[1] Active control or no treatment
[2]Exposure in these studies is not known
[3]Patient subtotal cannot be summed since some patients participated in more than one study

The US studies subjects were exposed to vigabatrin during 6 clinical pharmacology studies, 2 placebo controlled epilepsy studies (vigabatrin n=222, placebo n=135), and 4 uncontrolled epilepsy studies (vigabatrin n=414). The sponsor reported that 443 unique subjects were exposed to vigabatrin in US epilepsy studies (controlled + uncontrolled) (Source: Amendment review 10/28/97, p.11 and attachment p.20).

The non-US primary studies subjects were exposed to vigabatrin during 14 clinical pharmacology studies (vigabatrin n=178), 9 controlled epilepsy studies (vigabatrin n=335, placebo n=284), 17 uncontrolled epilepsy studies (vigabatrin n=430) and 25 studies for other indications (vigabatrin n=246). The sponsor reported that 765 unique subjects were exposed to vigabatrin in the primary non-US epilepsy studies included in the NDA amendment (Source: Amendment review 10/28/97, p.11 and attachment table B-19).

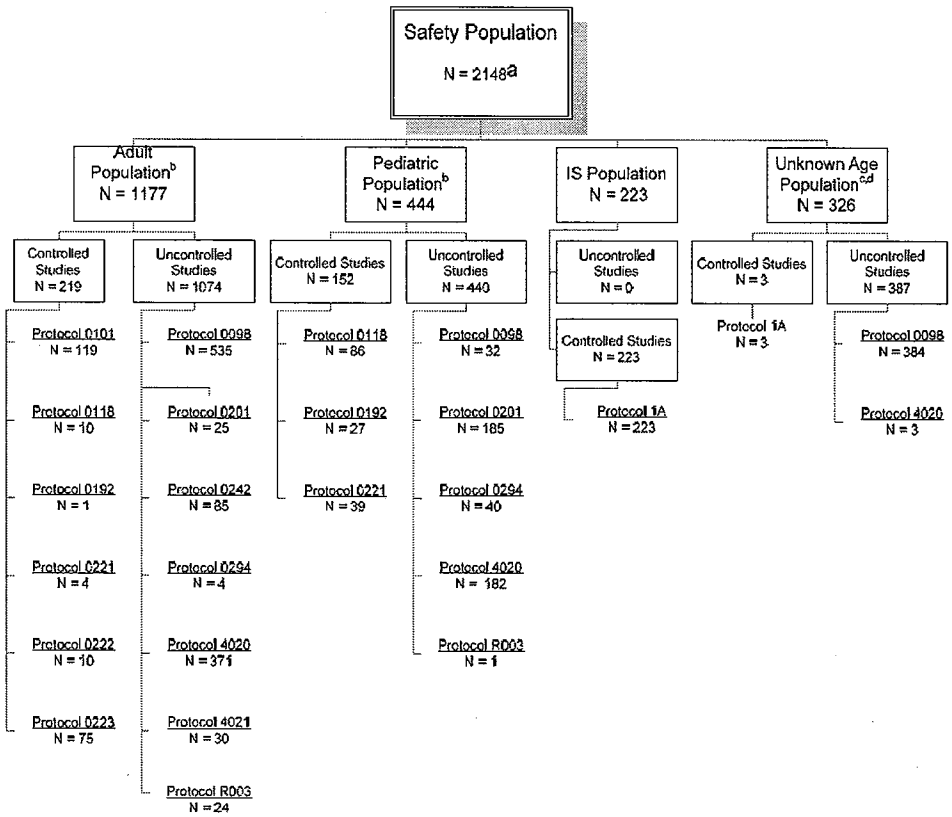
Safety Update (Cutoff Date 3/15/97)

The sponsor reported an additional 1,773 subjects were exposed to vigabatrin for the period of 1/1/96 through 3/15/97. Thirty-three subjects were exposed in clinical pharmacology trials, 338 in epilepsy controlled trials, 1329 in epilepsy uncontrolled trials, and 73 in trials for other indications (infantile spasms, weight loss) (Source: Final Safety Update Review, p.2).

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Ovation reported that 2,148 unique subjects were exposed to vigabatrin in the 14 studies included in the overall safety population data in the 12/28/07 submission. The appendix to this review includes brief summaries of the 15 studies that contribute new safety data. The sponsor presented safety analyses for 3 subpopulations of the overall population. Two of these groupings are age based; the adult subpopulation (age >=16 years, n=1,177), and the pediatric (non-IS) subpopulation (age <16 years, n=444). The third subpopulation, the IS subpopulation (n=223), is based on indication of use. Nineteen subjects were counted in both the adult and pediatric subgroups due to participation in multiple studies and their ages at enrollment. Due to incomplete data capture there were 326 subjects from the overall population with unknown age that could not be classified into one of the age-stratified subpopulations. An additional 3 infants from the IS subpopulation did not have their ages recorded. (Source 12/28/07 submission, pp. 27-8) The following table details the safety subpopulations.



[a] Overall safety population (n=2148) is comprised of 1177 adult subjects; 444 pediatric subjects; 223 infants; 326 subjects of unknown age minus 3 infants included in the IS population; minus 19 subjects included in both the adult and pediatric subpopulations (2148=1177+444+223+326-19-3).
[b] 19 subjects are included in both the adult and pediatric subpopulations.
[c] Exludes 3 subjects of unknown age counted in the IS subpopulation.
[d] Exludes 64 subjects in 0098 since age was determined from patient's enrollment in prior study.

Integrated Data

Ovation explained the source of the denominators they used in different safety data AE analyses. Ovation limited their Integrated Data analyses to epilepsy trials (no data included from clinical pharmacology trials or trials for indications other than epilepsy). Ovation presented three separate totals of subjects exposed to vigabatrin for different analyses and explains that the different totals result from the way safety data were presented in previous submissions. Ovation explains that for the purpose of analyzing AEs they use a total of 4,077 subjects exposed to vigabatrin, for the analyses of SAEs they use a total of 4,739 subjects, and for the analyses of discontinuations due to AEs and deaths they use a total of 4,855 subjects. Ovation explains that the cumulative totals differ for the different analyses because they relied on the previous sponsor's analyses that integrated only the US and primary non-US studies for AE analyses but integrated US, primary non US, and secondary non US studies for SAEs, discontinuations and deaths. The difference in exposure for the SAE analyses compared to the analyses of

discontinuations and deaths is due to the fact that Ovation presented the SAEs from studies 0098 and 4021 separately.

In their description of the integrated data, Ovation provided tables that included numbers of subjects exposed to vigabatrin for the regulatory submissions (5/97-NDA amendment, 1/98-Final Safety Update, NDA Amendment + Final Safety Update, Current submission, and the total across all submissions). As an example, I provide one such table below:

Table 4. Integrated Safety Population for Adverse Events (N=4077)

Submission Date	Reporting Period	N	Identified as
December 2007	Integrated Data (Current + Prior)	4077	Combined
	Currently Reported Data		
December 2007	16 March 1997 – 30 June 2007	2148	Period 2
	Prior Reported Data		
20 January 1998 Safety Update + 29 May 1997 Amendment	2 prior reporting periods combined: 16 March 1994 – 15 March 1997	2662 (2605[b] + 57)	Period 0 + 1
20 January 1998	1 January 1996 – 15 March 1997 Safety Population Infantile Spasms Studies (primary non-US)	1667[a] + 57	Period 1
29 May 1997	16 March 1994 – 31 December 1995 NDA Amendment (US, non-US primary studies)	1208	Period 0

[a] Infantile Spasms subjects excluded and addressed as a special population in the 20 January 1998 Safety Update.
[b] 1208 subjects from the 1997 NDA Amendment, 1667 subjects from the 20 January 1998 Safety Update, minus 733 subjects who participated in more than one study (Integrated Summary of All Adverse Events, Safety Update, 20 January 1998).

The differences in the exposure totals listed above when compared to the exposure totals from previous submissions is due to the fact that Ovation's Integrated Data analyses are restricted to epilepsy trials. For example, in Table 4 above Ovation identifies 1,208 subjects exposed to vigabatrin in US and primary non US studies in the NDA Amendment. In the Division review of the NDA Amendment, the previous sponsor reported that 1,726 subjects were exposed to vigabatrin in US and primary non US studies. The reason for this discrepancy is that Ovation did not include safety data for subjects from clinical pharmacology studies or studies for indications other than epilepsy (Response to Reviewer questions, 2/11/08).

In Amendment Tables 5 and 6 (not shown), Ovation reports that for the SAE, discontinuation for AE and death analyses, 1,942 subjects were exposed during studies reported in the NDA Amendment submission. The reason for this apparent discrepancy is that for these analyses, Ovation also included subjects in the Secondary (epilepsy) studies database (Response to Reviewer questions, 2/11/08).

7.2.1.2 Demographics

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

According the Amendment review, the sponsor did not provide a separate demographic profile for US studies in the NDA or the NDA Amendment. In the NDA Amendment, the sponsor provided table B-27 that summarized demographic factors for subjects enrolled in the non-US primary studies. I summarize that information in the table below.

Summary of Demographics for All Subjects Enrolled in Non-US Primary Studies						
	Clinical Pharmacology		Epilepsy		Other indications	
Demographic factor	Epilepsy patients N=25 % (n)	Non epilepsy patients N=154 % (n)	Controlled N=396 % (n)	Uncontrolled N=461 % (n)	Total N=254 % (n)	Total N=1290 % (n)
Sex						
Male	52% (13)	83% (128)	52% (205)	50% (228)	51% (130)	55% (704)
Female	48% (12)	12% (18)	48% (191)	41% (188)	47% (120)	41% (529)
Unknown	0	5% (8)	0	10% (45)	2% (4)	4% (57)
Age (years)						
Mean ±SD	31.8±9.3	32.8±19.8	31.8±10.4	24.2±15	40.4±23.5	30.9±17.4
Range	16, 47	18, 97	10, 64	0, 70	0, 87	0, 97
<2	0	0	0	2% (7)	13% (34)	3% (41)
2-<12	0	0	1% (5)	25% (113)	4% (9)	10% (127)
12-<16	0	0	2% (6)	5% (22)	1% (3)	2% (31)
16-<40	76% (19)	77% (118)	75% (297)	54% (248)	24% (62)	58% (744)
40-<65	24% (6)	7% (10)	22% (86)	14% (66)	41% (103)	21% (271)
≥65	0	10% (15)	0	1% (3)	15% (39)	4% (57)
Unknown	0	7% (11)	<1% (2)	<1% (2)	2% (4)	2% (19)
Race						
Caucasian	100% (25)	51% (79)	64% (255)	36% (168)	0	41% (527)
Black	0	0	0	0	0	0
Other	0	0	<1% (1)	<1% (1)	0	<1% (2)
Unknown	0	49% (75)	35% (140)	63% (292)	100% (254)	59% (761)

Safety Update, Cutoff Date 3/15/97

According to the Safety Update review, the demographics of the population exposed in the 14 completed trials were similar to the demographics of the population described in the NDA amendment. Except for the clinical pharmacology study and the infantile spasm trials, roughly equal numbers of males and females were exposed, most subjects were between the ages of 16 and 40, and most were Caucasian.

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Ovation provided Table 8 summarizing demographic factors for the subjects enrolled in the Safety Update trials in the current submission. I provide data from Table 8 below.

Demographics Overall Safety Population, 12/28/07 Submission						
	Controlled		Uncontrolled	Long Term		Total
	US N=566	Non-US N=28	Non-US N=611	US N=1169	Non-US N=44	N=2148
Sex	N=564	N=28	N=611	N=1158	N=44	N=2135
Male	49% (276)	43% (12)	51% (312)	51% (590)	46% (20)	50% (1074)
Female	51% (288)	57% (16)	49% (299)	49% (568)	54% (24)	50% (1061)
Age, years	N=563	N=28	N=608	N=815	N=44	N=1822
Mean (SD)	16.3 (17.6)	11.2 (3.3)	28.7 (15.8)	29.1 (14.9)	11.4 (3.3)	25.3 (17.1)
Range	0.1-66	5.0-16	7.7-74.7	3-78	4-16	0.1-78
Race	N=566	N=28	N=611	N=1169	N=44	N=2148
Caucasian	82% (465)	96% (27)	9% (53)	89% (1039)	100% (44)	65% (1386)
Black	10% (58)	4% (1)	0	7% (84)	0	6% (122)
Other	8% (43)	0	<1% (1)	3% (35)	0	3% (72)
Unknown	0	0	91% (557)	1% (11)	0	26% (568)

Integrated Data

Ovation did not provide a summary of demographic data for the Integrated population.

7.2.1.3 Extent of exposure (duration/dose)

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

Duration
The presentations in the NDA and NDA Amendment suggest that 679 subjects were exposed to vigabatrin for at least 6 months and 286 subjects were exposed to vigabatrin for at least 1 year in the US and non-US primary studies. The following table summarized the exposure by duration data for the US and primary non-US study populations.

Exposure by Duration, US and non-US Primary studies through 12/31/95, NDA Amendment

	Primary US		Primary Non US					
VGB Duration	Controlled Epilepsy	Open label Epilepsy	Clin Pharm Epilepsy	Clin Pharm Other	Controlled Epilepsy	Open label Epilepsy	Other	Total
≥2weeks	220	412	13	2	335	425	208	983
≥1month	217	407	13	0	330	414	155	912
≥3months	197	391	0	0	167	355	85	607
≥6months	0	307	0	0	89	229	54	372
≥1year	0	157	0	0	20	76	33	129
≥2years	0	40	0	0	0	19	4	23
≥4years	0	31	0	0	0	0	0	0
≥6years	0	26	0	0	0	0	0	0

Unknown	1	0	N/A	N/A	N/A	N/A	N/A	N/A
Total	**221**	**414**	**25**	**153**	**335**	**430**	**246**	**1189**

Source: Amendment review 10/28/97, attachment p.20 and attachment table B-19

Dose

Although the data were not presented in a manner that would allow an exact determination of exposure by dose, there appears to have been roughly 1,000 subjects in the US and non-US primary trials exposed to a maximum vigabatrin dose of at least 2.5g/day. The following table summarizes the exposure by maximum dose data for the US (controlled, open label) and primary non-US studies as presented in the NDA and NDA Amendment.

Exposure by Dose, US and non-US Primary studies through 12/31/95, NDA Amendment

	Primary US		Primary Non US					
VGB Dose (g/day)	Controlled Epilepsy	Open label Epilepsy	Clin Pharm Epilepsy	Clin Pharm Other	Controlled Epilepsy	Open label Epilepsy	Other	Total
0.5-<1.5	44	2	0	59	3	47	19	128
1.5-<2.5	0	13	0	21	126	116	115	378
2.5-<3.5	134	257	13	26	161	195	66	461
3.5-<4.5	0	80	12	47	45	47	31	182
4.5-<5.5	0	12	0	0	0	5	3	8
5.5-<6.5	44	48	0	0	0	11	9	20
>=6.5	0	1	0	0	0	9	3	12
Total	**222**	**414**	**25**	**153**	**335**	**430**	**246**	**1189**

Source: Amendment review 10/28/97, attachment p.21 and attachment table B-23

Safety Update (Cutoff Date 3/15/97)

The Final Safety Review did not summarize exposure by dose or duration.

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Duration

Ovation provided table 9 (p.39) documenting that 1,268 subjects from the Overall population had exposure to vigabatrin for greater than 6 months and 1,058 had exposure greater than 1 year. This table also documents that 599 subjects had missing data (573 from long term US studies) that did not allow determination of the duration of exposure. I provide duration of exposure data from Ovation's table 9 below.

Duration of Exposure, Overall Safety Population, 12/28/07 Submission						
	Controlled		Uncontrolled	Long Term		Total
Duration	US N=566	Non-US N=28	Non-US N=611	US N=1169	Non-US N=44	N=2148

1-14 days	6	0	3	8	0	16
>14-30 days	21	0	5	18	2	40
>30-60 days	56	0	8	10	1	47
>60-90 days	50	3	8	19	1	48
>90days-6months	170	21	23	64	36	130
>6 months-1 year	58	4	41	82	4	210
>1-2 years	144	0	72	139	0	305
>2-3 years	42	0	56	208	0	294
>3-5 years	13	0	136	48	0	220
>5-10 years	0	0	196	0	0	196
> 10 years	0	0	43	0	0	43
Missing	6	0	20	573	0	599

Note: Percentages are with respect to the number of subjects exposed for each study type.
Note: For subjects that participated in multiple studies, exposure duration are represented in each study separately and then represented in the "Total" column for the patients total exposure duration.

Integrated data
In response to a question from the Division, Ovation reported in the 5/1/08 submission that 3,476 epilepsy subjects were exposed for at least 6 months, and 2,758 were exposed for at least 1 year (Source 5/1/08 submission, p.140).

Dose and Duration

Overall Safety Population
In response to a request by the Division dated 3/14/08, Ovation provided a table summarizing exposure by dose and duration for the Overall population. I provide that information below.

	Vigabatrin Dose (g/day)									
Time	**0***	**>0 to<1**	**>1 to<2**	**>2 to<3**	**>3 to<4**	**>4 to<5**	**>5 to<6**	**>6 to<7**	**>=7**	**Unknown**
<=1week	188	381	386	302	43	20	14	5	4	42
1 wk to 1 mo	9	467	465	153	46	47	27	12	4	32
>1 to 3 mos	2	104	187	110	85	51	35	23	11	14
>3 to 6 mos	2	42	90	56	136	31	15	17	3	7
>6 to 9 mos		12	43	29	50	16	8	2		4
>9 to 12 mos	1	13	26	12	12	7	3	6		2
>12 to 18 mos	1	20	34	16	8	14	8	4	1	1
>18 to 24 mos	1	8	11	4	5	2	2	6		3
>24 to 36 mos			7	7	5	2		2		1
>36 to 48 mos			1	3						
>48 to 60 mos				1	1					
>60 to 72 mos				1	3					
>72 to 84 mos					1					
>84 mos					6					
Total pt days	2232	40438	79253	51955	83624	23475	11638	13474	1529	6927
Total pt years	6.11	110.71	216.98	142.25	228.95	64.27	31.86	36.89	4.19	18.97

*0 refers to time off drug, not Placebo

The table illustrates that the majority of exposure in terms of duration for the Overall population occurred at >1 g/day to <4g /day (70%, 588.18PY/836.1PY).

Integrated Data
The Division requested a table displaying dose and duration information for the Integrated population. In a response dated 3/14/08, Ovation provided a table summarizing exposure by dose and duration for the Integrated population. I provide that information below.

	Vigabatrin Dose (g/day)									
Time	**0***	**>0 to<1**	**>1 to<2**	**>2 to<3**	**>3 to<4**	**>4 to<5**	**>5 to<6**	**>6 to<7**	**>=7**	**Unknown**
<=1week	373	738	975	749	190	75	40	25	7	143
1 wk to 1 mo	60	642	2432	1296	297	175	103	21	2	105
>1 to 3 mos	17	186	676	1280	1119	498	195	82	8	54
>3 to 6 mos	5	72	250	412	541	280	118	53	9	42
>6 to 9 mos	1	22	117	169	273	133	59	33	6	39
>9 to 12 mos	3	15	62	146	231	105	34	28	5	42
>12 to 18 mos	5	22	58	105	250	101	32	39	2	101
>18 to 24 mos	1	5	23	40	133	68	6	31	3	138
>24 to 36 mos	1	4	16	46	99	35	10	19	2	87
>36 to 48 mos			3	12	41	16	7	18	1	
>48 to 60 mos				5	21	4		4		1
>60 to 72 mos			1	1	16	4				
>72 to 84 mos					8	1				
>84 mos				1	12	8				
Total pt days	7873	57485	218515	384511	744180	321729	88842	113649	10526	240384
Total pt years	21.6	157.4	598.3	1052.7	2037.5	880.9	243.2	311.2	28.8	658.1

*0 refers to time off drug, not Placebo

The table above illustrates that 86% of person time exposure was to vigabatrin doses ranging from 1g/day to less than 5g/day. Less than 14% of person time exposure to vigabatrin was at doses >=5g/day.

In response to a question from the Division, Ovation reported in the 5/1/08 submission that 1,112 epilepsy subjects were exposed to a vigabatrin dose between 3 to <4g/day for at least 6 months, and 587 subjects were exposed to a vigabatrin dose between 3 to <4g/day for at least 1 year (Source 5/1/08 submission, p.140).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

In the original NDA review, the Division reviewer documented that the sponsor submitted safety data for subjects from non US studies that did not have available case report forms and this was one of the reasons for not approving the NDA. In response to this identified deficiency, the

sponsor collected and reviewed available CRFs from non US study sites. Some CRFs were located and others were not. In instances where some but not all CRFs were located for a given study, the data for patients with CRFs were grouped into a cohort called Secondary data (n=968). Another cohort was created to include data for those patients for whom CRFs were not located (non-CRF data, n=925). In addition to "Secondary Data" and data from non-CRF supported studies, the sponsor submitted data from compassionate use programs.

Current Submission

Ovation did not identify any secondary data sources in their current submission.

7.2.2.1 Other studies

Ovation did not identify any data from other studies in their current submission.

7.2.2.2 Post marketing experience

Exposure
Ovation gathered post marketing exposure estimate data from Periodic Safety Update Reports written by Aventis. Ovation provided 2 tables with exposure information. Table 1 (12/28/07 submission, Postmarketing section, p.6) summarized exposure in patient months by region for the years 1989-1994. This table provided sales data that were converted to person time (patient months) estimates using the assumed daily dose of 2g/day. The estimated person time exposure for this interval was 166,377 person years (1,996,533 patient months). Table 2 provided estimates of the number of patients exposed for each year from 1992 through 2004. These estimates were created using sales data and were based on the assumptions of an average daily dose of 2g/day and an average duration of treatment of 6 months. I converted these patient estimates to person time estimates by multiplying the number of patients by 6 months (the average estimate of use) and then dividing by 12months (to convert to years). For the period of 1995-2004 (not covered in table 1), I estimated 616,906 person years of use. Summing the data from tables 1 and 2, I estimated a total of roughly 783,000 person years of use from 1989-2004.

In their 5/16/08 submission, Ovation responded to a Division request for estimates of use for 2005-2007. Ovation reported that for 2005, the estimated number of patients exposed to vigabatrin was 59,742. Based on the assumption of 6 months of use per patient as above, the estimated vigabatrin use for 2005 is 29,871 person years. For 1/06-6/06 Ovation estimated 14,794 person years of vigabatrin use and for 7/06-7/07 Ovation estimated 28,219 person years of use. Adding the person year estimates for 2005-6/07 (72,884 PYs) to the exposure estimate for 1989-2004 (783,000 PYs), yields an estimated person time exposure for 1989-6/07 of roughly 856,000 patient years exposure.

The exposure information from Ovation demonstrates that vigabatrin use peaked in 1998 and declined yearly since (with the exception of 2003). The first publication of vigabatrin related visual field defect cases occurred in 1997. The table below includes information from Ovation's

Table 2 included in the post marketing section of their current submission and data from their response to Division questions (5/16/08).

Estimated Number of Patients Exposed from Marketed Use of Vigabatrin 1992 through 2004

Worldwide Patient Exposure / Year						
1992	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**
50,546	87,638	108,762	126,989	137,193	153,152	162,958
1999	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**
151,992	119,024	98,577	84,672	114,611	84,648	59,742
1/06-6/07*						
86,026						

Exposure was calculated based on the assumption that each patient received 2 grams (4 tablets daily) for 6 months (183 days).
*Includes 18 months of data
Source Data: PSUR No. 13, 14, 15 (Appendix 3); Submission 8/16/08, p14.

Reports
Current submission
Ovation identified 1791 reports for the period 3/15/97-6/30/07 from the following sources: spontaneous reports (n=1466), medical literature (n=206), regulatory agencies (n=24), and unknown (n=95).

I provide demographic and indication information for the reports in the following table.

Table 3. Demographic and Baseline Characteristics of Patients Described in Vigabatrin Postmarketing Adverse Event Reports

Variable	Vigabatrin Reports[1] (N=1791) n (%)
Gender	
Male	747 (41.7)
Female	822 (45.9
Unknown	222 (12.4)
Age Groupings	
< 2 Yrs	92 (5.1)
2 to <12 Yrs	177 (9.9)
12 to <16 Yrs	68 (3.8)
16 to <40 Yrs	524 (29.3)
40 to <65 Yrs	366 (20.4)
>= 65 Yrs	46 (2.6)
Unknown	518 (28.9)
Race	
Asian	1 (0.1)
Caucasian	1 (0.1)
Other	1 (0.1)
Unknown	1788 (99.8)
Reported Indication for VGB Use	

Infantile spasms	53 (3.0)
Partial seizures[2]	134 (7.5)
Generalized seizures, and seizures NOS[3]	950 (53.0)
Other reported indications [4]	20 (1.1)
Unknown	634 (35.4)

NOS = not otherwise specified.
1 Includes events reported between 15 March 1997 and 30 June 2007
2 Partial seizures include the following indication terms: Complex partial seizures, Frontal lobe epilepsy, Partial seizures, Simple partial seizures, Temporal lobe epilepsy.
3 Generalized seizures include the following indication terms: Convulsion, Epilepsy, Grand mal convulsion, Petit mal epilepsy, Status epilepticus.
4 Other (non-seizures) include the following indication terms: Accidental exposure, Cerebral palsy, Congenital toxoplasmosis, Drug exposure during pregnancy, Electroencephalogram abnormal, Encephalopathy, Muscle spasms, Post herpetic neuralgia, Post-traumatic epilepsy, Sturge-Weber syndrome, Tuberous sclerosis.

Source NDA Amendment 12/28/07, Post Marketing Reports Section, p.8

Ovation reported that the top 5 countries with spontaneous adverse event reports were France (n=313), Great Britain (n=272), Australia (n=107), Canada (n=97), and Denmark (n=91). (Source NDA Amendment 12/28/07, Post Marketing Reports Section, p.7)

7.2.2.3 Literature

As part of the 12/28/07 amendment submission, Ovation provided a review of the medical literature. Ovation divided their presentation of vigabatrin related medical literature into publications discussing complex partial seizures and publications discussing infantile spasms. Ovation hired NERAC Inc. to search the medical literature. The searches spanned from the inception of the individual literature databases to June 30, 2007. NERAC Inc. searched the following databases: BIOSIS Previews (1972-Present), CAB Abstracts (1968-Present), Conference Papers Index (1973-Present), Embase (1974-Present), International Pharmaceutical Abstracts (1970-Present), Life Sciences Collection (1978-Present), MEDLINE (1966-Present), PsychINFO (1983-Present). NERAC used the following search terms: vigabatrin, infantile spasms, West syndrome, Tuberous sclerosis, and vigabatrin and prednisone or ACTH. Ovation discussed only the publications subsequent to 3/97 since earlier publications were discussed in the NDA.

CPS results
Ovation reported that the literature search identified 46 publications discussing the use of vigabatrin in CPS or other seizure disorders. The 46 publications were comprised of 13 journal articles, 6 case reports, 17 review articles, and 10 other publications.

Ovation identified 3 double blind placebo controlled trials. The publication by Spanaki et al did not present adverse event data. The publications by Bruni et al and Dean et al did provide AE data. Bruni et al identified the following events that occurred at least twice a frequently in vigabatrin subjects compared to placebo subjects: vision abnormal, diplopia, amnesia, ataxia, vertigo, speech disorder, aggressive reaction, and weight increased. Dean et al identified the following AEs occurring at least twice as frequently among vigabatrin subjects compared to placebo: nystagmus, agitation, amnesia, confusion, depression, abnormal coordination, diarrhea,

parasthesia, hyporeflexia, asthenia, diplopia, abnormal gait, abnormal thinking, and impaired concentration.

Ovation identified 10 publications reporting results from open label studies with vigabatrin. Seven of these publications dealt with ophthalmologic findings. The remaining publications reported AEs similar to those reported in the Amendment.

Of the 6 case reports, 3 were described ophthalmologic changes and one described MRI findings. Garcia Pastor et al described a 69 year old female that developed acute encephalopathy, psychotic state, and generalized myoclonic status after 4 months on vigabatrin. The patient's condition improved 24 hours after stopping vigabatrin. A report by Sorri et al described physical exam, neurological exam and ophthalmologic findings in 2 individual exposed to vigabatrin in utero. The first child's mother was treated with carbamazepine and vigabatrin through week 22 of pregnancy. At birth, the child required supplemental oxygen and a feeding catheter. At age 7, the child was described at normally developed, with retrognathis, large ears, and irregular tooth placement, and with normal neurological and ophthalmologic exams. The second child's mother was treated with carbamazepine and valproate and vigabatrin was added at 16 weeks following an episode of status epilepticus. The child was examined at age 6 and the investigators noted that the child had a seizure at age 4 and was diagnosed as mild mental retardation at age 5. The reporters noted multiple minor and major malformations (not described) but a normal ophthalmologic exam.

Among the group of 10 publications that Ovation described as "other", 2 were retrospective reviews assessing ophthalmologic findings. Two studies (Landmark et al and Ulmanova et al) looked at use of vigabatrin in Norway and the Czech Republic and documented that use was low in these countries. Two studies examined psychiatric AEs in AED users. Trimble et al found similar risks for psychosis and affective disorders among vigabatrin treated (n=50) and topiramate treated (n=34) patients. Weintraub et al found no psychiatric AEs reported for 13 patients treated with vigabatrin in their study cohort of 1394 patients treated with newer AEDs. Handoko et al conducted a case control study to examine the risk for aplastic anemia. The investigators found increased risk of aplastic anemia with valproate, carbamazepine, and phenytoin. The investigators noted that one patients that developed aplastic anemia was taking vigabatrin and phenytoin. Arif et al conducted a study to examine risk of rash among users of AEDs and reported no cases of rash among 47 vigabatrin treated subjects. Prasad et al conducted a chart review of 73 patients treated with vigabatrin and documented that 11% (n=8) developed irritability/aggression and 2.7% (n=2) developed worsening of myoclonic seizures. Iorio et al reviewed spontaneous reports for AEDs used in Italy and found that vigabatrin had the highest rate of hearing and vision reports.

Ovation listed 17 review articles that were identified in the medical literature search. The majority of these articles discussed issues arising across the class of AEDs (ex. psychiatric symptoms, weight change, etc.). On review article by Cohen et al examined the potential for IME among patients treated with vigabatrin. A review article by Ferrie et al commented on phsychotic and behavioral reactions with vigabatrin.

Infantile Spasms
Ovation reported that the literature search identified 40 publications discussing the use of vigabatrin in IS. The 40 publications were comprised of 21 journal articles, 6 case reports, 4 review articles, and 9 other publications.

The 21 journal articles were publications of 6 open label controlled trials and 15 open label uncontrolled trials. The publication by Gaily et al did not report AE data. Lux et al reported similar AE risks for 52 IS patients treated with vigabatrin and 55 patients treated with prednisolone or tetracosactide. In a follow up of subjects from that study, Lux et al reported that 2 prednisolone or tetracosactide patients died compared to 3 vigabatrin patients. The deaths were felt to be consistent with the course of IS. Vigevano et al reported that in a randomized open label cross over study of vigabatrin and ACTH, somnolence (n=2) and hypotonia (n=2), and irritability (n=1) was observed with vigabatrin and hyperexcitability, irritability and increased appetite with ACTH. In another study by Vigavano et al, the investigators reported lower AE risks with vigabatrin compared to ACTH. Hammoudi et al published results of a study looking at visual field in IS patients treated with vigabatrin. In the publications describing open label studies, a number of AEs were reported in vigabatrin treated subjects including drowsiness, somnolence, sleep disturbances, insomnia, irritability, nervousness, hyperactivity, behavioral changes, increased seizure frequency, weight gain, and edema. Villeneuve et al noted in their open label study of 70 children with IS that 2 infants died, one was a sudden death and the other was due to congenital nephritic syndrome.

Among the cited case reports, Haas Lude et al described a 6 year old female with Alexander disease and hydrocephalus who presented with uncontrolled seizures and was treated with vigabatrin. The patient developed apathy, somnolence, and sluggishness. Vigabatrin was stopped and the symptoms resolved over 2 days. Pearl published two case series of MRI changes in children treated with vigabatrin.

Among the other reports cited by Ovation, adverse events mentioned in vigabatrin treated patients included irritability, somnolence, decreased sleep, and sedation.

The four review articles identified by the search included the article by Cohen et al mentioned above examining IME in patients treated with vigabatrin, two articles about treatment of infantile spasms, and one article about vigabatrin in treating pediatric epilepsy.

The complete list of references identified by NERAC Inc. on behalf of Ovation is provided in an appendix to this review.

7.2.3 Adequacy of Overall Clinical Experience

The exposure, in terms of number of subjects, exceeded the minimum ICH recommendations for medications products intended for long term treatment. The ICH Guidance recommends that 1,500 subjects exposed with 300-600 subjects exposed for 6 months, and 100 exposed for 1 year (at relevant doses, with reasonable exposure to the highest proposed dose). In the Integrated database, which includes only the subjects exposed to vigabatrin during epilepsy trials, Ovation

reports that 4,077 subjects have been exposed to vigabatrin and have sufficient information to assess AEs. Ovation reported that 3,456 subjects were exposed for >6months, 2,753 subjects were exposed for >1year and 403 subjects were exposed for >5 years (Source 3/14/08 Submission, Table 2.2, p.3).

Ovation's proposed labeling states that the usual effective dose of vigabatrin is 3g/day. The labeling also states that doses up to 6g/day were studies but were not statistically superior in efficacy to 3g/day and were associated with higher adverse event risks. As noted above, Ovation reported that 1,112 epilepsy subjects were exposed to a vigabatrin dose between 3 to <4g/day for at least 6 months, and 587 subjects were exposed to a vigabatrin dose between 3 to <4g/day for at least 1 year.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The cardiac in vitro and animal testing, which included examination of electrical stimulation threshold or the ventricular fibrillation threshold in perfused rabbit heart preparations, long term toxicity study in dogs that included ECGs, studies of vigabatrin's effect on the hERG channel current, and follow up tests in isolated rabbit Purkinje fibers appeared adequate. Additional non clinical studies since the NDA submission designed to examine specific safety topics included visual field defect toxicity studies, and juvenile rat toxicity study looking at developmental toxicity in neonatal and juvenile development.

7.2.5 Adequacy of Routine Clinical Testing

The approach used to collect adverse event data in the development program studies appeared appropriate, with AEs recorded at each visit. One noted limitation related to AE capture was the use of a separate database (GADERS) to collect SAE data. Using this approach meant that SAE information was not recorded in the CRFs in several studies and it is not completely clear if investigators were able to review the information included in the GADERS database for accuracy. The use of this separate SAE database led the sponsor to overlook several SAEs in vigabatrin subjects. Ovation did eventually identify these events when asked by the Division.

The routine lab data testing in the vigabatrin development program appeared appropriate. One limitation of the lab data testing was that despite identifying vigabatrin related anemia, the sponsor made no attempt to include additional hematological testing in subsequent studies that would allow for further evaluation and classification of the anemia.

The ECG recording in clinical trial subjects was inadequate with little available pre and post exposure ECG data available for vigabatrin subjects. In addition, timing of ECG recording in relation to dose was not specified and there was no pre-specified interval measurement methodology. The available ECG data does not allow for a reliable assessment of the effect of vigabatrin on cardiac repolarization in humans.

Vital sign testing in the vigabatrin clinical trials was generally adequate. One notable deficiency for vital signs was the lack of height and weight data in children to allow assessment of development.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup
Ovation explains that vigabatrin is rapidly and completely absorbed, is not metabolized to a significant extent, does not induce cytochrome P450 enzymes systems in animals and is not protein bound. OCP reports that vigabatrin induces CYP2C9 and CYP2C19 in vitro. Vigabatrin is eliminated unchanged through renal excretion. A decrease in phenytoin levels of 20-30% occurs with vigabatrin. Studies of vigabatrin and carbamazepine found no effect, increases, or decreases in carbamazepine concentrations. Other antiepileptic drugs reportedly have minimal effect on vigabatrin concentrations.

As noted in Dr. Leber's Division Director's 11/18/97 memo, OCBP concluded that the sponsor's approach to studying interaction between vigabatrin and other AEDs was acceptable (Source Division Director Vigabatrin Approvable Action Memo, 11/18/97, pp.12-13).

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The most important safety issues with vigabatrin are the permanent visual field defects and MRI/IME findings. Dr. Farkas and Dr. Sheridan will address these topics in their reviews. In terms of the remaining general safety, there did not appear to be any major areas neglected in the application. Additional information regarding anemia, potential for liver injury, long term edema data, and implications of long term weight gain would be informative.

7.2.8 Assessment of Quality and Completeness of Data
Division reviewers have highlighted a number of deficiencies in the sponsors' presentations of adverse events over the course of the vigabatrin development program. These deficiencies have included lack of supporting information (narratives, CRFs) in applications, use of sources other than CRFs to capture data, including data from studies with no prespecified protocol, and the use of separate databases to capture serious adverse events. When these deficiencies have been identified, the sponsor has attempted to address them and the result has been generally acceptable.

There are several issues particular to this application that raise concerns about the quality and completeness of the data. The duration of the development program means that it is difficult to collect additional data about issues that are identified during the review. When questions arise about a particular case, the sponsor had difficulty amassing additional information to address the specific questions. The switching of sponsors over time also raises concerns. The current sponsor, Ovation, did not conduct any of the clinical trials included in the submission. When the Ovation obtained the rights to vigabatrin, data was transferred from Aventis to Ovation. An example of a difficulty arising from the switch is related to Ovation's uncertainty about classification of AEs. The Division asked Ovation why 2 rash SAEs were coded as serious given that the narratives did not provide any details that would support such a classification. Ovation

was only able to reply that they presented the events as SAEs to be consistent with how previous sponsor coded them. Ovation did not appear capable of addressing why the previous sponsor took that action, suggesting some loss of information in the transfer of data.

The approach to recording SAE data in some trials resulted in omissions in Ovation's safety presentation. The use of a separate data base to capture SAEs meant that 21 SAEs were not identified in the current submission, but instead were only subsequently discovered. Although Ovation attempted to convince the Division that all events were ultimately discovered and reported, it is not known if the effort was successful.

Another concern is related to the lack of data for subjects. For example, in the current submission, Ovation identified 599 subjects in the current submission with missing data that did not allow determination of the duration of exposure. Another example of lacking data is related to information presented in narratives. Many of the narratives provide woefully inadequate information for assessing what actually occurred to the subject.

The approach to presentation of lab data meant that not all subject labs were included in the lab data sets used for analyses. For example, for patients with SAEs during the study, if labs were captured during hospitalization, they could have been recorded with narratives but not in the lab data set. This was seen with the decreased platelet count event in patient 0242/1543003 and with the liver injury death in subject 0201/1621007. This approach could have limited the ability to identify extreme lab outliers.

7.2.9 Additional Submissions, Including Safety Update

In accordance with an agreement with the Division, Ovation did not provide a safety update for the adult CPS amendment submission. Ovation provided additional information in responses to Division questions submitted 2/11/08, 3/14/08, 4/15/08, 4/23/08, 5/1/08, 5/2/08, 5/7/08, 5/16/08, 5/23/08, 5/27/08, 6/2/08, and 6/6/08.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.3.1 Visual Field defects
See Dr. Farkas' review.

7.3.2 IME/MRI abnormalities
See Dr. Sheridan's review.

7.3.3 Anemia/Declines in Hemoglobin, Hematocrit
Lab data suggest that vigabatrin subjects experienced declines in hemoglobin and hematocrit that were not seen in subjects that received placebo. Vigabatrin subjects experienced mean decreases in hemoglobin and hematocrit from baseline and had higher risks for low hemoglobin and hematocrit result outliers. Analyses also suggested that these declines were dose related. Despite these laboratory findings, vigabatrin subjects did not appear to experience high frequencies of

concerning clinical events. Ovation reported that 3 vigabatrin subjects (0.06%, 3/4737) from the Integrated database experienced anemia SAEs, and 3 vigabatrin subjects (0.06%, 3/4855) from the Integrated database discontinued for anemia AEs. A search of the development program identified only 2 vigabatrin subjects that experienced unexplained declines in hemoglobin below 8g/dL and or hematocrit below 24%. In addition, there appeared to be few post marketing reports of anemia adverse events. The sponsors did not collect sufficient information to classify the observed anemia events.

Ovation would not include in the vigabatrin label information about anemia/decreases in hemoglobin and hematocrit. I have proposed labeling language discussing these events.

7.3.4 Weight gain
Weight data support that vigabatrin use is associated with weight gain. Data from controlled trials demonstrated that vigabatrin treated subjects had a higher mean increase in weight from baseline than did placebo treated subjects. In addition, vigabatrin subjects had a higher risk of gaining >=7% of baseline body weight. One analysis suggested that weight increase risk was greater among female vigabatrin subjects but there did not appear to be evidence suggesting differential weight increase risk by age. In the Integrated database, 10.2% (415/4077) of vigabatrin subjects had a weight increased AE. Ovation did not provide information about weight gain in their labeling proposal for vigabatrin. I have proposed labeling language for weight gain with vigabatrin.

7.3.5 Edema
Vigabatrin use was associated with development of edema. In the Integrated Database, Ovation identified 3% (124/4077) patients with AE of edema peripheral, 0.4% (16/4077) with edema, 0.1% (5/4077) with generalized edema, 0.1% (5/4077) with localized edema, 0.1% (4/4077) with facial edema, <0.1% (3/4077) with pitting edema <0.1% (3/4077) with gravitational edema. None of these events were SAEs, and only 5 edema peripheral events and 2 edema events led to discontinuation. In analyses of pooled controlled trial data, the risk of edema was higher among vigabatrin subjects compared to placebo subjects. Dose response analyses of controlled trials data suggested an increasing risk of edema peripheral and generalized edema with increasing vigabatrin dose but not other edema related adverse events.

In a separate analysis, 50 of 215 vigabatrin subjects with an edema related AE also had a weight gain AE (only 23 of these occurred within a month of the edema related AE). The edema AEs did not appear to be related to cardiac, renal, or hepatic AEs and did not appear to be associated with increased creatinine, low serum albumin, or proteinuria.

Ovation did not propose labeling language for edema adverse events. I have proposed labeling language for edema with vigabatrin.

7.3.6 Depression/Suicidality
Evidence supports an increased risk for depression with vigabatrin and insufficient evidence to support an increased risk of suicidal behavior.

A sponsor submitted expert review of psychiatric events with vigabatrin found an increased risk for depression among vigabatrin subjects and more serious outcomes (hospitalizations, discontinuations) among vigabatrin subjects.

In the Integrated database, 8.2% (334/4077) of subjects reported depression AEs, 1.0% (40/4077) reported depressed mood AEs, 0.6% (23/4077) reported suicidal ideation AEs 0.3% (13/4077) reported suicide attempt AEs, 0.1% (4/4077) reported depression suicidal AEs, and 0.07% (3/4077) reported major depression AEs and 1 subject committed suicide. In addition, there were 21 Depression SAEs (0.44%) 12 Suicidal ideation (0.25%) SAEs, 10 Suicide attempt (0.21%) SAEs, 2 (0.04%) Depression suicidal SAEs and 1 (0.02%) major depression SAE.

Data from 12 pooled controlled studies demonstrate slightly increased risks for depression AEs for vigabatrin and placebo subjects, and show an increased risk for depression and suicide related SAEs among vigabatrin subjects, although the number of SAEs was relatively small. In addition, data from these trials suggest an increased risk for depression AEs leading to discontinuation among vigabatrin subjects compared to the subjects randomized to other treatments.

There did not appear to be a clear dose response for depression related AEs in a pool of 5 randomized placebo controlled trials that included more than one dose of vigabatrin.

Ovation proposes including information about depression in a Warnings and Precautions statement titled "Neuropsychiatric Adverse events". This labeling statement covers a variety of AEs including psychiatric symptoms, somnolence, fatigue, and sleep disorders. Ovation would provide the risk for depression AEs among vigabatrin subjects in the Integrated database but would not provide comparative data from controlled trials.

I have proposed labeling language for depression and suicidality with vigabatrin that is similar to the class labeling being considered for all AEDs.

7.3.7 Peripheral Neuropathy

In the NDA review, Dr. McCormick noted that treatment emergent risks for parathesia and hyporeflexia adverse events were 3 times higher among vigabatrin subjects compared to placebo subjects. Dr. McCormick commented that neurological symptoms were not correlated with careful examinations and that affected subjects were not tested to determine if the process was axonal or demyelinative. Dr. McCormick suggested that the sponsor perform additional analyses to evaluate peripheral neuropathy AEs. In addition, Dr. McCormick suggested that patients with hyporeflexia and sensory loss be evaluated for "NCV and EMG changes", and study data be reviewed to determine if nerve biopsies had been performed (Source NDA Review, 3/5/95).

Dr. James Sherry reviewed the sponsor's response to the Division's request for additional information about peripheral neuropathy. The sponsor submitted a report evaluating peripheral neuropathy events that was written by their expert consultant. Dr. Sherry noted that the sponsor's consultant reviewed the peripheral neuropathy events "on the basis of their association with demyelination/IME rather than as a separate process." Dr. Sherry felt that the consultant's conclusion that none of the cases of peripheral neuropathy were demyelinating was not

substantiated. Dr. Sherry found that symptoms and signs of peripheral neuropathy occurred more frequently among vigabatrin subjects compared to placebo subjects in the US studies 024 and 025. Dr. Sherry requested that peripheral neuropathy be mentioned in the vigabatrin label and requested additional information about the course, onset, duration of exposure, and resolution of these events (Source, Clinical Review, 11/5/97).

In the current submission, Ovation summarized the previous submissions related to peripheral neuropathy, particularly the consultant report noted above, but provided no new information. Ovation noted that the reviewed studies were not designed to systematically evaluate peripheral neuropathy and did not include nerve conduction studies, quantitative sensory testing or skin or nerve biopsy.

In addition to summarizing the expert review, Ovation provided a review of post marketing reports of neurological events. Ovation commented that few postmarketing reports described events related to peripheral neuropathy.

In their proposed labeling, Ovation includes a Warnings and Precautions statement regarding peripheral neuropathy. Ovation's statement only provides absolute risks for peripheral neuropathy AEs among vigabatrin treated subjects from the Integrated database but includes no comparative data. I provide edits to the Ovation peripheral neuropathy labeling language.

7.3.8 Liver Injury

There have been cases of liver injury resulting in death or transplant in patients treated with vigabatrin but it is not clear if vigabatrin is causally related to these cases. In the development program studies that were part of the vigabatrin safety database, one study subject died from multiorgan failure (including hepatic failure) following an episode of status epilepticus. This event was likely related to the patient's underlying medical condition and not vigabatrin. A patient with metastatic cancer developed elevated transaminases and died. A third liver failure case resulting in death involved a study subject that had been taking vigabatrin for six years prior to the event and the liver injury was temporally related to treatment with clarithromycin. A subject in a Japanese study that was not part of the vigabatrin safety database died from hepatic failure but there were insufficient details about this event to allow a determination about whether vigabatrin was causally involved.

From post marketing reports, there were four hepatic related deaths and one liver transplant. In none of the cases was a likely alternative explanation documented but all were taking multiple medications at the time of the event. Excluding cases with exposure to vigabatrin for more than 1 year prior to developing liver injury leaves 3 cases of death/transplant. The reporting rate with of hepatic failure resulting in death or transplant with vigabatrin exceeds the general population background risk that we have relied on in the past, but liver injury risk may be elevated among patients with seizure disorders that are treated with medications that are known hepatotoxins.

Examination of available laboratory data did not identify any "Hy's law" (Transaminase 3x ULN with total bilirubin >2.0mg/dL) liver injury cases in the development program. From a pool of data from controlled trials there did not appear to be an increased risk of high transaminase

outlier results for vigabatrin subjects compared to placebo. These laboratory results must be intepreted in light of vigabatrin's ability to decrease transaminases.

I do not believe that available data are sufficient to allow the conclusion that vigabatrin causes liver injury but the data do merit close followup. I agree that a warning statement for hepatic injury is not required at this time. If vigabatrin is approved, Ovation should closely follow all post marketing reports of hepatic injury, collect complete follow up data on each case, and provide expedited reporting to FDA of any such cases.

7.3.9 CNS Effects
Vigabatrin was associated with an increased risk for a number of CNS AEs including somnolence, sedation, coordination abnormalities and confusional state. The occurrence of these events could impair a patient's ability to perform tasks such as driving or operating machinery. I include a labeling statement about the risk for these events.

7.3.10 Effects on Serum Transaminases
Vigabatrin causes reductions in serum transaminases (ALT>AST), presumably through its effect as a transaminase inhibitor. Vigabatrin treated subjects experienced mean declines in ALT and AST that were not observed among placebo subjects. In one analysis, 94% of subjects had a 60-100% maximum decrease in their ALT compared to baseline and 4% had an ALT result of 0. The magnitude of the declines appeared to be dose related. This effect could impair the ability to monitor for liver toxicity.

Recommendations
Any ongoing or planed vigabatrin clinical trials should incorporate monitoring of hemoglobin, hematocrit, serum iron, transferrin, ferritin, reticulocyte count, red cell morphology, red cell indices, haptoglobin, urine hemoglobin, and erythropoietin.

Any ongoing or planned vigabatrin clinical trials should incorporate hematologic testing during post-treatment washout in order to assess rate of recovery from reduction of hemoglobin and hematocrit.

Ovation should conduct a thorough QT study in humans. This could be conducted as a phase IV commitment.

If approved for pediatric indications, Ovation should collect data that address the effect of vigabatrin on growth and development.

Ovation should closely follow up any spontaneous reports of liver injury. Follow up should include complete description of the case, outcome information, lab test results, biopsy results, and post mortem test results. In addition, Ovation should submit any serious liver injury cases as 15-day reports.

Ovation should incorporate the labeling language that will be requested by the Division.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Prior submissions used separate pools of data to explore vigabatrin related adverse event risks. In the NDA, the comparative analyses were generally based on data from two controlled US epilepsy trials (024, 025). These studies were pooled because of their similar designs. The NDA also included data from non US studies, but these data were considered of lower value because the sponsor neither submitted with the NDA nor had available for audit/review the Case Report Forms (CRFs) for most of the non US studies that contributed safety data. In addition, the NDA lacked complete dose and duration of exposure data for non US studies subjects, and did not include narrative summaries of serious adverse events and discontinuations for these subjects. In the NDA Amendment the sponsor collected and reviewed available CRFs from non US study sites. Some CRFs were located and others were not. Using the available data, the sponsor assembled the safety data for resubmission. The sponsor created three separate cohorts of non-US studies safety data. The first cohort was comprised of data from non-US studies for which CRFs were available for all subjects, where data was designated to be captured by a prospectively written protocol and where data was contemporaneously captured in the CRF. These data were termed the non-US studies primary safety data. In instances where some but not all CRFs were located for a given study the data for patients with CRFs were grouped into the second cohort called Secondary data. A third cohort included data for those patients for whom CRFs were not located (non-CRF data). The NDA amendment focused mainly on data pooled from the primary non US studies and included additional information from the secondary data sources.

For the Current submission, Ovation presents results of analyses from pooled data for several different cohorts. The main focus of the Amendment submission safety presentation is the Overall cohort, which includes data from 15 studies (epilepsy, IS, and safety studies looking at VFDs) for the time period of 3/16/97 through 6/30/07. In addition, Ovation divided the data from the studies in the Overall cohort into the following subgroups: adult partial epilepsy studies, pediatric (non-IS) studies, and infantile spasms studies. Lastly, Ovation presented data for an Integrated cohort. The Integrated cohort includes data from all epilepsy studies in the development program, dating back to the original NDA submission. Ovation presented these data using 3 columns. The "Prior" column of the table includes information from US, primary non-US, and secondary studies (for SAEs only) through the 1998 Safety Update (3/1/07 submission, p.194). The "Current" column of the table includes information from the studies in the current submission except for studies 0098 and 4021, which were reported separately. The "Combined" column adds the data from the Prior and Current columns. This analysis allows for comparisons of risk across time.

During the course of the present review, the Division requested additional analyses from pooled controlled trial data that would allow comparisons of adverse event risk to assess causality. Ovation pooled data from 12 phase II/III epilepsy controlled trials that used a double blind, parallel group, dose, placebo or active control design. The choice of studies for pooling appeared appropriate although there were differences among the studies in terms of the durations (range 5 days to 52 weeks) and numbers of subjects enrolled (range 18- 457).

In response to a Division request for a dose response analysis, Ovation analyzed pooled data from 5 fixed-dose, randomized, placebo-controlled CPS trials.

Ovation did not provide pooled analyses of lab or vital sign data and the results for the current submission studies and the results cited above come from the study reports of individual studies.

7.4.1.2 Combining data

For the adverse event analyses using pooled data, the adverse event counts from the selected studies were summed and the numbers of subjects or the person time from each of the selected studies were summed. To calculate the pooled adverse event risk, the total number of adverse events was divided by the total number of subjects or the total person time. For the Integrated data analyses, Ovation had to re-code verbatim preferred terms to MedDRA prior to summing the numerator events, because prior submissions used a WHOART coding dictionary.

For the dose response AE analysis, Ovation summed the adverse events for the numerator of the risk calculation and summed person time exposure for the different dose groups for the denominator. Ovation then assigned adverse events to the dose category at which the event occurred.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Ovation did not provide dose response analyses in their NDA amendment submission. The Division requested dose response analyses using data from 12 pooled randomized controlled trials. Most clinical studies in the vigabatrin development program used titration designs which complicate interpretation of dose response analyses. One of the difficulties with titration designs is that subjects in these studies are exposed to a range of doses. For that reason subjects could be assigned to multiple dose groups so that calculating risks for a given dose becomes complicated and misclassifying events in terms of dose can occur. The Division requested analyses that determined the amount of person time at each dose and then assigned adverse events to the dose taken at the time of the event. AE rates across the dose groups were then compared to look for dose response.

7.4.2.2 Explorations for time dependency for adverse findings

Ovation submitted no time dependency analyses.

7.4.2.3 Explorations for drug-demographic interactions

Ovation submitted analyses that compared adverse event risks stratified by sex and age. These analyses are of limited usefulness because there are no comparator (non vigabatrin treated) data to allow one to assess if any observed differences in AE risks are due to drug-demographic interactions, or merely represent differences in adverse event risk that occur in the background.

7.4.2.4 Explorations for drug-disease interactions

Ovation submitted no drug-disease interaction analyses.

7.4.2.5 Explorations for drug-drug interactions

Ovation submitted no drug-drug interaction analyses for the 15 trials in the current submission. In their Clinical Summary, Ovation notes that clinical and pharmacokinetic studies show a vigabatrin phenytoin interaction. In one study, when vigabatrin was added in 8 patients who had been taking phenytoin for a month, the phentoin plasma levels decreased by 23%. Ovation states that this interaction may be due to induction of cytochrome P450 2C in some patients.

7.4.3 Causality Determination

Evidence for causality for specific adverse events is presented in section 7.3.

10 APPENDICES

Summary of completed studies included in the 12/28/07 submission that were not previously submitted

5 Adult epilepsy studies

0098- open label, flexible dose long term study as add on therapy in patients with partial seizure. This study enrolled subjects that previously participated in vigabatrin clinical trials and allowed them to continue vigabatrin treatment. Some data from this study were reported in the last safety update but the actual dataset used for that safety update was not available. Other data problems include missing age data for 384 subjects and use of different data fields for the SAE database resulting in inconsistent subject number capture and date of birth (12/28/07 submission, p. 19).

0101- A randomized double blind placebo controlled study of vigabatrin as add on to carbamazepine or phenytoin in adult patients with complex partial seizures. The study included a 4 week titration phase followed by a 24 week maintenance phase and then an open label phase. For the placebo controlled phase, 119 subjects were assigned to vigabatrin and 58 to placebo.

0222- A randomized double blind study of vigabatrin versus gabapentin in complex partial seizures. The study included an 8 week baseline phase followed by a 5 week titration phase where vigabatrin or gabapentin was added to the subjects' treatment regimen, and an 8 week withdrawal phase where baseline AEDs were withdrawn. Nineteen subjects were enrolled in this study (vigabatrin n=10, gabapentin n=9).

0223- A double blind study where subjects with complex partial seizures were randomized to one of four doses of vigabatrin. The study included an 8 week baseline phase where subjects were maintained on their usual AEDs, a 6 week titration phase (vigabatrin doses 1, 3, 4, and 6g/day), an 8 week phase where the baseline medications were withdrawn, an 8 week maintenance phase, and an open label phase. Seventeen subjects were randomized to 1g/day, 18 to 3g/day, 19 to 4g/day, and 21 to 6g/day.

0242- An open label long term maintenance study of vigabatrin in patients with complex partial seizures (enrolled subjects from studies 0222 and 0223). This study included 85 subjects.

5 pediatric complex partial seizure studies

0118- A randomized double blind placebo controlled add-on study in pediatric subjects with complex partial seizures. The study included a 10 week baseline phase (single blind placebo), a 6 week titration phase where vigabatrin subjects were titrated to their randomly assigned target dose of 20mg/kg/day, 60mg/kg/day, or 100mg/kg/day, and an 8 week maintenance phase. The study randomized 96 subjects to vigabatrin and 34 to placebo.

0192- A randomized double blind placebo controlled add-on study in pediatric subjects with complex partial seizures. This study included a 6 week baseline phase, a 10 week titration phase where vigabatrin patients were titrated to tolerability/response, and a 7 week maintenance phase. The study randomized 55 patients (28 vigabatrin, 27 placebo).

0201- An open label long term follow up study that enrolled subjects from 0118 and 0221. Subjects completing this study rolled over into 0098. This study included 210 subjects (185 children, 25 adults).

0221- A randomized double blind placebo controlled add-on study in pediatric patients with complex partial seizures. This study included a 6 week baseline phase, a 10 week titration phase where vigabatrin patients were titrated to tolerability/response, and a 7 week maintenance phase. This study randomized 88 subjects (43 vigabatrin, 45 placebo).

0294- An open label 24 week study that enrolled subjects from study 0192. Forty-four subjects enrolled in this study but data are available for only 43 subjects (one subject's record is missing 12/28/07 submission, p.23).

4 Studies Assessing Visual Field Defects

4020- An open label study of the prevalence, incidence and clinical course of VFD in patients with partial seizures. The study enrolled subjects with current, previous, and no vigabatrin exposure. The study enrolled 735 subjects (562 with vigabatrin exposure).

4021- An open label study of the clinical course of VFD in patients with partial seizures. The study enrolled 30 subjects.

4103- An observational cohort studying reversibility/progression and predictive factors of visual field loss with vigabatrin. This study enrolled 23 subjects.

R003 A prospective cohort study designed to detect early VFD, and to assess the frequency and clinical course of early VFD associated with first time vigabatrin treatment. This study enrolled 25 of a planned 200 subjects.

Infantile spasm study

1A- A randomized, single-blind parallel group study of vigabatrin in subjects younger than 2 years with new onset IS. This study included a 14-21 day single blind phase where subjects were randomized to low dose (18-36mg/kg/day) or high dose (100-148mg/kg/day) vigabatrin (7 day titration followed by maintenance of 7-14 days). This study also included a long term follow up phase (up to 3 years). The study enrolled 223 subjects but one subject was excluded from the safety analysis for lack of reliable dosing data.

Labeling Review

Pending the outcome of the planned advisory committee meeting, the following language should be considered for a black box warning.

Boxed Warning

Suicidal Behavior and Ideation and Antiepileptic Drugs
Antiepileptic drugs increase the risk of suicidal thoughts and behavior in patients taking the drugs for any indication. In a meta-analysis of placebo-controlled studies, antiepileptic drugs approximately doubled the risk of suicidal behavior and ideation compared to placebo. Anyone considering the use of vigabatrin or any other antiepileptic drug must balance this risk with the clinical need. Patients who take antiepileptic drugs should be monitored closely for suicidal thinking or actions, thoughts about self-harm, or any notable changes in behavior that could indicate the emergence or worsening of depression or suicidal thoughts or behavior.

Families and caregivers should be advised that close observation and communication with the prescriber are important.

Warnings and Precautions

Suicidal Behavior and Ideation
Antiepileptic drugs increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Pooled analyses of 199 placebo-controlled clinical trials of 11 different antiepileptic drugs showed that patients receiving one of the antiepileptic drugs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.6) of suicidal thinking or behavior compared to patients receiving placebo. The estimated incidence of suicidal behavior or ideation among 27,863 antiepileptic drug-treated patients was 0.37% compared to 0.24% among 16,029 placebo-treated patients. There were suicides in the trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior was observed as early as one week after starting drug treatment and continued to at least 24 weeks. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be reliably assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs and did not vary substantially by age in the clinical trials analyzed.

The relative risk for suicidal thoughts or behavior was higher in patients in clinical trials for epilepsy compared to those in clinical trials for psychiatric or other conditions. The absolute risk differences, however, were comparable in patients with epilepsy and psychiatric conditions.

The following table shows absolute and relative risk by indication.

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.5	3.6	2.5
Psychiatric	5.2	8.3	1.6	3.1
Other	0.8	2.0	2.3	1.1
Total	2.2	4.3	2.0	2.1

Anyone considering prescribing vigabatrin or any other antiepileptic drug must balance this risk with the clinical need. Patients treated with any antiepileptic drug for any indication should be monitored appropriately and observed closely for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

Patients, their caregivers, and families should be informed that antiepileptic drugs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with vigabatrin and should counsel them in its appropriate use. A patient Medication Guide is available for vigabatrin. The prescriber or healthcare professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking vigabatrin.

Suicidal Thinking and Behavior - Patients, their caregivers, and families should be informed that antiepileptic drugs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or

thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Warnings and Precautions

Peripheral Neuropathy
During randomized controlled trials, vigabatrin treated study subjects experienced an increased risk compared to placebo treated subjects for adverse events suggestive of peripheral neuropathy including parathesia, diminished reflexes, and diminished vibratory sense. In the overall epilepsy development program, among 4,077 vigabatrin-treated patients, adverse events related to peripheral nerves included paresthesia (2.7%), hypoesthesia (2.2%), neuropathy peripheral (0.4%), reflexes abnormal (0.2%), areflexia (0.2%), sensory loss (0.2%), peripheral sensory neuropathy (0.1%), neuropathy (0.1%) and polyneuropathy (0.02%).

[Note to Sponsor: There is a clear increase in the incidence of symptoms and signs consistent with peripheral neuropathy e.g.,paresthesia, stocking glove distribution, diminished vibratory sense and reflexes,etc.] with vigabatrin. Please develop a proposed case definition for peripheral neuropathy which should be discussed with us before additional work is done. Once we have agreed on a case definition, please submit comprehensive information about all cases in your database, including nerve conduction studies, if available. Please also provide incidence estimates from your controlled trials, as well as from open and post-marketing experience. Examine the effects of dose, duration, and vigabatrin discontinuation on the symptoms and signs of peripheral neuropathy.]

Peripheral Edema
Vigabatrin treatment is associated with an increased risk of developing peripheral edema. Pooled data from controlled trials demonstrated increases in risk among vigabatrin treated study subjects compared to placebo treated study subjects for edema peripheral (vigabatrin 4.3/100PY, 19/446PY; placebo 3/100PY, 3/101PY), edema (vigabatrin 1.1/100PY, 5/446PY; placebo 0/101PY) and generalized edema (vigabatrin 0.7/100PY, 3/446PY; placebo 0/101PY). In these studies, one vigabatrin (0.2/100PY, 1/446PY) and no placebo subjects (0/101PY) discontinued for an edema related AE. There was no apparent association between peripheral edema and cardiovascular adverse events such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

Vigabatrin should be used with caution in patients with existing peripheral edema and in patients with a history of congestive heart failure.

Weight Gain
Vigabatrin may cause weight gain. Data pooled from randomized controlled trials found that 17% (77/443) of vigabatrin study subjects gained >=7% of baseline body weight compared to 8% (22/275) of placebo treated subjects. In epilepsy trials, 0.6% (31/4855) discontinued for weight gain. The long term effects of vigabatrin related weight gain are not known.

Decreases in Hemoglobin and Hematocrit
In controlled trials, vigabatrin was associated with declines in hemoglobin and hematocrit. Data pooled from 2 epilepsy studies found a mean decline in hemoglobin among vigabatrin treated study subjects of -0.29g/dL and a mean increase in hemoglobin among placebo treated study subjects of 0.53g/dL. In those same studies, there was a mean decline in hematocrit among vigabatrin treated study subjects of -0.46% and a mean increase in hematocrit among placebo treated study subjects of 0.02%. The declines in hemoglobin and hematocrit among vigabatrin treated study subjects appeared dose related. It is not known whether these changes are readily reversible with discontinuation of vigabatrin.

Despite these laboratory findings, only 3 vigabatrin treated study subjects (0.06%, 3/4855) from epilepsy trials discontinued for anemia and 2 vigabatrin treated subjects experienced unexplained declines in hemoglobin below 8g/dL and or hematocrit below 24%.

CNS Adverse Events
Vigabatrin was associated with an increased risk for a number of CNS adverse events including somnolence, sedation, coordination abnormalities and confusional state. The occurrence of these events could impair a patient's ability to perform tasks such as driving or operating machinery.

Decreases in ALT and AST
In North American controlled studies, vigabatrin decreased alanine transaminase (ALT) and, to a lesser extent, aspartate transaminase (AST) plasma activity. This represents a chemical interference with the assays, not an effect of vigabatrin on the liver. The magnitude of ALT suppressions in over 90% of vigabatrin treated patients ranged from 60 to 100% while the magnitude of AST suppressions in over 90% of vigabatrin treated patients ranged from 0 to 60%. In patients with maximum ALT decreases of 80 to 100%, a greater percentage occurred in patients with higher vigabatrin doses (95.1%; 39/41 at 6 g) than in patients with lower vigabatrin doses (11.1%; 5/45 at 1 g). Dose trends were not as evident in vigabatrin treated patients with AST suppression. The time to onset of the first abnormal value in vigabatrin treated patients occurred most frequently during the first three weeks for ALT and between 4 to 8 weeks for AST, after starting vigabatrin therapy. The majority of vigabatrin treated patients reached their maximum decrease in ALT and AST values 4 to 8 weeks after starting vigabatrin therapy. Therefore, the suppression of ALT and AST activity by vigabatrin may preclude the use of these markers, especially ALT, to detect early hepatic injury.

Increases in Amino Acids in Urine
Sabril may increase the amount of amino acids in the urine, possibly leading to a false positive test for certain rare genetic metabolic diseases (e.g., alpha aminoadipic aciduria).

Table 5: Studies Included in Pooled Mortality Analysis				
		Total Number of Patients		
Study Number	**Design / Duration of Double-Blind Treatment**	**Vigabatrin**	**Active Comparator**	**Placebo**
71754-3-C-024	Double-blind, placebo controlled, parallel group, multicenter study / 18 weeks	92	0	90
71754-3-C-025	Double-blind, placebo controlled, parallel group, multicenter study / 18 weeks	129	0	45
097-WUK04	Double-blind, placebo controlled, parallel group, single center study / 2 weeks	22[a]	0	23
71754-3-C-021	Multicenter, double-blind, placebo-controlled, parallel group trial / 36 weeks	58	0	53
71754-3-W-007	Multicenter, randomized, double-blind, active-controlled, parallel group trial / 52 weeks	228	229 (CBZ)	0
71754-3-W-012	Multicenter, randomized, double-blind, active-controlled, parallel group trial / 40 weeks	110	113 (VPA)	0
0101	Multicenter, randomized, double-blind, placebo-controlled, parallel group trial / 28-32 weeks	119	0	58
0222	Multicenter, randomized, double-blind, double-dummy, parallel group trial / 21 weeks	9	9 (GBP)	0
0118	Multicenter, randomized, double-blind, placebo-controlled, parallel group trial / 14-17 weeks	94	0	32
0221	Multicenter, randomized, double-blind, placebo-controlled, parallel group trial / 17-20 weeks	43	0	45
0192	Multicenter, randomized, double-blind, placebo-controlled, parallel group trial / 17-20 weeks	28	0	27
71754-3-W-019	Multicenter, randomized, double-blind, placebo-controlled, parallel group trial / 5 days	20	0	20

a In this study the 2 week double-blind phase was followed by a 4-month phase in which all patients received vigabatrin. For the double-blind phase alone, the correct numbers are 22 vigabatrin and 23 placebo. When the 4-month phase is included, the number on vigabatrin is 22+23=45, which is consistent with Table B-1 from the 1997 Amendment.

Sources: Table of All Studies (Table 8.1) from original NDA; Table of All non-US Studies (Table B-1)and V2 p 89 from 1997 Amendment; Table of All Clinical Studies for Final Safety Update (Table 9-1) from 1998 Safety Update; Tabular Listing of Clinical Studies (5.2) from 2007 submission.

Post Marketing Liver Failure Deaths Reported In the 5/97 NDA Amendment

Patient 31730707, a 39 year old male died of hepatic failure. This patient who was being treated with vigabatrin (3.5g/day for 6 years) presented with fever and was treated with clarithromycin, aspirin, and noraminopyridine. Less than 30 days later he developed hepatic failure and died.

Patient VGZ-9500-1102, an 18 year old male treated with only vigabatrin (5g/day for 4 years) died of hepatic failure. A liver biopsy showed massive acute hepatitis and serologies were reportedly non-diagnostic.

Patient VGZ-9400-3033, a 10 year old female treated with vigabatrin (1.5g/day for 1 year) died of hepatic failure. She presented with "febrile enteritis" and subsequently developed abnormalities of transaminases and indicators of liver synthetic function. An autopsy reported "subacute hepatic dystrophy, extensive parenchymal necrosis, and intrahepatic cholestasis." Viral serologies were reportedly negative. Concomitant medications were carbamazepine and clonazepam.

Patient VGZ-9400-1440, a 34 year old female treated with vigabatrin (2g/day for 26 months) carbamazepine, and phenytoin, died of hepatic failure. The patient developed elevated transaminases. The patient's physician stopped the carbamazepine with slight improvement, but her transaminases increased again and she was hospitalized. Vigabatrin was stopped and her phenytoin dose reduced. Her liver function continued to deteriorate. A liver biopsy showed subacute hepatitis. She developed hepato-renal syndrome and died.

Patient VGZ-9300-3075, a 37 year old male treated with vigabatrin (1g/day for 4 days) phenytoin, and carbamazepine, died of hepatic failure. The patient developed status epilepticus that was treated with paraldehyde and diazepam. The next morning he was hypotensive and vomited blood. He developed altered mental status and left sided hemiparesis. He subsequently experienced a cardiac arrest and was resuscitated. He subsequently developed liver failure, renal failure, and died.

Patient VGZ-9203-130, a 10 year old male treated with vigabatrin (1g/day for 17 days) and carbamazepine, died of hepatic failure. The patient experienced a generalized tonic-clonic seizure and prolonged unconsciousness and was admitted to a hospital. Admission labs included abnormal LFTs. The patient died and a liver biopsy immediately following death demonstrated massive hepatic necrosis. The patent did not have serology testing.

Summaries of Clinical Details for the 16 Clinical Trial Deaths Reported in the Current Submission

0098/11920014 Cause of death: seizure
This 48 year old female with a history of complex partial seizures and partial generalized seizures who was treated with vigabatrin for 28 months (dose 5.5g/day at the time of the event) was found dead by her daughter. The reported cause of death was natural death as a result of seizure disorder. There was no documented preceding illness or injury. The narrative mentioned that she was seen by neighbors earlier that day as she walked her dog and was "frothing at the mouth" and complaining of arm and shoulder pain. Concomitant medications included gabapentin and premarin.

0098/12110008 Cause of death: grand mal seizure, sudden death
This 38 year old male subject with a history of seizures, Osler Weber Rendu syndrome with pulmonary arterio-venous malformation, and anxiety attacks died six hours after experiencing a grand mal seizure. The narrative mentioned that an autopsy was performed but that the results were not available. Concomitant medications were dilantin, ativan, and herbal vitamins.

0098/13040004 Cause of death: seizure
This 35 year old male subject with a history of seizures, asthma (no episodes since age 12), environmental allergies, and upper respiratory congestion died and seizure was listed as the case of death. No details were provided about the subject's death. The narrative noted that subject had been seizure free for 1 year and lowered his own vigabatrin dose against medical advice.

R003/0405010 Cause of death: seizure
This 58-year-old white male presented with a 55-year history of secondary generalized seizures consequent to a head injury sustained at the age of three. His medical history included chest pain and cardiac arrhythmia (summer of 2000), severe psoriasis, constipation, mild depression, and decreased hearing along with different nervous system disorders (poor memory, somnolence and bilateral hand tremors). He began vigabatrin therapy on December 19, 2001 and discontinued study medication on December 15, 2002, due to an acquired visual field defect. He had a fatal seizure that was not considered related to study medication but resulted in his death on May 21, 2003.

0098/12340002 Cause of death: myocardial infarction
This 52 year old male subject with a history of seizures, learning disability, memory deficits, s/p left temporal lobectomy for seizures was found dead in bed. No autopsy was performed and the death certificate listed myocardial infarction as the cause of death. The subject had no history of heart disease. The narrative listed only tegretol as a concomitant medication.

0098/13030106 Cause of death: myocardial infarction
This 63 year old male with a history of seizures, coronary artery disease, myocardial infarctions, congestive heart failure, ischemic cardiomyopathy, angina pectoris, hypertension, and cataracts died and the narrative reported that the cause of death was a massive myocardial infarction at home. The narrative provided no information about the evidence supporting this diagnosis. Concomitant medications at the time of death were lamictal and tegretol.

0098/13040002 Cause of death: myocardial infarction
This 53 year old male with a history of seizures, cardiomegaly, chronic edema, pulmonary hypertension, possible sleep apnea, paroxysmal nocturnal dyspnea, hand tremors, IQ 77, cerebellar atrophy, and obesity died and the reported cause of death was myocardial infarction. The narrative provided no information about the evidence supporting this diagnosis. The only listed concomitant medication was dilantin.

4020/0034014 Cause of death: cardiac arrest while sleeping
This 56 year old female subject with a history of seizures and closed head injury died and the reported cause of death was cardiac arrest while sleeping. An autopsy was not performed and the narrative provided no information about the evidence supporting this diagnosis. Concomitant medications included tegretol and paroxetine.

1A/911 Cause of death: sudden death
This was a sudden death occurring in a 7-1/2-month-old, 6.4 kg, African American female child with symptomatic Aicardi's Syndrome, sickle cell trait, and a history of clonic and tonic-clonic seizures. She initiated vigabatrin therapy on March 21, 1997. The subject had been receiving phenobarbital at baseline but this was abruptly discontinued due to change in caregiver. The subject was seen by the pediatrician for a well-baby checkup and age-appropriate immunizations on the day prior to death. The physician reported that she was more alert, interactive, and "much better" seizure-wise compared to baseline. At the time of death she had been on vigabatrin therapy for 74 days and was receiving a vigabatrin dose of 195 mg/kg for 3 consecutive weeks. On June 3, 1997 at 1:30 pm, the infant's caregiver put her down for a nap. When the caregiver attempted to wake the infant at 3:30pm, the infant was not breathing. The infant was taken to a local hospital and given vigorous cardiopulmonary resuscitation but could not be revived. The child had no intercurrent illness and did not receive pertussis immunization. An autopsy was performed; however, repeated attempts to obtain the report were unsuccessful. The sponsor believes this death would be considered a SUDEP (Sudden Unexplained Death in Epilepsy) (*Aicardi's syndrome is an X-linked disorder that includes agenesis of the corpus callosum, cystic intracerebral anomalies, infantile spasms, mental retardation, lacunar chorioretinopathy, and vertebral body abnormalities).*

0098/12040015 Cause of death: pneumonia, respiratory arrest
This 30 year old female with a history of seizures, profound mental retardation, cerebral palsy, and respiratory arrest was in hospice (reason not explicitly noted but narrative suggested a debilitated state) and died with pneumonia listed as the cause of death.

0098/12300010 Cause of death: pneumonia, pulmonary carcinoma, multiple organ failure
This 46 year old male subject with a history of seizures, mild mental retardation, and tobacco abuse was diagnosed with lung cancer during a vigabatrin clinical trial. The narrative reported that the subject developed pneumonia, multi organ failure and died.

1A/461 Cause of death: pneumonia
This subject had been off vigabatrin for three weeks at the time of onset of the adverse event. This subject was a 10-3/4 month 5 kg old female with infantile spasms and Miller-Dieker Syndrome, a genetic disorder associated with lissencephaly, microcephaly, severe mental deficiency, seizures, and frequent infections. She had begun vigabatrin therapy on August 8, 1997. Due to lack of efficacy, vigabatrin was tapered and discontinued with the last dose given on November 13, 1997. At this time, she started clonazepam, 0.5 mg bid. Lamictal® therapy was started for seizure control on November 20, 1997. She was hospitalized on ——— with a diagnosis of upper lobe pneumonia. "Do Not Resuscitate" orders were written at least 24 hours prior to her death. Supplemental oxygen was discontinued the evening of ——— as agreed upon by her parents and the attending physician. She continued to receive feedings per a gastrostomy tube, antibiotics, and acetaminophen for comfort measures until she died on ———. No autopsy was performed.

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1A/559 Cause of death: pulmonary hemorrhage secondary to pulmonary angiomatosis
This death occurred in a 3-month-old, 4.2 kg female with a history of severe encephalopathy of unknown etiology with onset of IS at 5 weeks of age. The infant also had a history of another unclassified seizure type. Vigabatrin treatment was initiated in June 12, 1997 and the dose was increased to a maximum dose of 750 mg without obvious improvement. The infant was also receiving an unspecified dose of chloral hydrate in addition to vigabatrin. She was initially treated with vitamin B6, but the spasms continued. Once on vigabatrin, her spasms decreased from 3 per day to 1-2 per day; however, startle seizures increased and she had development of a new seizure type during which she stared and was unresponsive. She was also diagnosed with cortical blindness. Metabolic studies and an MRI were normal. The infant was in hospice care and had developed increasing spasm activity the weekend prior to her death. At midnight on the day before her death, she began to bleed from the mouth and expired 2 hours later. At the time of death she was receiving a dose of 148.8 mg/kg vigabatrin and had been on this dose for 3-1/2 weeks. Autopsy findings showed the infant died from a pulmonary hemorrhage secondary to pulmonary angiomatosis. Plexuses of large abnormal muscularized vessels with focal subintimal fibrosis were present next to the right and left bronchi of the lungs, which raises the possibility of arteriovenous shunting. Left ventricular hypertrophy in the heart is additional evidence that there was an abnormal hemodynamic state.

0098/12370012 Cause of death: carcinoma
This 54 year old male with a history of seizures was diagnosed with pancreatic cancer during a vigabatrin trial. The narrative provided descriptions of the imaging and laboratory evidence supporting this diagnosis. The subject died and pancreatic cancer was listed as the cause of death.

0242/1540001 Cause of death: adenocarcinoma
This 60 year old male with a history of complex partial seizures died after approximately 22 months of vigabatrin therapy. The patient was diagnosed with adenocarcinoma of the "windpipe" and was treated with chemotherapy and radiation. Approximately three months later, he expired. No autopsy was completed. This event was considered severe in intensity and the investigator felt the causality to be not related to study drug but to the concurrent illness of adenocarcinoma. There were no concomitant AEDs at the time of the event.

0201/1621007 Cause of Death: hepatic necrosis with multisystem organ failure
This 17 year-old female had received vigabatrin 1g QD for approximately 20 months prior to hospitalization for elective intracranial monitoring prior to a possible lobectomy for intractable epilepsy. During treatment with vigabatrin, AST and ALT values decreased, but were still within normal limits, with the exception of a low ALT at the study visit prior to hospitalization.

The subject was admitted on [redacted] and had surgery the following day. Her dose of vigabatrin had been reduced to 500 mg BID for this procedure and the final dose was on the day of surgery. The evening after surgery, she was found seizing with generalized tonic clonic seizures that progressed to status epilepticus. The seizures lasted approximately 50 minutes. She was treated with phosphenytoin, phenobarbital, IV fluids and was intubated. Upon examination the patient was afebrile, hypotensive and unresponsive; broad spectrum antibiotics (including ceftazadine, clindamycin, gentamycin) were initiated as well as hemodynamic support with levophed and dopamine. Her clinical course continued to decompensate with liver enzymes escalating rapidly until her death 4 days after last vigabatin dose. Post-mortem report described the cause of death as extensive hepatic necrosis with multisystem organ failure. The investigator assessed this case as "definitely" drug related when completing the CRF, however, it was assessed as "possibly" related on the SAE Reporting Form. Concomitant medications included carbamazepine 400 mg BID (duration unknown) and Prozac (dose / duration unknown). Post mortem examination revealed extensive hepatocellular necrosis with prominent steatosis evident in the remaining viable parenchyma. Examination of the brain showed right hippocampal sclerosis, malrotation of the left hippocampus (findings consistent with old injury or a developmental abnormality), and diffuse acute ischemic injury in the cortex and brainstem. The acute ischemic injury was felt to be a consequence, not a cause, of her clinical course.

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Liver Enzymes:	AST (U/L)	ALT (U/L)	GGT (U/L)	AlkPhos (U/L)
Clinical Study:				
[redacted]	15	12	n/a	68
[redacted]	13	8	n/a	276
[redacted]	9	4 (low)	n/a	231
Hospital:				
[redacted]	67	41	103	125
[redacted]	245	86	140	150
[redacted]	4700	4609	149	183
Normal values:	(0-31)	(7-56)	(0-65)	(39-117)

Summaries of Clinical Details for the Select Serious Adverse Events Reported in the Current Submission

Rash

Subject 0101/1325-0002 This 56-year old Caucasian male with a history of non-refractory complex partial seizures since age 10, experienced a mild rash on his arms lasting 23 days, when he had been taking vigabatrin for 32 days. The rash resolved without sequelae, there was no change in study medication and the subject completed the study. The subject was also treated with carbamazepine at the time of the event. The investigator noted in the CRF that the alternative etiology was poison ivy. When asked why this event was considered an SAE, Ovation responded that the previous sponsor had flagged the event as an SAE and that they took a conservative approach to be consistent with how the previous sponsor classified the event (Submission dated 3/14/08).

Subject 0101/1335-0004 This 40-year old black female with a history of complex partial seizures since age 37, experienced moderate agitation, moderate amnesia, and a mild skin rash all lasting 173 days and mild increased appetite lasting 127 days, while randomized to vigabatrin. The subject was on study medication for 35 days prior to the onset of agitation, 81 days prior to the onset of rash, 35 days prior to the onset of amnesia, and 81 days prior to the onset of increased appetite. All of the events resolved without sequelae; however, the subject discontinued from the study due to these events. Theo-Dur was the only concurrent medication taken. In the CRF, the rash was characterized as mild and located on the subject's hands. As with the previous event, Ovation categorized this event as an SAE because the previous sponsor had flagged the event as an SAE. (Submission dated 3/14/08).

Subject 0101/1359-0007 This 21 year old Caucasian female with a history of complex partial seizures developed a rash on vigabatrin. The narrative did not characterize the rash. At the time of the event she was taking vigabatrin 1g BID. She discontinued from the trial for the rash. The rash resolved. Concomitant medications at the time of the event were carbamazepine, ibuprofen, and naproxen. Ovation noted that the CRF captured 2 events of rash in this subject but that the sequence of these events was not clear. The investigator diagnosed one rash as atopic dermatitis and described the rash as dry and scaly and moderate in intensity. Ovation was unable to characterize the second rash and provided no explanation for why rash was an SAE for this subject.

Subject 0118/1272-0002 This 12 year old Caucasian female with complex partial seizures experienced confusional state, disorientation, hallucination, headache, rash, and tremor while taking vigabatrin. Twenty-one days after receiving her first vigabatrin dose, she was hospitalized for the events listed above. She was treated with acetaminophen, morphine, naloxone, diphenhydramine, and pyridoxine. The events were reportedly resolved 4 days after stopping vigabatrin. Concomitant medications at the time of the event were phenytoin and acetaminophen.

Rash maculopapular

Subject 0101/1359-0001 This 32-year old Caucasian female with a history of complex partial seizures since age 30 reported a severe migraine headache lasting for 4 hours and a moderate macropapular rash lasting for 38 days while on vigabatrin. The subject was on study medication for 38 days prior to the migraine and 64 days prior to the rash event. Study medication was unchanged and the events resolved without sequelae. The subject did not discontinue from the study due to these events. Concurrent medications included aspirin, ibuprofen, sertraline hydrochloride, hydrocortisone cream, Ortho-Novum, Elocon cream and Temovate.

Subject 0201/1386-0002 This 14-year old female Caucasian with a history of complex partial seizures was hospitalized for increased seizure frequency. The subject was also noted to have a bilateral extremity erythematous rash with crusts and excoriation that was described as moderate intensity. The subject was discontinued from the study. The narrative provides no diagnosis for the rash and does not indicate how the rash was treated. The rash was decreased when the subject was discharged from the hospital.

Leucocytoclastic vaculitis

Subject 0223/1480-0005 This 57 year old Caucasian female with a history of simple partial seizures, complex partial seizures and partial generalized seizures experienced leukocytoclastic vasculitis and shortness of breath while

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on vigabatrin. Subject was on vigabatrin for 23 days prior to the events. On ' —— the subject noted a rash (described as bilateral petechia of the lower extremities) on the back of her legs (more severe on the left leg) which worsened the next day. Subject also complained of shortness of breath and wheezing. She took two of her husband's nitroglycerin tablets to relieve the shortness of breath. The outcome of the events was not provided but the subject was hospitalized due to the events. The physical and neurological exams were unremarkable. Lab and x-ray results were not provided. A dermatologist diagnosed leukocytoclastic vasculitis as 'commonly seen' in drug-type reactions. The intensity of the reaction was considered moderate, with a duration of four days. The event resolved. Vigabatrin was discontinued on 28Feb1996 due to the events. Medical history included renal failure, arthritis, left hip fracture 1995, hysterectomy due to carcinoma and fibroids with chemotherapy treatment, carpal tunnel syndrome of the right hand and release, poor memory and drug allergy to Feldene. Concomitant medications included Dilantin, Tegretol, Tylenol, Aleve, Didronel, aspirin, Premarin, Nitrostat and calcium carbonate.

Stevens Johnson Syndrome

Subject 0201/1398-0009 This 12 year old Caucasian male with a history of complex partial seizures was hospitalized for Stevens-Johnson Syndrome on —— after 3 months of treatment with vigabatrin in this study. The patient received his first dose of vigabatrin on 14Jan1997 in this study and his last dose on 22Apr1997. The event was considered by the investigator to be severe in intensity, and not related to study drug, but rather to a concurrent drug. Concomitant anti-epileptic medications included Tegretol and Lamictal. The patient discontinued study medication and the event was still under treatment at the conclusion of the study. Use of these medications was discontinued on 22Apr1997. Phosphenytoin was administered on 22Apr1997 through 26Apr1997. Other concomitant medications at the time of the event included Ritalin (discontinued on 22Apr1997), ibuprofen and Sulfacetamide Ophthalmologic (15Apr1997 to 19Apr1997).

Approximately 3 months after discontinuation of vigabatrin treatment, the patient was hospitalized for conjunctivitis and stomatitis (onset date of 22Jul1997) and erythema (onset date of 25Jul1997). The investigator assessed the events to be moderate in intensity and not related to study drug, and the events resolved on 29Jul1997. Concomitant anti-epileptic medications at the time of the events were Depakote and IV Depacon. Depakote 500 mg TID was taken by the patient from 25Apr1997 through 25Jul1997, and then re-initiated on 29Jul1997. Depacon 500 mg TID was administered on 25Jul1997 only. Other concomitant medications administered at the time of the events were: Ibuprofen; Benadryl (alcohol free)/Maalox 50/50 (25Jul1997 to 29Jul1997); Tylenol (25Jul1997 to 26Jul1997); acetaminophen (26Jul1997 to 29Jul1997); Lacrilube (26Jul1997 to 29Jul1997); Artificial Tears (26Jul1997 to 29Jul1997); Indocin (26Jul1997 to 10Aug1997); Sustasol (28Jul1997 to 29Jul1997); and Nubain (28Jul1997).

Prior to this current study, the patient participated in Study 0221 and received vigabatrin for 117 days.

Acute Renal Failure

Subject 0242/1504-0003 This 25 year old Caucasian male with a history of refractory epilepsy since childhood experienced acute renal failure secondary to dehydration and altered mental status changes while on vigabatrin. Subject was on vigabatrin for one year and five months prior to the events. Subject experienced two generalized seizures on 30Jan1998. On 01Feb1998 subject had flu-like symptoms. On —— he became less coherent with alteration in mental status and was hospitalized. Admission labs revealed a creatinine of 8.6 and BUN of 70. The subject had a creatinine of 1.1 in —— A renal consultant felt that the renal failure was most likely secondary to dehydration, and that the renal failure was acute tubular necrosis, secondary to decreased volume. The subject was rehydrated with large amounts of fluid and the creatinine steadily declined over the course of hospitalization. Discharge creatinine level was 1.7. Renal ultrasound and urine eosinophils were negative. Also on admission subject was noted to be extremely slow to respond to questions, although responded appropriately and was oriented. Subject was unable to perform calculations or digit span; had prominent asterixis and twitches of the eye brows, corners of the mouth and lips. Admission EEG showed generalized delta waves and multi-focal spikes. There was no EEG correlation for the myoclonic jerking. Vigabatrin was stopped and the subject showed gradual improvement of mental status. An EEG on —— showed marked improvement. Carbamazepine therapy was continued. Discharge status was good; subject was able to function independently. Hospital discharge diagnosis was acute renal failure and vigabatrin toxicity. The subject was withdrawn from the study and the events resolved on

08Feb 1998. Medical history included migraines. Concomitant medications included Tegretol, aspirin and nortriptyline.

Subject 0201/1400-0003 This 13 year old Caucasian male, 145 pounds, with a history of complex partial seizures experienced aggression, anorexia, coma, diarrhea, disseminated intravascular coagulation, encephalitis, hypoxia, lethargy, pyrexia, renal failure and abnormal visual evoked potentials, abnormal optic nerve in right eye, optic neuropathy and two episodes of visual field defect while on vigabatrin. Prior to this current study, subject participated in another vigabatrin study. For this study, subject received first dose of vigabatrin on 08Nov1996 and last dose of vigabatrin on 07Sept1998. On the subject was hospitalized in the pediatric intensive care unit for meningeal encephalitis with decreased oxygen saturation, increased creatinine, decreased platelets, lethargy, decreased mental status, decreased oral intake, diarrhea, fever and combativeness. The encephalitis was treated with ceftriaxone 2 gm BID for 6 days and acyclovir 650 mg BID for 8 days. On the subject was in a coma. While hospitalized, the subject had transient increases in blood pressure that were treated with nifedipine. The subject had unknown number of episodes of multiple loose stools of unknown etiology. Stool enteric pathogen studies were negative. The subject developed a new onset acute renal failure while hospitalized (baseline creatinine 0.8). On admission, BUN was 56 and creatinine was 2.8, which was initially thought to be secondary to dehydration/prerenal azotemia. Despite vigorous fluid rehydration, the subject urine output remained low. Urine analysis on admission revealed moderate blood. Specific gravity was 1.045 and WBCs were 8 to 10 with some cellular casts. The subject was noted to have proteinuria, which resolved. Lumbar puncture on admission revealed WBCs 209 with 74% PMNs (polymorphonuclear leukocytes), glucose 55 and protein 47.

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There was a history of the subject's intake of some hamburger meat, which in conjunction with other data raises suspicions for hemolytic uremic syndrome. The subject's renal status slowly improved and on the day of discharge, the BUN was 29 and creatinine 1.5. The subject also developed disseminated intravascular coagulation (DIC) while hospitalized. The subject was given fresh frozen plasma and had an allergic reaction with chills and hives. The allergic reaction was treated with diphenhydramine. The subject remained on vigabatrin while hospitalized and received valproic acid 1750 mg/day. The start/stop date, severity, action taken/outcome were not provided for aggression/anorexia/coma/lethargy/pyrexia. The events of diarrhea/DIC/encephalitis/hypoxia were severe in intensity, unlikely related to study drug, and resolved on The subject was discharged on The principle discharge diagnosis was meningeal encephalitis and the secondary discharge diagnoses were acute renal failure and DIC. Medical history was not provided. The investigator assessed all of the events as not related to vigabatrin, but rather due to concurrent illnesses. Concomitant medications included Topamax, Lamictal 75 mg QHS, Depakote 500 mg BID, Depakote 750 mg QHS, acetaminophen 650 mg PRN and Tofranil 25 mg QHS.

Hypersensitivity

Subject 0101/1358-0001 This 27 year old Caucasian female with a history of simple partial seizures, complex partial seizures and partial generalized seizures experienced depression, headache and hypersensitivity while on vigabatrin. Subject was on study medication for 21 days prior to onset of event of hypersensitivity. The investigator assessed the event of hypersensitivity as possibly related to study medication and moderate in intensity. The subject was discontinued due to the event and the event resolved. Study medication was reintroduced at the same dosage (1 gram BID) and the event did not reappear. Medical history included tonsillectomy 1975, lungs "underdeveloped" as a premature infant, tubal ligation 1989, occasional yeast infections, cyst removal left knee 1983, bipolar – non active, suicide attempt ten years ago.

Tongue edema

Subject 0101/1342-0006 This 34 year old Caucasian female with a history of complex partial seizures experienced tongue edema while on vigabatrin. The subject was on vigabatrin since 27Sep1995. The narrative supplied by Ovation did not mention tongue edema. In response to a request from the Division, Ovation reported that the subject experienced tongue edema that was moderate in intensity and that lasted approximately 1 week (2/20/96-2/27/96). The investigatory noted a possible alternative etiology of infection. Ovation reported that vigabatrin was continued and that the event resolved (Source 3/14/08 submission).

Adverse Events Occurring Between 0.1 % and 1 % of Vigabatrin- Treated Subjects (Overall Safety Population)

Nervous System Disorders Cognitive disorder, Dyskinesia, Complex partial seizures, Dyscalculia, Grand mal convulsion, Hypotonia, Nervous system disorder, Speech disorder, Aphasia, Drooling, Hemiparesis, Migraine, Partial seizures, Carpal tunnel syndrome, Depressed level of consciousness, Movement disorder, Postictal state, Simple partial seizures, Febrile convulsion, Hemianopia homonymous, Hypertonia, Mental impairment, Myoclonus, Neuropathy peripheral, Clumsiness, Epilepsy Reflexes abnormal, Extensor plantar response, Facial paresis, Hypokinesia, Infantile spasms, Sinus headache, Asterixis, Clonus, Neurological symptom, Sensory disturbance, Burning sensation, Cerebellar syndrome, Dysgeusia, Dysgraphia, Epileptic aura, Facial palsy, Hemiplegia transient, Hypersomnia, Hyporeflexia, Intention tremor, Myoclonic epilepsy, Psychomotor skills impaired, Restless legs syndrome, Syncope

Infections and Infestations Infection, Rhinitis, Candidiasis, Varicella, Tooth infection, Croup infectious, Fungal infection, Vaginal mycosis, Hordeolum, Respiratory syncytial virus infection, Respiratory tract infection, Roseola, Localized infection, Streptococcal infection, Bronchiolitis, Dental caries, Impetigo, Otitis media chronic, Postoperative infection, Tonsillitis, Viral upper respiratory tract infection, Conjunctivitis infective, Cystitis, Eye infection, Gastrointestinal infection, Otitis externa, Tooth abscess, Vaginal infection, Lobar pneumonia, Candida nappy rash, Herpes simplex, Infected insect bite, Tinea infection, Viral rash, Genital candidiasis, Prostate infection

Psychiatric Disorders Affect lability, Nervousness, Disorientation, Sleep disorder, Hallucination, Bradyphrenia, Crying, Depressed mood, Libido decreased, Anger, Cognitive deterioration, Dysphemia, Mood altered, Nightmare, Stress, Attention deficit/hyperactivity disorder, Dissociation, Panic attack, Personality change, Restlessness, Self injurious behavior, Conversion disorder, Hallucination auditory, Initial insomnia, Mental status changes, Middle insomnia, Psychotic disorder, Thinking abnormal, Depersonalisation, Distractibility,Hostility, Mental disorder, Paranoia

General Disorders and Administration Site Conditions Pain, Gait disturbance, Feeling abnormal, Adverse drug reaction, Influenza like illness, Malaise, Drug interaction, Swelling, Chills, Cyst, Oedema, Death, Feeling drunk, Feeling hot, General symptom, Sluggishness, Thirst

Gastrointestinal Disorders Abdominal pain, Stomach discomfort, Flatulence, Gastrooesophageal reflux disease, Gastrointestinal disorder, Abdominal distension, Toothache, Dry mouth, Mouth ulceration, Salivary hypersecretion, Abdominal discomfort, Gingival hyperplasia, Gingival hypertrophy, Gingivitis, Teething, Tooth disorder, Dysphagia, Gingival bleeding, Haematochezia, Rectal haemorrhage, Faecaloma, Frequent bowel movements, Gastritis, Gingival pain, Gingival swelling, Halitosis, Stomatitis, Tooth discolouration, Tooth loss

Injury, Poisoning and Procedural Complications Contusion, Foot fracture, Head injury, Thermal burn, Joint sprain, Drug toxicity, Excoriation, Back injury, Hand fracture, Joint injury, Road traffic accident, Ankle fracture, Laceration, Limb injury, Mouth injury, Post procedural pain, Facial bones fracture, Fracture, Joint dislocation, Lower limb fracture, Muscle strain, Rib fracture, Wrist fracture, Clavicle fracture, Face injury, Incision site complication, Ligament injury, Polytraumatism, Arthropod bite, Arthropod sting, Concussion, Post procedural complication, Animal bite, Burns second degree, Eye injury, Femur fracture, Shunt occlusion, Sunburn, Upper limb fracture, Wound

Eye Disorders Conjunctivitis, Strabismus, Visual acuity reduced, Eye pain, Blepharitis, Hypermetropia, Astigmatism, Eye irritation, Myopia, Blepharospasm, Ocular hyperaemia, Optic nerve disorder, Retinal disorder, Amblyopia, Conjunctival haemorrhage, Corneal disorder, Corneal opacity,Dry eye, Eye discharge, Eye haemorrhage, Eyelid ptosis, Keratitis, Optic disc disorder, Scotoma, Vitreous detachment, Vitreous floaters

Investigations Blood alkaline phosphatase increased, Body temperature increased, Retinogram abnormal, Anticonvulsant drug level increased, Anticonvulsant drug level decreased, Cardiac murmur, Platelet count decreased, Tandem gait test abnormal, Blood pressure increased, Gamma-glutamyltransferase increased,

Blood creatinine increased, Blood glucose increased, Alanine aminotransferase increased, Anticonvulsant drug level below therapeutic, Blood potassium decreased, Blood potassium increased, Heart rate increased, Nuclear magnetic resonance imaging abnormal, Visual evoked potentials abnormal, White blood cell count decreased

Skin and Subcutaneous Tissue Disorders Eczema, Dermatitis contact, Dry skin, Urticaria, Rash macular, Skin lesion, Hyperhidrosis, Pruritus, Rash popular, Dermatitis diaper, Ingrowing nail, Rash erythematous, Rash maculo-papular, Dermatitis, Erythema, Dermal cyst, Ecchymosis, Hypotrichosis, Increased tendency to bruise, Photosensitivity reaction, Night sweats Purpura, Rash generalized,Rash pruritic, Rosacea, Swelling face

Respiratory, Thoracic and Mediastinal Disorders Dyspnoea, Rhinorrhoea, Epistaxis, Sinus congestion, Asthma, Upper respiratory tract congestion, Wheezing, Respiratory disorder, Aspiration, Pneumonia aspiration, Bronchospasm, Respiratory tract congestion, Dysphonia, Sinus disorder, Respiratory distress, Apnoea, Productive cough, Respiratory arrest, Rhinitis allergic, Sleep apnoea syndrome

Musculoskeletal and Connective Tissue Disorders Muscle spasms, Myalgia, Muscular weakness, Neck pain, Musculoskeletal pain, Arthritis, Muscle twitching, Bursitis, Joint swelling, Musculoskeletal discomfort, Musculoskeletal stiffness, Shoulder pain, Chest wall pain, Osteoarthritis, Osteoporosis, Scoliosis, Tendonitis, Arthropathy, Exostosis, Flank pain, Limb discomfort, Pain in jaw

Metabolism and Nutrition Disorders Anorexia, Feeding disorder, Dehydration, Fluid retention, Hypercholesterolaemia, Hypoglycaemia, Hypokalaemia

Reproductive System and Breast Disorders Amenorrhoea, Menstruation irregular, Breast mass, Erectile dysfunction, Breast pain, Menstrual disorder, Endometriosis, Metrorrhagia, Ovarian cyst, Prostatitis, Benign prostatic hyperplasia, Menorrhagia

Ear and Labyrinth Disorders Tinnitus, Ear pain, Ear disorder, Vertigo, Hypoacusis, Hearing impaired, Middle ear effusion, Tympanic membrane disorder

Renal and Urinary Disorders Urinary incontinence, Proteinuria, Dysuria, Enuresis, Urinary retention, Haematuria, Pollakiuria, Nephrolithiasis, Incontinence, Renal pain

Blood and Lymphatic System Disorders Anaemia, Lymphadenopathy, Neutropenia, Iron deficiency anaemia, Leukopenia, Vascular Disorders, Hypertension, Hot flush, Orthostatic hypotension

Surgical and Medical Procedures Brain lobectomy, Cataract operation, Tooth extraction

Immune System Disorders Hypersensitivity, Seasonal allergy, Drug hypersensitivity

Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps) Skin papilloma, Uterine leiomyoma,

Cardiac Disorders Palpitations, Tachycardia, Bradycardia

Congenital, Familial and Genetic Disorders Cleft palate, Tuberous sclerosis

Endocrine Disorders Cushingoid

Pregnancy, Puerperium and Perinatal Conditions Pregnancy

Adverse Events Occurring in <0.1% of Vigabatrin-Treated Subjects (Overall Safety Population)

Nervous System Disorders Areflexia, Atonic seizures, Coma, Dizziness postural, Encephalitis, Essential tremor, Facial nerve disorder, Gait spastic, Hydrocephalus, Hyperkinesia, Hyperreflexia, Neuralgia, Sensory loss, Stupor, Temporal lobe epilepsy, Tunnel vision, Ageusia, Athetosis, Aura, Brain oedema, Cerebrosclerosis, Cerebrovascular accident, Dizziness exertional, Drop attacks, Dysaesthesia, Dysphasia, Dystonia, Encephalitis toxic, Encephalopathy, Head discomfort, Hemianopia heteronymous, Horner's syndrome, Intracranial pressure increased, Meralgia paraesthetica, Monoplegia, Muscle spasticity,Neuropathic pain, Neuropathy, Neurotoxicity, Paraesthesia oral, Paresis, Parosmia, Partial seizures with secondary generalization, Peripheral sensory neuropathy, Peroneal nerve palsy, Petit mal epilepsy, Polyneuropathy, Poor quality sleep, Post-traumatic headache, Postictal headache, Pyramidal tract syndrome, Quadriparesis,Radicular pain, Sciatica, Speech disorder developmental, Subdural hygroma, Syncope vasovagal, Tongue paralysis

Infections and Infestations Bronchitis acute, Cellulitis, Chronic sinusitis, Enterobiasis, Erythema infectiosum, Febrile infection, Fungal skin infection, Gingival infection, Herpes zoster, Infected sebaceous cyst, Kidney infection, Laryngitis, Mycetoma mycotic, Onychomycosis, Oral candidiasis, Pneumonia respiratory syncytial viral, Pneumonia viral, Respiratory tract infection viral, Skin infection, Staphylococcal infection, Tinea pedis, Viral pharyngitis, Abscess oral, Acute sinusitis, Adenovirus infection, Appendicitis, Bacteraemia, Bacterial infection, Breast abscess, Bronchitis viral, Bronchopneumonia, Cervicitis, Clostridium colitis, Conjunctivitis viral, Corneal infection, Diverticulitis, Ear lobe infection, Endocarditis, Folliculitis, Fungal rash, Gastroenteritis rotavirus, Genital infection fungal, Genitourinary chlamydia infection, Hand-foot-and-mouth disease, Herpes virus infection, Infectious mononucleosis, Infusion site infection, Kawasaki's disease, Laryngotracheitis, Lice infestation, Lower respiratory tract infection, Mastitis, Meningitis, Nail infection, Osteomyelitis, Parametritis, Pelvic inflammatory disease, Pharyngotonsillitis, Pneumococcal bacteraemia, Pneumonia streptococcal, Purulent discharge, Rash pustular, Sepsis, Tinea cruris, Tracheitis, Urinary tract infection pseudomonal, Vaginal candidiasis

Psychiatric Disorders Abnormal dreams, Apathy, Decreased activity, Delusion, Dysphoria, Eating disorder, Euphoric mood, Flat affect, Hallucination visual, Indifference, Logorrhoea, Major depression, Obsessive-compulsive disorder, Suicidal ideation, Acute stress disorder, Adjustment disorder, Affective disorder, Antisocial behaviour, Belligerence, Communication disorder, Daydreaming, Delirium, Delusional disorder persecutory type, Delusional disorder unspecified type, Depression suicidal, Depressive symptom, Disturbance in sexual arousal, Early morning awakening, Emotional disorder, Excitability, Factitious disorder, Hallucinations mixed, Hypervigilance, Inappropriate affect, Listless, Mania, Orgasm abnormal, Panic disorder, Personality disorder, Posturing, Pressure of speech, Reading disorder, Self esteem decreased, Social avoidant behaviour, Suicide attempt, Tearfulness, Tension, Tic

General Disorders and Administration Site Conditions Difficulty in walking, Face oedema, Facial pain, Feeling jittery, Gravitational oedema, Infusion site reaction, Local swelling, Localised oedema, Nodule, Secretion discharge, Abasia, Catheter related complication, Chest discomfort, Developmental delay, Discomfort, Drug intolerance, Feeling cold, Hangover, Hunger, Inflammation, Infusion site swelling, Mass, Non-cardiac chest pain, Pitting oedema, Polyp, Submandibular mass, Temperature intolerance, Tenderness, Ulcer
Gastrointestinal Disorders Abdominal pain lower, Eructation, Faecal incontinence, Gastric ulcer, Haemorrhoids, Hypoaesthesia oral, Inguinal hernia, Irritable bowel syndrome, Lip ulceration, Pancreatic mass, Tongue disorder, Tooth fracture, Tooth impacted, Abdominal distention, Abnormal faeces, Anal fissure, Anorectal disorder, Aphthous stomatitis, Cheilitis, Colitis, Colonic polyp, Defaecation urgency, Enamel anomaly, Food poisoning, Gastrointestinal haemorrhage, Gastrointestinal motility disorder, Gastrointestinal pain, Gingival disorder, Glossodynia, Hiatus hernia, Ileus paralytic, Inflammatory bowel disease, Lip pain, Oesophagitis, Oesophagitis ulcerative, Oral pain, Parotid gland enlargement, Periodontal disease, Proctitis, Pruritus ani, Rectocele, Reflux gastritis, Reflux oesophagitis, Retching, Salivary gland enlargement, Sensitivity of teeth, Swollen tongue, Tongue coated, Tongue oedema

Injury, Poisoning and Procedural Complications Accident, Accidental overdose, Fibula fracture, Heat exhaustion, Neck injury, Overdose, Periorbital haematoma, Stress fracture, Alcohol poisoning, Anaesthetic complication, Brain contusion, Cephalhaematoma, Cervical vertebral fracture, Corneal abrasion, Delayed recovery from anaesthesia, Ear injury, Epicondylitis, Feeding tube complication, Femoral neck fracture, Foreign body in eye, Headache postoperative, Hip fracture, Incorrect dose administered, Limb crushing injury, Medication error, Meniscus lesion, Near drowning, Poisoning, Postmastectomy lymphoedema syndrome, Postoperative fever, Scratch, Snake bite, Soft tissue injury, Spinal compression fracture, Subdural haematoma, Subdural haemorrhage, Surgical procedure repeated, Thoracic vertebra injury, Tongue injury, Tooth injury, Traumatic brain injury, Ulna fracture, Vaccination complication, Ventriculoperitoneal shunt malfunction, Wound complication

Eye Disorders Altered visual depth perception, Asthenopia, Blindness cortical, Cataract, Cataract nuclear, Chalazion, Eye movement disorder, Eye swelling, Eyelid disorder, Eyelid oedema, Maculopathy, Photopsia, Pupillary disorder, Retinal detachment, Vitreous disorder, Arcus lipoides, Blindness, Blindness transient, Cataract cortical, Cataract subcapsular, Chorioretinal disorder, Conjunctival cyst, Conjunctival follicles, Conjunctival hyperaemia, Conjunctivitis allergic, Erythema of eyelid, Exophthalmos, Extraocular muscle paresis, Eye inflammation, Eye pruritus, Eyelid cyst, Eyelid margin crusting, Heterophoria, Lacrimation increased, Macular degeneration, Optic atrophy, Optic neuropathy, Orbital cyst, Oscillopsia, Periorbital disorder, Photophobia, Pinguecula, Presbyopia, Punctate keratitis, Pupils unequal, Refraction disorder, Retinal naevus, Vitreous degeneration, Xerophthalmia

Investigations Blood amylase increased, Blood creatine increased, Blood glucose decreased, Blood sodium decreased, Blood urine present, Liver function test abnormal, Neutrophil count decreased, Ophthalmological examination abnormal, Positive rombergism, Tuberculin test positive, Urine analysis abnormal, White blood cells urine positive, Ammonia increased, Anticonvulsant drug level above therapeutic, Antinuclear antibody positive, Arthroscopy, Biopsy breast, Biopsy kidney, Blood albumin abnormal, Blood albumin decreased, Blood cholesterol increased, Blood corticotrophin abnormal, Blood growth hormone decreased, Blood insulin increased, Blood magnesium decreased, Bone density decreased, Colour vision tests abnormal, Corneal reflex decreased, Cystoscopy, Diagnostic procedure, Drug level increased, Electroencephalogram, Faecal occult blood, Glycosylated haemoglobin, Haematocrit decreased, Haemoglobin abnormal, Haemoglobin decreased, Heart sounds abnormal, Hepatic enzyme increased, Laboratory test abnormal, Liver palpable subcostal, Low density lipoprotein increased, Lymph node palpable, Neurological examination abnormal, Optic nerve cup/disc ratio increased, Pedal pulse absent, Pedal pulse decreased, Protein total decreased, Pupillary light reflex tests abnormal, Red blood cell count decreased, Red blood cell count increased, Respiratory rate increased, Thyroid function test abnormal, Thyroxine decreased, Vibration test abnormal, Visual tracking test abnormal, White blood cell count increased

Skin and Subcutaneous Tissue Disorders Dermatitis acneiform, Dermatitis allergic, Hirsutism,Hypohidrosis, Nail disorder, Periorbital oedema, Petechiae, Scar, Seborrhoea, Skin disorder, Skin hypopigmentation, Skin irritation, Anhidrosis, Blister, Cafe au lait spots, Dandruff, Dermatitis atopic, Fat atrophy, Hair disorder, Hair growth abnormal, Hyperkeratosis, Leukocytoclastic vasculitis, Neurodermatitis, Oily skin, Onychorrhexis, Pruritus allergic, Pruritus generalized, Rash follicular, Skin discolouration, Skin exfoliation, Skin odour abnormal, Skin tightness, Skin ulcer, Stevens-johnson syndrome, Urticaria localized

Respiratory, Thoracic and Mediastinal Disorders Hiccups, Hypoxia, Nasal septum deviation, Obstructive airways disorder, Paranasal sinus hypersecretion, Pharyngeal erythema, Pulmonary congestion, Throat irritation, Tonsillar disorder, Apnoeic attack, Choking, Crackles lung, Dyspnoea exacerbated, Grunting, Increased upper airway secretion, Laryngeal stenosis, Lower respiratory tract inflammation, Nasal discomfort, Pleural effusion, Pleurisy, Pleuritic pain, Pneumomediastinum, Pneumonitis, Postnasal drip, Pulmonary embolism, Pulmonary haemorrhage, Pulmonary oedema, Respiratory failure, Rhinitis seasonal, Rhonchi, Sputum discoloured, Stridor, Throat tightness, Tonsillar hypertrophy, Upper respiratory tract inflammation

Musculoskeletal and Connective Tissue Disorders Groin pain, Joint stiffness, Muscle atrophy, Osteopenia, Sensation of heaviness, Spinal osteoarthritis, Back disorder, Bone pain, Costochondritis, Hip deformity, Intervertebral disc disorder, Intervertebral disc protrusion, Kyphoscoliosis, Kyphosis, Lumbar spinal stenosis,

Muscle contracture, Muscle swelling, Musculoskeletal chest pain, Spinal deformity, Tendon disorder, Toe deformity, Trismus,

Metabolism and Nutrition Disorders Diet refusal, Hyperglycaemia, Oral intake reduced, Weight fluctuation, Acidosis hyperchloraemic, Diabetes mellitus non-insulin-dependent, Feeding problem in newborn, Gout, Hyperlipidaemia, Hypernatraemia, Hypomagnesaemia, Metabolic acidosis, Metabolic disorder, Obesity, Vitamin b12 deficiency

Reproductive System and Breast Disorders Breast discharge, Reproductive tract disorder, Breast swelling, Breast tenderness, Dyspareunia, Ejaculation disorder, Genital erythema, Genital pain female, Genital rash, Menometrorrhagia, Ovarian cyst ruptured, Pelvic pain, Perineal pain, Polycystic ovaries, Testicular pain, Vaginal discharge, Vaginal disorder, Vulva cyst

Ear and Labyrinth Disorders Deafness, Deafness unilateral, Tympanic membrane perforation, Cerumen impaction, Deafness bilateral, Ear haemorrhage, Hyperacusis, Tympanic membrane hyperaemia

Renal and Urinary Disorders Glomerulonephritis focal, Micturition frequency decreased, Renal failure acute, Bladder disorder, Glycosuria, Ketonuria, Kidney enlargement, Leukocyturia, Micturition disorder, Micturition urgency, Polyuria, Renal cyst, Stress incontinence, Urethral disorder, Urinary hesitation, Urinary tract disorder

Blood and Lymphatic System Disorders Lymphadenitis, Disseminated intravascular coagulation, Leukocytosis, Lymph node pain, Monocytosis, Nephrogenic anaemia, Thrombocythaemia

Vascular Disorders Circulatory collapse, Flushing, Hypotension, Pallor, Aortic stenosis, Deep vein thrombosis, Infarction, Varicose vein

Surgical and Medical Procedures Brain operation, Colon polypectomy, Fundoplication, Hospitalisation, Suture insertion, Brain tumour operation, Breast lump removal, Coronary artery bypass, Drug delivery device implantation, Endodontic procedure, Eye operation, Gastrointestinal tube insertion, Haemorrhoid operation, Mole excision, Osteotomy, Shoulder arthroplasty, Surgery Toe operation, Tooth repair, Tubal ligation, Tumor excision, Uterine operation, Vagal nerve stimulator implantation, Wisdom teeth removal

Immune System Disorders Immunisation reaction, Allergy to arthropod bite, Food allergy, Milk allergy

Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps) Benign breast neoplasm, Adenocarcinoma, Angiosarcoma, Astrocytoma, Basal cell carcinoma, Benign uterine neoplasm, Breast cancer, Fibroadenoma of breast, Glioma, Meningioma, Neoplasm, Neuroblastoma, Rhabdomyoma, Sebaceous adenoma

Cardiac Disorders Angina pectoris, Angina unstable, Atrioventricular block second degree, Cardiac failure congestive, Cardio-respiratory arrest, Cardiomegaly, Cyanosis, Myocardial infarction, Ventricular extrasystoles, Ventricular tachycardia, Wolff-parkinson-white syndrome

Congenital, Familial and Genetic Disorders Colour blindness, Congenital eye naevus, Talipes, Arteriovenous malformation, Bronchial cyst, Cryptorchism, Dermoid cyst, Epidermal naevus, Facial dysmorphism, Hip dysplasia, Phakomatosis, Porphyria non-acute, Retinitis pigmentosa, Skull malformation
Endocrine Disorders Hypothyroidism, Diabetes insipidus, Goitre, Growth hormone deficiency, Hypothalamo-pituitary disorders, Precocious puberty

Social Circumstances Corrective lens user, Educational problem, Alcohol use, Illiteracy, Sexual assault victim

Hepatobiliary Disorders Cholecystitis, Hepatomegaly, Cholelithiasis, Hepatic cyst, Hepatic failure, Hepatic necrosis

Pregnancy, Puerperium and Perinatal Conditions Abortion spontaneous, Normal delivery

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Sally Yasuda
7/9/2008 04:41:10 PM
BIOPHARMACEUTICS

Memo: Expert Opinion of VGB Neuropathology Reports

Based on my training in the anatomy, pathology and histochemistry of the brain, I feel that the lesions resulting from vigabatrin (VGB) exposure in the juvenile rat are of a qualitatively different nature from those seen in the adult. The lesions seen in the adult involve an intramyelinic edema (IME) of the white matter. In contrast, the juvenile exhibits a different pattern of pathology, either in isolation or in combination with the IME seen in the adult. The novel pattern of lesions seen in the juvenile rat appears to primarily involve the neuropil. These grey matter regions are composed primarily of the axons and dendrites of adjacent neurons and not myelinated fibers. Most of the anatomical regions reported to contain vacuolization in the initial study (#OV-1007) were consistent with regions containing primarily clusters (nuclei) of neurons, including the substantia nigra compacta, the thalamus, the hippocampus, the subiculum and the deep cerebellar nuclei. The fact that the involvement of neurons in this vacuolization was not definitively proved should also not be construed as proof that they were not involved. Thus, it would be easy to miss such neuronal degeneration by using either inappropriate histological stains or inappropriate survival intervals. For example, it is known that from a few days pre natal to about 2 weeks post natal the developing rat brain undergoes a natural burst of neuronal apoptosis. It is also known that during this critical period the administration of anesthetics, sedatives and anti-convulsants [including GABA transaminase inhibitors] result insignificantly increased neuronal apoptosis]. Therefore, one would especially want to examine the brains shortly after this critical window for evidence of increased neuronal cell death as detected by special histochemical stains [e.g. the Fluoro-Jade dyes, Capsase 3 immunocytochemistry or suppressed silver methods] for localizing neuronal degeneration. However, both studies under review used survival intervals of 1-2 months, at which time one would expect any degenerating neurons to be completely absorbed and thus be undetectable. Although a count of total surviving neurons might detect increased neuronal degeneration, such counts were not made.

Although the aforementioned study [#0V-1007] and associated pathology working group [PWG] review credibly reported a different type of vacuolization seen in various gray matter structures of the juvenile rat, it may have missed definitively identifying neuronal degeneration for the aforementioned reasons. The follow up study [#OVNC-9004], however, appears to be less credible for a number of reasons. One drawback of this study relates to the fact that only routine H&E staining was employed for all light microscopic studies. A second and major limitation of this study was the decision by the investigators to limit the scope of the study to essentially just the brainstem and midbrain. This constitutes a sampling bias by looking at only caudle white matter rich brain regions such as the tegmentum and the cerebellum. Forebrain regions should have also been examined since it is these areas that: 1) are involved in seizure generation; 2) contain a much higher ratio of gray matter/white matter; and 3) use GABA as its major inhibitory neurotransmitter [as opposed to the brainstem in which uses glycine as its major inhibitory transmitter]. A third shortcoming of this study, also found in the original study, was the lack of cases with an appropriately short survival intervals [2-3 week] as opposed to the longer 4-8 week survival intervals that were actually employed.

Should the sponsors wish to definitively resolve whether VGB can result in neuronal degeneration in the juvenile rat, the following approach is suggested:

1) Commence dosing of animals at 4 days of age.
2) Sacrifice animals at 2, 3 and 4 weeks of age.
3) Histologically stain brain tissue sections using highly specific and sensitive markers of brain pathology. Neuronal degeneration can be detected by using either Fluoro-Jade B, Fluoro-Jade C, Capsase-3 immunocytochemistry, or suppressed silver methods. Myelin pathologies can be detected by employing high resolution myelin specific stains such as Black-Gold II or myelin basic protein immunocytochemistry.
4) Count all examples of degenerating neurons and myelin lesions observed and compare this number with that seen in untreated animals of a comparable age. At the very least, all brain regions examined in the first study [#OV-1007] should be replicated, as opposed to examining only the brainstem and midbrain as was done in the second study [#OVNC-9004].

Larry C. Schmued, PhD

Division of Neurotoxicology
National Center for Toxicological Research
Food and Drug Administration

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	July 10, 2008
To:	FDA Peripheral and Central Nervous System Drugs Advisory Committee
Thru:	Gerald Dal Pan, M.D., M.H.S.
From:	OSE Sabril Risk Evaluation and Mitigation Strategy Review Team: Suzanne Berkman, Pharm.D., Acting Team Leader, Division of Risk Management (DRISK) Mary Dempsey, Risk Management Program Coordinator, DRISK Claudia Karwoski, Pharm.D., Acting Division Director, DRISK Joyce Weaver, Pharm.D., Senior Risk Management Analyst, DRISK
Subject:	Review of Risk Management Proposal
Drug Name(s):	Sabril (vigabatrin)
Application Type/Number:	20-427 (Complex Partial Seizures), 22-006 (Infantile Spasms)
Applicant/sponsor:	Ovation Pharmaceuticals

1 INTRODUCTION AND BACKGROUND

Vigabatrin is an enzyme-activated irreversible inhibitor of Gamma-aminobutyric acid (GABA)-transaminase, an enzyme responsible for the catabolism of the inhibitory neurotransmitter GABA. Vigabatrin increases GABA concentrations in the brain, thereby enhancing GABA-mediated neurotransmission. Vigabatrin has not been approved for marketing in the U.S., but applications for the treatment of infantile spasms and complex partial seizures are pending with the FDA.

Vigabatrin was first approved for marketing in 1989 in the United Kingdom, with other approvals occurring subsequently in many other jurisdictions. Currently, vigabatrin is authorized in the European Union through a Mutual Recognition Procedure. In Europe, vigabatrin is approved as second-line treatment for resistant partial epilepsies, with or without secondary generalization, and for the management of infantile spasms. In 1998, after about a decade of use in Europe, a role of vigabatrin in causing defects in peripheral vision became known. The Committee for Proprietary Medicinal Products (CPMP) recommended that marketing authorization be maintained with strengthened labeling. Prescribing is limited to neurologists and other physicians with experience in the treatment of epilepsy.

Data presented in the Sponsor's Periodic Safety Update Reports for vigabatrin indicate that the worldwide exposure to vigabatrin in commercial marketing has been about 970,000 patient-years.[1] About 975 cases of visual field defect have been spontaneously reported during commercial marketing.

The Agency has taken two previous actions on vigabatrin. The first, an approvable action for the use of vigabatrin to treat complex partial seizures, was issued in November 1997. Subsequent to this approvable action, information emerged regarding the visual adverse effects of vigabatrin. In October 1998, the Agency believed that the evidence relating to vision toxicity tipped the risk-benefit balance such that the application was not approvable. FDA requested additional information characterizing the visual effects of vigabatrin, including information addressing if a rational monitoring protocol could be expected to prevent loss of vision in patients taking vigabatrin. Based on the draft review of Dr. Ronald Farkas, there remains doubt that such a monitoring protocol is possible.

Intramyelinic edema (IME), a second serious safety issue for vigabatrin, was first noted in animal models, and subsequently was observed in infants receiving vigabatrin. A retrospective epidemiological study of patients with infantile spasms confirmed previous reports linking the use of vigabatrin with IME.

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[1] Exposure data calculated by the Sponsor for marketing through September 2007, and based on an assumption of average daily dose; data presented to NDA.

2 SUMMARY OF PROPOSED RISK MITIGATION MEASURES FOR VIGABATRIN

In December 2007 Ovation Pharmaceuticals submitted a proposed Risk Management Plan for vigabatrin for use in infantile spasms and complex partial seizures. The plan addresses the risk of vision loss associated with vigabatrin, but does not address IME.

Proposed Labeling

The proposed labeling presents the risk of vision loss in a boxed warning. The *Warnings and Precautions* section sets out the following monitoring protocols: for patients receiving vigabatrin for infantile spasms, ophthalmologic testing would be performed at baseline, every 3 months for the first 18 months of treatment, and then every 6 months thereafter; for patients receiving vigabatrin for partial complex seizures, ophthalmologic testing would be performed at baseline and then every 6 months thereafter. The method of testing is not specified.

Development of IME is included as a warning in the proposed labeling; however, the proposed labeling provides no guidance to prescribers on whether pediatric patients receiving vigabatrin should be monitored for IME. The proposed labeling states that periodic monitoring with magnetic resonance imaging (MRI) is not needed for adults receiving vigabatrin.

The sponsor also proposes a Medication Guide.

In addition, the proposed Risk Management Plan[2] comprises the following components:

Physician Attestation
To prescribe vigabatrin, prescribers must receive education about the risks of vigabatrin, and they must attest that they understand the risks and the monitoring protocol.

Product Distribution via Specialty Pharmacies
Product distribution would be accomplished via specialty pharmacies only when prescribed by prescribers who have received education and who have attested as described above.

Implementation
All prescriptions for vigabatrin must be cleared through the Share Central Call Center, the Sponsor's organizational unit that implements the program. The prescription would be processed only after the physician's education and attestation are confirmed.

Patient-Physician Agreement
The patient-physician agreement provides education regarding the risks of vigabatrin, and provides a structured approach to consider the benefits and risks of vigabatrin after a period of use. After a 12-week period of therapy the patient and physician agree to

[2] Ovation Pharmaceuticals Proposed Risk Management Plan for Vigabatrin, dated December 14, 2007; submitted to the NDA.

consider the whether the product is effective for the individual patient. This agreement is not monitored by or shared with the Sponsor or the Agency; therefore, this would be entirely voluntary.

Evaluation of Risk Mitigation Measures
The program would be evaluated based on patient/caretaker and prescriber surveys, and evaluation of data from the Specialty Pharmacies. The proposal does not explain how the Specialty Pharmacies would gather this data (e.g., compliance with monitoring of visual field).

Pharmacovigilance
The Sponsor proposes routine pharmacovigilance to monitor product safety.

3 RISK TO VISION WITH USE OF VIGABATRIN

It is not clear that the risks of vigabatrin to the vision of patients using the product can be sufficiently mitigated; that is, that the degree of visual field loss can be limited to one that is justified by the benefits of the drug. Dr. Farkas' draft ophthalmic safety review raises the following issues important to the potential to mitigate the risks of vigabatrin:

1. Onset of visual defect may occur very early in some patients, and there is no reliable evidence for a "safe" period of exposure (for example, during the 12-week effectiveness evaluation period proposed by the Sponsor in the risk mitigation protocol);
2. Loss of visual field may progress in some patients even after long periods of apparent stability in the visual field;
3. Progression to severe visual field defect may occur in a sudden, unpredictable manner, even after a long period of apparent stability in the field; given this fact, establishing a rational monitoring interval is problematic;
4. There are not uniform, highly sensitive screening tools that can ensure accurate assessment of visual field defects; the use of perimetry or electroretinography cannot ensure the early detection of mild-to-moderate damage to visual field; the electroretinogram (ERG), a test that does not require patients to be highly cooperative, is not a useful tool to detect early or mild-to-moderate visual field defects; tests that require extensive cooperation (e.g., visual field tests) can also have a learning effect, and are not suitable for many patients (e.g., the very young).
5. Visual field testing should be repeated to increase the likelihood that the test results are reliable, but repeat testing delays diagnosis of a visual field defect;
6. Monitoring of visual fields in very young or cognitively impaired children is especially challenging;
7. Visual defect might progress in some patients even after discontinuation of vigabatrin; and

8. Should patients experience a clinically significant loss of visual field with vigabatrin, a number of these patients most assuredly will be rendered blind eventually as they experience loss of central vision that occurs commonly with age, for example, with age-related macular degeneration.

4 RISK OF IME WITH USE OF VIGABATRIN

A retrospective epidemiological study of patients with infantile spasms confirmed previous reports linking the use of vigabatrin with IME. In the study, lesions consistent with IME were present in 21.5% of vigabatrin-exposed patients, compared with 4.1% in the patients who had not received vigabatrin ($p<0.001$). This study also supported previous observations that the MRI abnormalities are transient in most cases, and they are more likely to be found in infants exposed to high doses of vigabatrin (defined as 125 mg per kg of body weight per day). Evidence so far suggests that IME occurs in infants, but perhaps not in adults exposed to vigabatrin. An age presumed to be safe from the development of IME remains undefined. The clinical significance of the lesions is not clear. Dr. Philip Sheridan, the Medical Officer in the Division of Neurology Products who reviewed this issue, recommended that, should vigabatrin be approved for the treatment of infantile spasms, patients receiving vigabatrin should be followed with periodic MRIs.

5 DISCUSSION

We note that the Sponsor has not yet submitted full details of the risk mitigation proposal. However, the proposal submitted raises the following issues that should be discussed during the August 6, 2008 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee.

Considering the issues regarding product safety and visual field monitoring raised in Dr. Farkas' review, is there <u>any</u> risk mitigation strategy that could mitigate the product risks sufficiently?

Although monitoring of visual fields and prompt discontinuation of vigabatrin in patients in whom a visual field defect is found will spare some patients from further loss of vision, it is likely that visual field defect, including severe defect, will occur in some patients regardless of the monitoring regimen that is implemented. Is there a patient population for which the risk-benefit profile of vigabatrin acceptable? Is there a monitoring regimen that would render the risk-benefit profile of vigabatrin acceptable? We would appreciate advice on the specific protocol (type of testing, interval between testing, findings that would warrant discontinuation of the drug, and length of follow-up after drug discontinuation) from the Advisory Committee.

Is monitoring with periodic MRIs a workable solution to mitigate the risk of IME?

Do we fully understand the conditions under which IME develops? If not, should this issue be resolved prior to making vigabatrin available for commercial use? Is it practical to expect patients to undergo periodic MRI monitoring? We note that this might require sedation of infants (which is not without risk) who would be unable to cooperate with the study otherwise.

If vigabatrin is approved with a Risk Evaluation and Mitigation Strategy, should the strategy link monitoring of visual field and monitoring with MRIs to access to vigabatrin?

The Sponsor's proposal asks only that the prescriber understand the risks to vision. A commitment to following a monitoring protocol for vision loss or IME is not included. Furthermore, access to vigabatrin is not contingent on follow a monitoring protocol. Given the severity of the risks, this linkage between monitoring and drug access might be advisable, and should be discussed by the advisory committee.

6 CONCLUSION

The Sponsor submitted a risk mitigation proposal to mitigate the risk of loss of vision with the use of vigabatrin. The primary methods proposed to mitigate the risk of loss of vision are prescriber education and attestation of an understanding of the risks of vigabatrin, and distribution of vigabatrin through Specialty Pharmacies. The full role of the Specialty Pharmacies within the plan is not explained in the proposal. The proposal envisages that the Specialty Pharmacies will collect data on the monitoring of visual fields (the specifics of this collection are not explained), but the proposal does not link the visual field monitoring to access to the drug.

Given the issues raised in Dr. Farkas' review, we are not confident that the risks of vigabatrin can be sufficiently mitigated for patients; that is, it is not clear that the degree of visual field loss can be limited to one that is justified by the benefits of the drug. However, should such a program be attempted, we would suggest that consideration be given to linking access to vigabatrin with required safety monitoring.

Neither the proposed labeling nor the plan fully addressed the risk of IME. The clinical significance of this risk needs to be fully addressed to determine an approach to mitigate this risk. We are concerned that a monitoring protocol to mitigate the risk of IME via mandated periodic monitoring with MRI could place a large and perhaps unworkable burden on patients and their caretakers. This should be considered only if the expected benefits of vigabatrin outweigh its risks.

The details of the committee's discussion will be considered in the final design of the risk mitigation program, should one or both of the pending applications for vigabatrin be approved. We look forward to the committee's advice regarding whether periodic visual testing might sufficiently mitigate the risks to vision of vigabatrin, and, if so, what monitoring protocols might be appropriate for adults and for children. Likewise, we look forward to the committee's advice regarding whether periodic monitoring with MRIs is a workable approach to mitigate the risk of IME.

NDA 22-006: Infantile Spasms

January 8, 2009

CLINICAL REVIEW

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Reviewer Name	Philip H. Sheridan, M.D.
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Established Name	Vigabatrin
(Proposed) Trade Name	Sabril
Therapeutic Class	Antiepileptic
Applicant	Ovation
Priority Designation	P
Formulation	Powder for Oral Solution
Dosing Regimen	BID
Indication	Infantile Spasms
Intended Population	Pediatric

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Cannot be approved on basis of usual efficacy standards

Refer to Advisory Committee and consider limited distribution of vigabatrin for the treatment of infantile spasms (IS) as discussed in (1.2) of this Executive Summary.

The design and results of the three primary efficacy studies submitted in support of this application do not meet the usual Agency standards for establishing efficacy of a new drug. In addition, there are two safety concerns that are difficult to address in the IS population: retinal toxicity and MRI-signal changes. The retinal toxicity produces a permanent progressive peripheral field deficit that cannot be adequately assessed in the IS patient population and could result in total blindness. There are also vigabatrin-induced MRI signal changes occurring in about 20% of infants less than age 3 years that may correspond to the intramyelinic edema (IME) observed in the preclinical rat and dog model and which may or may not have a clinical correlation. These safety concerns make the usual consideration of the benefit to risk ratio of vigabatrin therapy problematic.

However, given the inherent difficulties of studying the efficacy and safety of vigabatrin therapy for IS and the lack of any currently approved treatment for IS, the appropriateness of approving vigabatrin for IS for limited distribution should be reviewed by an Advisory Committee.

1.2 Recommendation on Postmarketing Actions

In the event that the Advisory Committee recommends limited, controlled distribution of vigabatrin for IS patients and that the Agency would concur with this possible recommendation, consideration should be given to enrolling all treated IS patients into a registry with mandatory monitoring and reporting of adverse events and/or enrolling all treated IS patients into a large simple trial so that the use, efficacy, and safety of this therapy could be carefully assessed on an ongoing basis.

1.2.1 Risk Management Activity

The Sponsor's proposed REMS submission is pending

1.2.2 Required Phase 4 Commitments

Pending

1.2.3 Other Phase 4 Requests

Pending

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Three Phase 3 studies conducted in infants and young children with IS have been selected by the Sponsor for submission with this application in support of the efficacy of vigabatrin for the indication of IS.

The Sponsor argues that, because of the widespread belief within the medical community that vigabatrin's effectiveness has been established, it has been impractical and arguably unethical to conduct clinical studies that required actively ill children to forego treatment with vigabatrin for any extended period of time. Accordingly, the comparison phases of each of the three controlled studies were of short duration, ranging from 5 days to 4 weeks. All studies included an extended open-label phase. One of the studies was double blinded (Study W019 by Appleton), one single blinded (Study 1A by Elterman and Shields), and one open label (Study FR03 by Chiron).

Reviewer's Note:
This review will focus primarily on Studies 1A and W019 which provided the best chance of demonstrating efficacy because they were at least partially blinded and both used CCTV-EEG of the spasms (interpreted by a blinded electroencephalographer) as part of the efficacy evaluation. The third study (FR03) was open label and did not use CCTV-EEG confirmation of cessation of spasms. None of the three studies were designed specifically to support the approval of vigabatrin, and each has significant shortcomings in this regard as discussed below.

The Sponsor also summarizes the results of two uncontrolled studies (Studies 3325 and 3E01) as supporting information for NDA approval.

1.3.2 Efficacy

Study 1A Elterman and Shields:
Clinical Experience and Use of Vigabatrin (Sabril®) in Subjects with Infantile Spasms

Design of Study 1A

Study 1A was a Phase III, multicenter, outpatient, randomized, parallel group, single-blind, low-dose/high-dose study that evaluated the safety and efficacy of vigabatrin in 221 subjects younger than 2 years of age with new-onset IS. "New-onset" IS was defined as IS diagnosed 3 months or

less prior to study entry. The study originated as a compassionate use program that was reconfigured as a low-dose/high-dose study (see "Prospective Analysis Plan" below). This study allowed prior treatment with AEDs known not to have efficacy in IS as long as subjects had been on a stable dose prior to study enrollment.

Execution of Study 1A

The study was comprised of 2 phases. During the 14- to 21-day single-blind therapy phase (titration and treatment), subjects were randomized to receive either low-dose (18-36 mg/kg/day) or high-dose (100-148 mg/kg/day) vigabatrin. The caregivers were informed that subjects would be randomized to low-or high-dose but were not told what the target dosing ranges were for these two study arms.

Reviewer's Note:
Although the caregivers knew the dose in mg. being given to the infant in their care, the study was considered a single-blind study because the caregivers were blinded as to which arm of the study (low or high dose) their infant was randomized to. It is possible that the caregivers could have guessed which arm their infant was enrolled in by comparing doses with other caregivers. Also, the results of the second interim analysis were published in the journal Neurology in October 2001 with an enrollment of 179; the last subjects of the total of 221 subjects did not finish the study until April 2002. Thus, the "single-blind" was potentially breakable; this study weakness was largely remedied by the CCTV-EEG component (with blinded EEG-reader) of the primary endpoint discussed below. See also discussion below under Results: Primary Endpoint of Study 1A: Reviewer's Note: Issues in Interim Analyses.

Study drug was titrated over 7 days, followed by a constant dose for 7 days. If the subject became spasm-free on or before day 14, another 7 days of constant dose was administered. Treatment compliance was not recorded in this study.

Primary Endpoint of Study 1A

The primary efficacy endpoint was the proportion of subjects achieving spasm cessation that persisted for 7 consecutive days beginning within the first 14 days of therapy and confirmed both by caregiver assessment and by CCTV EEG monitoring within 3 days of the seventh day of spasm freedom. The CCTV EEG is an objective measure, evaluated by a blinded electroencephalographer, which increases the rigor of the primary variable.

Reviewer's Note:
The fact that the electroencephalographer interpreting the confirmatory CCTV-EEG sessions was blinded largely obviates the concern that the single-blind may have been inadvertently broken for some caregivers. However, the concern about blind-breaking is not completely eliminated since the blindly-interpreted confirmatory CCTV-EEG was only done when the caregiver reported that the spasms had ceased and since the caregivers might have suspected which arm their infant was in at the time they were deciding whether or not their infant was spasm-free. After all, it is sometimes difficult-to-impossible to determine if a particular

observed movement of an infant is a spasm or not. It is reassuring that patients deemed clinically spasm-free required CCTV-EEG confirmation, but we don't know if any of the infants not deemed to be spasm-free might have had similarly improved CCTV-EEG sessions.

Prospective Analysis Plan of Study 1A

The original study was designed as a compassionate use program. However, the Agency requested that the study be redesigned as a high/low-dose comparative study. With this modification, the study's initially approved protocol called for a minimum of 44 subjects (22 subjects in the high-dose arm and 22 subjects in the low-dose arm) to be enrolled to attain 80% power to detect a difference in the proportion of patients attaining seven consecutive days of spasm cessation within 14 to 21 days following randomization.

The sample size was subsequently increased by protocol amendment, first to a maximum of 150 subjects and later to 250 subjects. As stated in the Investigational Plan of the Study Report, **these increases in enrollment were not made with the intent of increasing the study's statistical power, but to allow additional patients to receive vigabatrin** during its development under the IND.

For the primary efficacy variable, a comparison of the two treatment groups on the proportions of subjects who become spasm-free was completed using a chi-square test. The determination of whether a subject was spasm-free took into consideration the date of last spasm as reported by the caregiver and the date the CCTV EEG was obtained, when they were available. When the date of last spasm was not available, the determination of being spasm-free was based on the response (yes/no) to the question "Is patient infantile spasm-free (by criteria)?" on the week 2 (visit 3) or the month 1 (visit 4) case report form (CRF).

Results: Primary Endpoint of Study 1A

A total of 226 subjects were enrolled in this study and 221 subjects were analyzed for efficacy (114 received low-dose vigabatrin and 107 received high-dose vigabatrin). The ages of the subjects in the efficacy population ranged from 0.1 to 1.7 years. The primary efficacy analysis of this study compared the proportions of subjects in the high- and low-dose vigabatrin treatment groups who were free of spasms determined by caregiver assessment and CCTV EEG confirmation. In the first 2-week period of the study, 11% (25/221) of the subjects were spasm-free: 16% (17/107) of the subjects in the high-dose treatment group and 7% (8/114) of subjects in the low-dose treatment group. **The Sponsor reports that the difference between treatment groups was statistically significant (Pearson chi-square test, p=0.0375).**

Reviewer's Note:
The complicated issues of the multiple nonprespecified interim analyses done during the study, of the continued enrollment of patients in excess of the originally planned number of subjects, and of the lack of a statistical analysis plan until after enrollment was completed are discussed in detail in the Statistical Review by Dr. Jingyu Luan. The following excerpts from her review indicate Dr. Luan's concerns:

Based on the primary efficacy results, it appears that there is a positive signal of treatment effect of vigabatrin for subjects with new onset infantile spasm. However, it is very difficult to make sound statistical inference due to concerns in Statistical Analysis Plan and issues in sample size increases and interim analyses.

Concerns in Statistical Analysis Plan

In the Clinical Study Report, the sponsor states that the final data analysis was in accordance with the Statistical Analysis Plan (SAP) included as Appendix 16.1.15. In the response to the Agency's request, the sponsor states that this SAP was signed-off in October 2004 and not submitted to IND 47, 707 as the IND had been placed on inactive status prior to the creation of the SAP; the sponsor also states that Dr. Roy Elterman verified for Ovation that Aventis did not develop an SAP for Study 1A, but Drs. Elterman and Shields included statistical methods in both the first and second interim Clinical Study Report that were used in efficacy analyses. However, it is not clear to this reviewer [Dr. Luan] what impact of the first and second interim analysis was on the development of this SAP (i.e., Appendix 16.1.15) and on the final analysis.

Issues in Sample Size Increases

According to the Clinical Study Report, Study 1A was initially planned as a compassionate use study to allow physicians to distribute study drug while a New Drug Application (NDA) for vigabatrin was under FDA review. According to the original efficacy assumptions, 37-40 subjects needed to be enrolled. The protocol allowed for a maximum of 60 subjects. However, the study was redesigned as a high/low-dose comparative trial and a minimum of 44 subjects were to be enrolled. Furthermore, the sponsor states that, due to a delay in the expected marketing approval, the protocol was amended to include up to 150 subjects and further amended to allow up to 250 subjects. There was no additional power analysis conducted to determine the final two increases in sample size; the adjustment was made to allow physicians to continue to administer drug while awaiting FDA approval.

It seems that the sample size for Study 1A was never fixed, and when the study was initiated, there was no pre-specified plan regarding how many subjects were to be enrolled and under what circumstance the sample size was to be increased.

Issues in Interim Analyses

According to the Clinical Study Report, three analyses were performed on the collected data. The sponsor states that the first analysis was performed in response to the FDA's request for information on pediatric use of vigabatrin to be included in the proposed package insert. A second analysis, requested by Aventis Pharmaceuticals Inc, was

performed to fulfill a request from the FDA. The results of this analysis were published in Neurology in 2001. The following table summarizes the results of the two interim analyses and final analysis by the sponsor, as well as the results for the first 40 and 44 subjects by this reviewer [Dr. Luan].

Table 12 Summary of Analyses for Study 1A

	Reviewer's Analysis		Sponsor's Analysis			
	First 40	First 44	1st Interim	2nd Interim (a)	2nd Interim (b)[2]	Final
Cut-off date	9/11/1996[1]	9/27/1996[1]	5/31/1997[4]	2/28/1999	2/28/1999	4/2/2002
No. of subjects randomized	-	-	89	179	179	227
No. of Subjects Included in Analysis	40 MITT	44 MITT	62 Efficacy Evaluable	142 Efficacy Evaluable	142 Efficacy Evaluable	221 (MITT)
Responder rate for low dose	0% (0/21)	0% (0/22)	15% (5/33)	11% (8/75)	5% (4/75)	7 % (8/114)
Responder rate for high dose	11% (2/19)	14% (3/22)	28% (8/29)	36% (24/67)	15% (10/67)	16% (17/107)
P-value[3]	0.2192	0.2326	0.349	P<0.001	P=0.0883	0.0375[5]

Source: Reviewer's Analysis and sponsor's Reports.

1: The 40th and 44th MITT subject were enrolled into the study on September 11, 1996 and September 27, 1996, respectively.

2: The number of responders were provided by the sponsor upon request (please see the paragraph below for details); this reviewer used Fisher's Exact test to generate the p-value.

3: P-values are nominal p-values;
Fisher's Exact test were used by this review to analyze the data for the first 40 and 44 subjects and the 2nd interim analysis (b), due to some small cell counts.
The sponsor used Fisher's Exact Test, Mantel Haenszel Chi-square test, and Pearson Chi-square test for the 1st interim analysis, the 2nd interim analysis (a) and the final analysis, respectively.

4: Interim analysis report indicates the cut-off date was June 30, 1997.

5: The p-value is 0.0544, based on Fisher's Exact Test.

The results for the second interim analysis (a) was excerpted from sponsor's 2nd interim analysis report dated 1 Feb 2000. However, since noticing that the number of responders for high dose group was decreased from 24 to 17 from the second interim analysis (a) to the final analysis, this reviewer [Dr. Luan] raised this question to the sponsor and the sponsor states that the definition of a responder is the same but for the final analysis the

responder definition was applied in a more conservative manner (please refer to Table 1 for details). This reviewer asked the sponsor to re-produce the results of the responder rate for the second interim analysis according to this "more conservative manner". The results are presented as 2nd Interim Analysis (b), in which the sponsor provided the number of responders by dose group and this reviewer used Fisher's Exact Test to generate the p-value.
There are three issues associated with interim analyses.

Firstly, it seems that the two interim analyses were not pre-specified and the p-value for the final analysis was not adjusted for the two interim analyses.

Secondly, the results of the second analysis were published in Neurology in October, 2001 and the last subject completed the study in April, 2002. The impact of the publication of the results of this interim analysis on the trial conduct and final analysis is unknown.

Thirdly, it is not clear whether or not any type of analysis was conducted for this study before the first interim analysis. By the time of Protocol Amendment 4 in which the sample size was increased from 44 to 150, 64 subjects had been enrolled into the study. This means, before Amendment 4, Study 1A had enrolled more subjects than the planned sample size of 44 subjects. However, it is not clear whether the sponsor conducted any type of analysis before Amendment 4 and first interim analysis. Below is sponsor's response to this reviewer's question "Before the first interim analysis, was there any type of analysis conducted on the data for Study 1A?"
Ovation conferred with Dr. Elterman and he confirmed that there was no compilation of results from the participating sites or analyses until issuance of the first interim analysis (i.e. first interim clinical study report).
From this response, it is still not clear whether the participating sites had conducted any type of analyses before the first interim analysis.

The issues raised by Dr. Luan call into question the validity of the p value of 0.0375 from the Pearson chi square test.

In summary, an ideal study would have been double-blind with daily CCTV-EEG monitoring of all infants to allow a primary endpoint based on combined clinical and EEG findings. Such a study is not very practical. Study 1A would have been closer to the ideal study if a full study protocol and statistical analysis plan had been formulated prior to starting the study and if the study had been double-blind rather than incompletely single-blind.

Other Information about the Primary Endpoint of Study 1A

In Study 1A, the primary efficacy endpoint was the proportion of subjects who were free of spasms for 7 consecutive days beginning within the first 14 days of initiation of vigabatrin

therapy. Whether a patient became spasm free clinically and remained so was determined on the basis of caregiver response to direct questioning by the investigator or monitor. However, a patient deemed clinically free of spasms could not be considered spasm free for purposes of the primary data analysis unless that finding was confirmed by EEG. Specifically, there could be no indication of spasms or hypsarrhythmia during the 8-hour recording of CCTV EEG. The recording period included at least one sleep-wake-sleep cycle and was to be performed within 3 days of the 7 day spasm-free period.

For logistical reasons, most subjects were not able to obtain CCTV EEG within the specified 3 days. As previously noted, using the prespecified 3 day time limit for CCTV EEG monitoring, 16% (17/107) of the high dose subjects and 7% (8/114) of the low dose subjects were spasm free (p=.0375). **In the Sponsor's sensitivity analysis of the primary endpoint, as the CCTV EEG monitoring date was extended beyond the 3 days specified in the primary endpoint, both the total number of responders in each treatment group and the separation between high and low dose continued to increase.** By Day 9, the response rates were 26% (28/107) and 11% percent (12/114) for high and low dose, respectively (p=0.0025). Relaxing the EEG timing criterion even further to allow confirmation at a subsequent clinic visit, rather than only within 3 to 9 days, resulted in cessation rates for the high- and low-dose treatment groups of 31% (33/107) and 13% (15/114) respectively (p=0.0014.).

Reviewer's Note:
The sensitivity analysis results (from extending the CCTV-EEG monitoring time from within the specified 3 days to either Day 9 or even longer to the next clinic visit) certainly suggest efficacy. However, the time extensions subtly change the primary endpoint (the proportion of subjects achieving spasm cessation that persisted for 7 consecutive days beginning within the first 14 days of therapy and confirmed both by caregiver assessment and by CCTV EEG monitoring within 3 days of the seventh day of spasm freedom). Also the previously discussed problems of the incomplete single-blinding, multiple interim analyses, continued enrollment over the prespecified number of subjects, and the lack of a statistical analysis plan prior to completion of enrollment remain serious shortcomings.

Results: Secondary Endpoints of Study 1A

1. In a comparison of the proportions of subjects in high-dose and low-dose treatment groups who became spasm free and remained free of spasms for the duration of the study, the response rates were significantly greater in the high-dose treatment group (68%) compared with the low-dose treatment group (52%) (p=0.0126).

2. Time to response analysis revealed a clear separation (p= 0.0016) between treatment arms beginning within a week of vigabatrin exposure.

3. Physician global assessment scores increased over time from mild to moderate improvement (p=0.0008) and by week 2, the high dose group achieved and maintained higher assessment scores than the low dose group (p=0.0285).

Reviewer's Note:
The physicians determining the global assessment scores were apparently not blinded as to which arm a given baby was randomized. This lack of blinding could introduce bias.

These secondary endpoint results also suggest efficacy but again do not fully compensate for the study's flaws as discussed above.

Subgroup analyses of Study 1A

1. A secondary efficacy analysis comparing 3 etiologic categories (cryptogenic, symptomatic-other, and symptomatic-tuberous sclerosis) was performed on the primary efficacy endpoint (proportion of subjects free of spasms by both caregiver assessment and CCTV EEG confirmation within 3 days following 7 days of spasm freedom). Response rates trended higher in the high-dose treatment group for all etiologies: symptomatic-tuberous sclerosis (high-dose, 25%; low-dose, 17%); symptomatic-other (high-dose, 13%; low-dose, 3%); and cryptogenic (high-dose, 15%; low-dose, 10%). This observed dose effect was similar among the etiology groups and was consistent with the non-significant interaction between treatment and etiology (p=0.53). The 3 IS etiology groups did not differ significantly (p=0.0736), after adjusting for the treatment factor. Twenty-one percent (8/38) of subjects in the symptomatic-tuberous sclerosis group achieved spasm-free status, 7.9% (10/126) of symptomatic-other group and 12% (7/57) of cryptogenic etiology group achieved spasm-free status.

Reviewer's Note:
These results suggest but do not establish that IS patients with tuberous sclerosis as the underlying etiology respond particularly well to vigabatrin. Such clinical impressions lead to the FR03 open label study being done exclusively with IS patients with tuberous sclerosis as the underlying etiology.

2. Baseline AED use had no effect on high- vs low-dose treatment outcomes (p=0.93), in other words, the effect of high- vs low-dose vigabatrin was maintained regardless of baseline AED use.

Conclusion of Study 1A

The short-term use of vigabatrin suggests efficacy with a dose-response in this population. The patients on the high dose appear to have fewer spasms than did patients on the low dose. There are flaws in the study when it is considered as a pivotal study for NDA approval.

Long-Term Follow-Up Data of Study 1A

Although not part of this single-blind study, long term follow-up was performed in an open label manner. In this open phase follow-up, 125 subjects were exposed to vigabatrin for at least 1 year, including 54 subjects with at least 2 years and 16 subjects with 3 years or more of exposure.

Rate and Time of Relapse:

In the next three paragraphs, each subsequent subset of the 221 infants in Study 1A (25 subjects, 48 subjects, and 171 subjects) includes the subset preceding it.

Of the 25 subjects (17/107 of high dose infants and 8/114 of low dose infants which gave the efficacy p value of 0.0375) attaining spasm-freedom according to the primary efficacy analysis (spasm-free for 7 consecutive days beginning within the first 14 days and with CCTV EEG confirmation within 3 days of the seventh day of spasm-freedom), 2/17 in the high-dose group and 2/8 in the low-dose group relapsed (p=0.5700). The mean time to relapse was 162 days (range of 53 to 270 days) in the high-dose group and 45 days (range of 31 to 58 days) in the low-dose group.

Of the 48 subjects (33/107 of high dose infants and 15/114 of low dose infants which gave the efficacy p value of 0.0014) attaining 7 consecutive days of spasm-freedom within the first 14 days with CCTV EEG confirmation by the first subsequent clinic visit (i.e., not within the 3 days specified in the primary efficacy variable), 2/33 in the high-dose group and 3/15 in the low-dose group relapsed (p=0.3070). The mean time to relapse was 162 days (range of 53 to 270 days) in the high-dose group and 46 days (range of 31 to 58 days) in the low-dose group. Of the 71 subjects attaining 7 consecutive days of spasm-freedom within the first 14 days without CCTV EEG confirmation, 5/43 (12%) in the high-dose group and 13/28 (46%) in the low-dose group relapsed (p=0.0017). The mean time to relapse was 87 days (range of 31 to 270 days) in the high-dose group and 88 days (range of 29 to 334 days) in the low-dose group.

Thirty-nine (23%) of the 171 subjects (84/107 of high dose infants and 87/114 of low dose infants) attaining 7 consecutive days of spasm-freedom (according to the caregiver but not necessarily with any CCTV EEG confirmation) anytime during the course of the single-blind study relapsed, 11/84 (13.1%) in the high dose group, 28/87 (32.2%) in the low dose group (p=0.0035). Twenty-eight (72%) of the 39 subjects who relapsed achieved subsequent spasm-free status, while 11 (28%) of the 39 subjects who relapsed did not achieve spasm-free status again. Twenty-two (79%) of the 28 subjects who achieved spasm-freedom again remained spasm-free for the remainder of their follow-up.

Among these 39 subjects who relapsed the average time from initial spasm-free status to relapse was 111 days and the median was 50 days, ranging from 14 to 605 days. Twenty subjects had their vigabatrin dose increased 1 to 625 days after their relapse. Fifteen subjects had their vigabatrin dose decreased 8 to 601 days after their relapse. Four subjects did not have sufficient dose data past the relapse date to assess any change.

The average follow-up time for all 39 subjects who relapsed was 22 months, ranging from 2-43 months. For the 28 of the 39 subjects who achieved spasm-freedom again, the follow-up time was 25 months, ranging from 6 to 43 months. Eleven of the 39 subjects who did not become spasm-free again had an average follow-up of 15 months, ranging from 2 to 35 months. The 22 of the 28 subjects who relapsed, became spasm-free again and remained spasm-free had an average follow-up time of 24 months, with a range of 6 to 36 months. Six of the 28 subjects who

relapsed, became spasm-free again but did not remain spasm-free had an average follow-up time of 29 months, with a range of 18 to 43 months.

An assessment of the change in IS therapy in the time interval between relapse and subsequent spasm-freedom indicates that, of the 6 subjects who became spasm-free after relapse, but did not remain spasm-free through follow-up:
• 4 had no additional AEDs added or any change in vigabatrin dose
• 1 received an additional AED with an increase in vigabatrin dose
• 1 received an additional AED and an increase, followed by a decrease, in vigabatrin dose

Of the 22 subjects who achieved spasm-freedom after relapse and remained spasm-free for the duration of their follow-up:
• 5 had no additional AEDs added with an increase in vigabatrin dose
• 2 had no change in AED or vigabatrin dose
• 6 received an additional AED with no change in vigabatrin dose
• 4 received an additional AED with an increase in vigabatrin dose
• 3 received an additional AED with a decrease in vigabatrin dose
• 2 received an additional AED with an increase, followed by a decrease, then an increase, then a decrease in vigabatrin dose

Reviewer Note:

It is reassuring that most subjects who became spasm-free on either high or low dose vigabatrin remained spasm-free. Most of those who relapsed became spasm-free after a vigabatrin dose adjustment and most of those remained spasm-free.

One problem in interpreting these results is that there is understandably no placebo control and that, by the natural history of IS, a cohort of infants with IS will have progressively less infants with infantile spasm over time even in the absence of therapy.

Another consideration is that we have no good data to determine if it was necessary to continue vigabatrin therapy for 1-3 years or more after spasm cessation in order to prevent spasm recurrence in most patients. This is an important consideration since the principal toxicity of concern (insidiously progressive, irreversible peripheral field defect) appears to increase in incidence and severity in proportion to the duration of therapy. Thus it would be preferable to change an infant to another type of AED after a certain number of weeks/months following vigabatrin-induced spasm cessation of this could be done without likelihood of spasm relapse. The natural history of infantile spasms and experience with ACTH as a therapy suggests that this approach has potential for decreasing retinal toxicity but the likelihood of its success has not been studied.

Quality of Study Design and Performance of Study 1A

The study was only partially single-blind since caretakers knew the dose.

Compliance with the assigned dose was not verified.

In Study 1A, the primary efficacy endpoint was defined to be the proportion of subjects free of spasms, based on caregiver assessment of 7 consecutive days beginning within the first 14 days of vigabatrin therapy and confirmed by the electrophysiological assessment--closed circuit television electroencephalogram (CCTV EEG) performed within 3 days of the end of the 7 day spasm free period. Use of this laboratory measurement was intended to add an objective evaluation technique to the clinical assessment of spasm freedom.

However, many subjects were unable to achieve the primary endpoint due to logistical reasons, namely the difficulty of obtaining access to a monitoring bed necessary for CCTV-EEG evaluation within the specified time period of 3 days. *Most subjects did obtain evaluation within the ensuing week.*

In summary, an ideal study would have been double-blind with daily CCTV-EEG monitoring of all infants to allow a primary endpoint based on combined clinical and EEG findings. Such a study is not very practical. Study 1A would have been closer to the ideal study if a full study protocol and statistical analysis plan had been formulated prior to starting the study and if the study had been double-blind rather than incompletely single-blind.

Study W019 Appleton:
A Multicenter, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Safety and Efficacy of Vigabatrin Versus Placebo as First Line Therapy for the Treatment of Newly-Diagnosed Infantile Spasms

Design of Study W019

Study W019 was a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel group, in-patient study of 40 patients. **It was designed to evaluate the safety and efficacy of vigabatrin as first-line therapy in the treatment of newly diagnosed IS and to assess the duration of response to treatment via relapse rate and time to relapse**. Subjects enrolled in this study were to be either sex, between 1 and 18 months of age, and with newly diagnosed and previously untreated IS (spasms could be associated with partial seizures). Patients could not enroll in W019 if an investigational new drug or medication deemed to be an "anticonvulsant" had been used within 2 months prior to study entry.

Execution of Study W019

The study consisted of a pre-treatment (baseline) period of 2 - 3 days followed by a 5 - day double-blind treatment phase during which subjects were treated with vigabatrin (in ascending dose to 150 mg/kg/day if required and tolerated) or placebo (according to a predetermined randomization code).

The initial dose of 50 mg/kg/day was to be maintained for a period of 24 hours. If a 100% reduction in spasms was not observed, the dose was to be increased to 100 mg/kg/day and maintained for a further 48 hours. If, after this time, it was deemed necessary to increase the dose further, then the dose could be raised to the maximum allowable dose of 150 mg/kg/day. Once a subject had been established on a dose for longer than 48 hours during the double-blind period, this dose could only be changed in response to a safety problem.

Primary Endpoint of Study W019

The primary efficacy endpoint in this study was the percent change in daily average spasm frequency (assessed by video-EEG during a pre-defined 2-hour window) from baseline, compared to the end of the double-blind treatment phase, where end of the double-blind treatment phase was defined as the final 2 days of the period. The primary endpoint was spasm count reduction, and was evaluated at the end of the 5-day double-blind treatment phase. The number of seizures occurring within in a 24-hour window by caregiver count was also assessed as an important (see below *Results: Secondary Endpoints*).

Dosing began on day 1 at 50mg/kg/day for 24 hours and if spasms were observed, the dose was increased to 100mg/kg/day for 48 hours. If spasms were again observed, the dose was increased to 150mg/kg/day. Therefore, this was a **titration-to-effect rather than a fixed dose design.**

Prospective Analysis Plan of Study W019

This study was a randomized, double-blind investigation. Assignment of subjects to study medication was randomized according to a computer-generated code. Subjects who met all the study entry criteria were allocated a subject number sequentially in order of recruitment according to the supplies provided to each site. Each treatment allocation number was associated with a treatment from the randomization code, which was prepared in blocks of 6 by a Marion Merrell Dow Ltd. statistician. Supplies were pre-packaged and numbered serially in accordance with the randomization code. No stratification procedures were used.

The data for the primary efficacy variable were summarized by frequency of categories of percentage improvement from baseline (= 0%, 1 - 39%, 40 - 69%, and =70%). A log analysis was also performed and least square means and 95% confidence intervals (CIs) calculated as estimates of the percentage of baseline spasms still present after treatment. The log analysis compared the treatment groups. These data were also analyzed by the Wilcoxon Rank Sum test and Mantel-Haenszel tests. Other efficacy data were analyzed by the Wilcoxon Rank Sum test alone.

Results: Primary Endpoint of Study W019

At the end of the double-blind phase, the randomization code was broken. Forty subjects (between 4 and 20 months of age) were enrolled. Twenty subjects received vigabatrin treatment and 20 subjects received placebo for 5 days during the double-blind phase. The primary efficacy variable was the percentage change in the average frequency of spasms as assessed from the 2-hour intensive monitoring window, from baseline to the end of the double-blind period, where the end of the double-blind period was defined as the last 2 days of that treatment period.

In an analysis of the primary endpoint, using a log analysis, least squares means (i.e., the estimates of the percentage of baseline spasms still present after treatment) (95% CIs) in the 2-hour sampling window were 45.6% (24-88%) in the vigabatrin group and 59.5% (30- 117%) in the placebo group, indicating a relative ratio benefit of vigabatrin over placebo of 0.766 (0.305-1.929). In this case, a relative ratio benefit of vigabatrin over placebo exists if this ratio is less than one. Equivalently, this means that the percentage reduction in spasms in the vigabatrin group was 54.4% (95% CIs, 12%-76%) compared with 41.5% (-17%-70%) in the placebo group. **However, this treatment difference was not statistically significant (p=0.562).**

In conclusion, using the primary endpoint, the difference in reduction of spasms between vigabatrin and placebo was not statistically significant.

Other Information about the Primary Endpoint of Study W019

Unfortunately, the sampling window of 2 hours per day for the primary endpoint was poorly chosen since 1) it provided an inadequate observation window to detect spasms and 2) it assumed constancy of spasms at the same time each day; therefore, treatment effects were less likely to be discerned.

However, since spasms were counted by the caregivers over the entire 24-hour period, it was possible to do a double blind comparison of the percent reduction in number of spasms over a 24 hour window as a secondary endpoint. (Unfortunately, this count was done by observation of the caregiver and not by continuous video-EEG monitoring). This secondary endpoint (which arguably should have been the prespecified primary endpoint) demonstrated a difference between groups which was statistically significant (p=0.030).

Efficacy - Double-blind phase

Efficacy parameter	Treatment		P value
	Vigabatrin	Placebo	
% of reduction in spasms from baseline to final two days (2-hour window)	54.4%	41.5%	0.562
% of reduction in spasms from baseline to final two days (24-hour window)	68.9%	17.0%	0.030
Patients achieving complete cessation of spasms on final day (0 or 1 spasms)	45.0%	15.0%	0.036
Patients achieving complete cessation of spasms on final day (0 spasms)	35.0%	10.0%	0.063
Patients achieving disappearance of hypsarrhythmia on final day	20.0%	5.0%	0.342
Investigator's Overall assessment - marked or moderate improvement - minimal improvement or unchanged - minimally or much worse	 80.0% 20.0% 0.0%	 15.0% 65.0% 20.0%	 <0.0001

Reviewer note:

Study W019 has a better design than Study 1A in that it is a double blind placebo control study. Unfortunately, a very short treatment period was chosen (5 days) because of concern that infants diagnosed with infantile spasms should not be untreated (if assigned to placebo) for more than about a week. Also, the number of patients in the study is quite small (only 40 although 50 had been originally planned. Finally, the endpoint is different from most studies of infantile spasms and was not the most likely endpoint to allow demonstration of efficacy. According to the study report, the 2 hour video EEG recording was done at the time of day that the caretakers reported as the time of day when spasms were most frequent for their individual infants. In retrospect, it would have been better if a similar approach to that of Study 1 A had been used: a video EEG monitoring session lengthy enough to include at least one full sleep-wake cycle.

Results: Secondary Endpoints of Study W019

In the secondary efficacy analysis of the 24-hour monitoring window, the double-blind differences between the treatment groups were much greater than for the 2-hour window. The overall percentage reduction in spasms in the vigabatrin group in this analysis was 68.9% (42%-83%) compared with 17.0% (-59%-57%) in the placebo group; this difference was statistically significant (p=0.030). This result signified that a reduction of spasms began within 3 to 4 days after treatment initiation. The investigators increased the stringency of the evaluation by determining the number of subjects who achieved a reduction in spasms to only one per day. By day 5, a significant difference was observed between groups, with 45% of the vigabatrin-treated subjects versus 15% of placebo-treated subjects achieving only one spasm per day (p=0.036).

Subgroup Analyses *of Study W019*

Analysis by etiology, age at onset of IS and EEG findings was attempted. Subject numbers in subgroups were very small and no formal statistics were able to be performed.

Conclusion of Study W019

The primary endpoint, using 2-hour windows of observation, did not demonstrate an effect of vigabatrin on spasm frequency. In retrospect, the choice of this narrow window was a serious design flaw, as noted above. Better data are obtained from the major secondary variable, in which, during the double-blind period, a substantial and significant difference was observed between the vigabatrin-treated patients and the placebo patients. The study report concludes that vigabatrin is effective and well tolerated by infants. It notes that the response is usually established within weeks of treatment initiation "thus avoiding lengthy patient exposure".

Long-Term Follow-Up Data of Study W019

Although not part of this double-blind study, long term follow-up was performed in an open label manner. Of the 40 subjects in the double blinded study, 36 subjects were followed for a period of up to 6 months, during which all subjects were treated with vigabatrin in an open-label fashion. Twenty-eight infants completed the full six month open phase follow-up. Efficacy was assessed by the frequency of spasms per week which was based on the caregivers'' account of spasms. Data collected at the end of the open-label period included physician global rating scale and psychomotor development (Denver test).

Efficacy - Open Phase

	Number of patients
Completed study	28
Completed study on vigabatrin monotherapy	15
Responder (4 week spasm free and only receiving vigabatrin)	15 (42%)
Therapeutic success (spasm free for final 12 weeks and only receiving vigabatrin)	11 (31%)
Total number of patients	36

In Study W019, following the double-blind period, subjects were followed for a period of 6 months during which time efficacy was assessed by measuring frequency of spasms per week. Outcome variables included the number of "responders", the number of "therapeutic successes", time to response and number of patients who relapsed. A "responder" was

defined as a subject on vigabatrin monotherapy who was spasm free for at least 4 consecutive weeks. A "therapeutic success" was a subject who completed the study on vigabatrin monotherapy and who was spasm free for the last 12 weeks of the study. Decreases in spasm counts of at least 70% were seen at week 24 in 22 of 25 subjects. Three of 25 had an increase in spasm count compared to baseline. Fifteen subjects (42%) of those entering the open phase were considered responders. Eleven subjects were classified as therapeutic successes on vigabatrin first-line monotherapy.

In Study W019, 3/15 subjects (20%) relapsed in the 24-week open-label phase. Two of these 3 subjects regained control, 1 subject with a dose increase of vigabatrin and the other without a dose alteration in vigabatrin or change in AED.

Reviewer Note:

These long-term results are similar to Study 1A in that about 20% of infants relapsed during an approximately 6 month follow-up period and most of these became spasm-free again with or without an adjustment of therapy. Again, this is reassuring but still leaves the question open as to whether it was necessary for the infants to remain on vigabatrin for prolonged periods of 1-2 years. Prolonged therapeutic exposure to vigabatrin appears to increase the risk of significant retinal toxicity.

Quality of Study Design and Performance of Study W019
In Study W019, the primary endpoint was spasm count reduction. It was evaluated at the end of the 8 day double-blind phase. Spasms were recorded over a 24 hour monitoring period. A predefined 2 hour window within this 24 hour period was used in the determination of the primary endpoint. The number of spasms occurring within the entire 24 hour period was also assessed. A limitation of the study design was the short length of evaluation time for the primary endpoint. A two hour window was inadequate both in ability to collect sufficient numbers of events and in the constancy of spasms from day to day. Dosing began on day 1 at 50mg/kg/day for 24 hours and if spasms were observed, the dose was increased to 100mg/kg/day for 48 hours. If spasms were again observed, the dose was increased to 150mg/kg/day. Therefore, this was a titration-to-effect rather than a fixed dose design

Study FR03 Tuberous Sclerosis Chiron
Study FR03: Open, Randomized Comparative Study of Vigabatrin versus Hydrocortisone in Infantile Spasms due to Tuberous Sclerosis

Design of Study FR03

Study FR03 was a Phase III, multicenter, **open-label,** randomized, comparative, response-mediated, 2-month cross-over study of 23 patients. It was designed to compare the efficacy and safety of vigabatrin (150 mg/kg/day without titration) and hydrocortisone (15 mg/kg/day) as first-line monotherapy in the treatment of infants with newly diagnosed IS due to tuberous

sclerosis. This study specified that infants be previously untreated for IS with any other anticonvulsant.

Execution of Study FR03

Subjects were evaluated every 2 weeks during the study. After 1 month (4 weeks) of therapy, subjects who had an incomplete response to the first treatment or had signs of intolerance crossed over to the other treatment, whereas subjects who responded (total disappearance of spasms) were not crossed over. Hydrocortisone responders were tapered off of hydrocortisone (over a 15-day period) after 1 month of treatment in order to limit steroid induced adverse effects, whereas for vigabatrin responders, a stable vigabatrin dose was maintained throughout. At the end of 2 months (8 weeks), responders to vigabatrin could be maintained on this drug on a long-term basis.

Primary Endpoint of Study FR03

The primary efficacy endpoint in this study was the proportion of infants with a total disappearance of IS. Seizure counting was conducted each day by the nurse and/or the investigator (if the subject was hospitalized) and/or by the parents (guardian) at home. Seizures were recorded in a calendar provided by the sponsor. Study duration was 2 months with an evaluation at 1 month. If the subject had incomplete efficacy (defined by less than 100% control of spasms) and/or intolerance, they were crossed over to the alternate therapy without intervening taper.

Prospective Analysis Plan of Study FR03

There was no formal statistical analysis plan for this study; all statistical methods are described in the study report text. For quantitative data, means and standard deviations were determined. Quantitative data were compared using Student's t-test for means and the F test for variance. Qualitative data were analyzed by the chi-square test with Yate's correction for small samples. Statistical significance was defined as **$p \leq 0.05$.**

Results: Primary Endpoint of Study FR03

Twenty-three subjects were enrolled in this study (11 were randomized to vigabatrin and 12 were randomized to hydrocortisone). Seven hydrocortisone subjects crossed over to vigabatrin for the second 4 weeks of the study; none of the vigabatrin subjects crossed-over to hydrocortisone. The primary efficacy analysis was based on the proportion of subjects with a total (not partial) disappearance of IS after either hydrocortisone or vigabatrin treatment. Twenty-two of the 23 subjects enrolled were included in the efficacy analyses.

A total disappearance of spasms was observed in all of the 11 subjects receiving vigabatrin first; therefore, no subjects were crossed over to the hydrocortisone group. Of the 11 subjects receiving hydrocortisone first, only 4 achieved total cessation of IS and remained on hydrocortisone. The proportions of subjects with a total response to treatment were significantly different between the 2 treatment groups (p=0.001). The other 7 hydrocortisone subjects had to be crossed over to the vigabatrin group, 6 because of lack of efficacy (i.e., incomplete control of IS) and one because of adverse events. All 7 of these latter patients achieved total disappearance of IS after receiving vigabatrin.

Other Information about the Primary Endpoint of Study FR03

None

Results: Secondary Endpoints of Study FR03

Efficacy was also assessed by 1) count of other types of seizures, 2) EEG pattern variations, 3) global efficacy assessment, and 4) psychomotor assessment using the Brunet Lézine test.

1. One subject (in the vigabatrin-first group) had other types of seizures, specifically, subclinical partial seizures; however, these seizures did not justify the prescription of concomitant antiepileptic medications.

2. Although EEG data were missing for some subjects, an improvement was observed after 8 weeks of treatment in subjects receiving vigabatrin. In the hydrocortisone first group, the influence of hydrocortisone was more difficult to evaluate since most subjects had been crossed over to the vigabatrin group (the effect of each drug separately was therefore impossible to assess). However, the 4 subjects who remained on hydrocortisone had an EEG pattern assessed as improved.

3. In the physician's global efficacy assessment, 11/11 vigabatrin subjects had seizure frequency/severity classified as markedly improved, and 9/11 had general well-being classified as markedly improved. Marked improvement in behavior was also observed for 6/11 vigabatrin subjects, and 4/11 subjects had moderate improvement in behavior. The results in the hydrocortisone group were less clear, particularly in the 4 subjects maintained with hydrocortisone; there was no apparent correlation between marked improvement in seizure frequency/severity and the lack of improvement in general well-being and/or behavior in 2 of these subjects.

4. In the assessment of psychomotor development, the evaluation of a developmental quotient (assessed with the Brunet Lézine test) was not performed for all subjects before and after treatment, precluding any statistical testing. Definitive conclusions are not possible, but there was no evidence of worsening with either treatment.

Conclusion of Study FR03

This short-term study of patients with IS, using either vigabatrin or hydrocortisone, suggests that vigabatrin is much better tolerated than hydrocortisone and shows evidence of efficacy at least equal to that of hydrocortisone.

Long-Term Follow-Up Data of Study FR03

In the open label follow-up to Study FR03, 14 subjects were treated with vigabatrin for at least 2 years. Long-term effectiveness of vigabatrin was simply assessed by the maintenance of spasm cessation. Three of 14 subjects (21%) relapsed; however, no information is available on relapse causality or any subsequent attainment of control.

Quality of Study Design and Performance of Study FR03

In Study FR03, 30 subjects were originally planned; 15 were to be treated with hydrocortisone and 15 with vigabatrin. Study enrollment closed after 23 subjects had been randomized because of evidence in the literature supporting efficacy of vigabatrin as first line monotherapy in IS and concerns regarding the safety of hydrocortisone in this indication. All treated subjects initially received vigabatrin 150mg/kg/day or hydrocortisone 15mg/kg/day.

Reviewer Note:

Because Study FR03 is an open label study, it serves as confirmatory data rather than as a pivotal study. Depending on whether one judges the hydrocortisone dose to be adequate and whether one considers oral hydrocortisone to be likely as effective as ACTH (ACTH itself not being approved for this indication at point in time), one could say that hydrocortisone was an active control or a pseudo-placebo. In either event, the vigabatrin appears superior in the TS-IS population studied in this open label population. This supports the subpopulation observation from the Elterman/Shields study that tuberous sclerosis patients appeared to respond in higher percentages than IS patients due to other etiologies.

Uncontrolled Clinical Studies

Two uncontrolled studies in subjects with IS are also submitted and are designated as follows:

Study 3325 was an open-label, single-center study designed to evaluate the safety and efficacy of vigabatrin in infants and children with drug-resistant infantile spasms. This study included infants and children with drug-resistant IS (i.e., subjects had been previously treated with other AEDs without success). The study was composed of 3 phases. During the first phase, subjects maintained a stable dose of their usual AEDs for 2 to 4 weeks to collect baseline data. During the second 3-month evaluation phase, vigabatrin was added to the usual antiepileptic medication

regimen and the dose of vigabatrin (50 to 150mg/kg/day) was optimized. During the final long-term phase, subjects who achieved >50% reduction in seizure frequency continued to receive long-term vigabatrin treatment. Efficacy endpoints included seizure frequency and severity and physician and subject overall assessment. Safety was assessed by evaluating AEs, clinical laboratory results, physical examinations (including height and weight), neurologic examinations, and ophthalmologic examinations.

A greater than 50% reduction in spasms was observed in 31/43 subjects (72%) and complete suppression was achieved in 20 subjects (46.5%) at the end of the evaluation phase. In this study, which studied vigabatrin-treated subjects with symptomatic IS (tuberous sclerosis or other), 15/16 subjects (94%) with a symptomatic etiology had a greater than 50% decrease in spasms compared with 16/27 subjects (59%) with cryptogenic IS. In 6/8 subjects (75%) with tuberous sclerosis, complete suppression of spasms was reported. The remaining 2 subjects had their spasms reduced by 80%. In comparison, subjects with cryptogenic etiology achieved complete cessation at a rate of 37.5%. Complete cessation of spasms in subjects with tuberous sclerosis was achieved within 1 month of therapy initiation.

Study 3E01 was a retrospective analysis of data that were extracted from the records of subjects diagnosed with IS who had been given vigabatrin as their initial treatment for IS. Sites in 11 different countries contributed cases. This study included only subjects who had been treated initially for IS with vigabatrin.

Data elements were extracted from original case records and recorded on standardized case report forms. Before a subject's data could be included in the analysis, his/her diagnosis of IS had to be confirmed by EEG (and video EEG, if available), magnetic resonance imaging and/or computed tomography scans, and clinical records. All source data were verified during on-site monitoring visits. All subjects identified as appropriate candidates for inclusion in the analysis were subsequently presented to a peer review committee which had to confirm their diagnosis and suitability for inclusion in the data pool. The effects of vigabatrin on IS were assessed on the basis of pre-treatment, post-treatment comparisons. Efficacy assessments included the number of spasm clusters per day, occurrence of relapse, (any reappearance or increase of spasms under vigabatrin monotherapy) and response to treatment at the final visit. Safety was assessed by evaluation of AEs and deaths; however, only AEs and deaths that occurred during or immediately related to the time of vigabatrin therapy and which were considered by prescribers as being possibly related to treatment were reported.

One-hundred thirty-one subjects (68%) were classified as having complete cessation of spasm clusters after initiation of vigabatrin. An additional 37 subjects (19.3%) were reported to have had a decrease in the frequency of clusters. Twenty-four subjects (12.5%) showed no improvement in spasm frequency and one subject (0.5%) was reported to have deteriorated following vigabatrin treatment. In this study, vigabatrin treatment was also most effective in subjects with tuberous sclerosis: 27/28 (97%) had initial total cessation of spasms. There appeared to be no difference in the response to treatment overall between other symptomatic etiologies (71.7% total response) and cryptogenic cases (69.4% total response).

Long-term follow-up for Studies 3325 and 3E01

After initially achieving spasm-free status, 33/164 subjects (20%) in the uncontrolled studies relapsed over a range of approximately 1 to 20 months. In Study 3325, 5/33 subjects (15%) relapsed. In Study 3E01, 28/131 subjects (21%) experienced relapse after complete cessation of spasms with the majority of relapses (70%) occurring within the first 3 months of seizure control and not during long-term therapy.

1.3.3 Safety

A separate review of the overall safety data of this NDA has been written by Dr. Gerard Boehm.

A separate review of the data on visual field defects has been written by Dr. Ronald Farkas.

The Assessment of Intramyelinic Edema (IME) and MRI abnormalities are discussed in this review below in section 7.1.12 Special Safety Studies

1.3.4 Dosing Regimen and Administration

Target doses selected for the three controlled studies centered on 100mg/kg, which was based upon previously conducted open-label studies. Doses of vigabatrin evaluated in the controlled studies ranged from 18mg/kg/day to 150mg/kg/day and were subject to protocol-allowed titration, especially during the long-term follow-up periods. Doses of vigabatrin in the two uncontrolled studies ranged from 20 to 400 g/day and were also subject to protocol-allowed titration. These doses were based on previous studies of vigabatrin in other seizure disorders and on results in the published literature describing use of vigabatrin in pediatric populations.

1.3.5 Drug-Drug Interactions

Drug interactions were not specifically analyzed in studies included in the IS submission.

In the original NDA 20-427 submission (April 1994), the drug-drug interaction profile was assessed with a number of medications including: clonazepam, phenytoin, carbamazepine, primidone, valproate, phenobarbital, and clorazepate, along with studies of the combination effects of vigabatrin with ethanol and oral contraceptives.

For phenytoin, a possible clinically significant interaction may occur. It was noted that vigabatrin consistently lowers plasma phenytoin levels by an average of 16% to 33%; based upon recent in vitro experiments, the mechanism of the interaction between vigabatrin and phenytoin is likely due to the induction of CYP 2C enzymes by vigabatrin in some patients. As always, dose adjustment of phenytoin or any concomitant AED should be considered if clinically indicated, and not by predetermined serum level. If for some reason the clinician feels maintenance of

serum level concentrations of phenytoin following addition of vigabatrin addition is important, then serum level measurements may be of benefit in the immediate period of vigabatrin addition.

Close clinical monitoring is necessary when any anticonvulsant medication is added to another, but given the relatively small alteration in phenytoin concentrations upon institution of vigabatrin, uniform alterations of phenytoin dose should not be recommended.

One possible drug interaction resulting in death was reported in the Safety Update submitted in the amendment to NDA 20-427 (December 2007). A 16 year-old subject in Study 0201 died due to hepatic necrosis with multisystem organ failure in the setting of status epilepticus that was classified by the investigator both as "definitely" and "possibly" related to study medication. The possibility that the cause of the hepatic necrosis was a drug interaction between vigabatrin and an unspecified medication(s) was raised. Concomitant medications noted for this subject were phosphenytoin, phenobarbital, several antibiotics, noradrenaline, dopamine, and carbamazepine. This subject had received a recent implantation of intracranial electrodes and developed anticonvulsant resistant status epilepticus. The subject then developed eventual cardiac insufficiency, with resultant multiorgan failure even though she had previously tolerated even higher doses of vigabatrin without sign of hepatic injury. In view of these data, the Sponsor does not consider that vigabatrin is directly related to this death.

1.3.6 Special Populations

As discussed above, subgroup analysis of Study 1A and the results of the open label Study FR03 suggest but do not establish that vigabatrin may be more effective in stopping spasms when the underlying etiology is tuberous sclerosis.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Vigabatrin is a specific, enzyme-activated, irreversible inhibitor of gamma aminobutyric acid (GABA)-transaminase, the enzyme catalyzing the breakdown of the inhibitory neurotransmitter, GABA. Studies have shown that oral administration of vigabatrin produces dose-related increases in central nervous system GABA concentrations in both laboratory animals and in patients.

2.2 Currently Available Treatment for Indications

There is no Agency approved treatment for infantile spasms.

The most commonly used therapies for the treatment of IS are steroids, including ACTH and prednisone in the United States (US). Hormonal therapy such as ACTH may have substantial and potentially fatal adverse effects. Other therapies have also been used to treat IS, including sodium valproate, benzodiazepines, and some newer antiepileptic drugs (AEDs). However, the efficacy of these agents has generally not been established in controlled clinical trials.

Vigabatrin was first approved in the United Kingdom in 1989 and is currently approved in more than 80 countries worldwide. Approved indications include the treatment of partial epilepsy in subjects who have not responded adequately to other antiepileptic drugs and for monotherapy in the treatment of IS. Since the time of the initial approval, the total exposure to vigabatrin has exceeded 1.5 million patients. Several studies as discussed in this review have suggested that vigabatrin is effective in the treatment of IS, especially in patients with an etiology of tuberous sclerosis (TS).

2.3 Availability of Proposed Active Ingredient in the United States

See CMC review.

2.4 Important Issues with Pharmacologically Related Products

Not applicable.

2.5 Presubmission Regulatory Activity

Vigabatrin was first approved in the United Kingdom in 1989 and is currently approved in over 50 countries worldwide. Vigabatrin has not been removed from any market due to safety reasons. Approved indications include monotherapy for the treatment of IS, and adjunctive treatment of partial epilepsy in subjects who have not responded adequately to other antiepileptic drugs.

An approvable letter for the indication of adjunct therapy for complex partial seizures in adults was issued by the Agency to the then U.S. sponsor Hoechst Marion Roussel on November 26, 1997 for the indication of adjunct therapy for complex partial seizures. However, the subsequent reports of associated insidiously progressive peripheral visual field deficits VFD led the FDA to issue a not approvable letter on October 27, 1998.

Authorities in Europe kept the drug on the market and, after obtaining new clinical data, restricted it to adjunctive therapy for refractory partial seizures and as monotherapy for infantile spasms (IS). Aventis Pharmaceutials acquired the North American rights to vigabatrin, and subsequently Ovation acquired the North American rights to vigabatrin in early 2004.

A pre-NDA meeting was held between Ovation (the current sponsor) and the Agency on December 1, 2004 to discuss an NDA submission for vigabatrin sachet as monotherapy in the treatment of IS. As part of the submission, the Agency had several requests:

- A formal evaluation of bioequivalence of the tablet and sachet;
- A toxicity study in juvenile rats evaluating the effect of vigabatrin on the brain, reproduction and mating;
- Primary data/study reports from the key studies (Studies 1a, W019, and FR03 as discussed in this review) that support the application.

The Agency also encouraged submission of test results to determine visual function of pediatric subjects exposed to vigabatrin during infancy.

In December 2005, an amendment to the CPS NDA 20-427 was submitted, but was judged by the FDA to be an incomplete response to their action letter of 1998. The Sponsor responded to this notification by re-submitting the CPS amendment on March 2, 2007.

On March 9, 2007, the Sponsor submitted NDA 22-006 for the indication of infantile spasms.

The FDA response to these March 2007 submissions was an incomplete response to their 1998 action letter for CPS and a refusal to file for IS. The primary concern expressed by the Agency was the then-recent reports of MRI changes in 3 infants treated with vigabatrin for IS and the possible relationship to the prior findings of IME in animals.

A Type A meeting was held with the Agency on 06 June 2007 to discuss the recent findings of MRI abnormalities in children with Infantile Spasms being treated with vigabatrin. The June 6, 2007 Type A meeting is discussed in this review below in section 7.1.12 Special Safety Studies

2.6 Other Relevant Background Information

According to exposure estimates presented in the Postmarketing Safety Update Report, the number of subjects exposed to vigabatrin from mid-1997 through 2004 is estimated at 890,000 patients with a total exposure, since initial approval, of greater than 1.5 million patients.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Not applicable.

3.2 Animal Pharmacology/Toxicology

See discussion below of intramyelinic edema in 7.1.12 Special Safety Studies: Background/

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Three Phase 3 studies conducted in infants with IS have been selected by the Sponsor for submission in support of the efficacy of vigabatrin for the indication of IS.

4.2 Tables of Clinical Studies

Table 1. Description of Clinical Efficacy Studies - Controlled Studies

Study ID	Number of Study Centers (Locations)	Study Start Enrollment Status (Date) Total Enrollment	Design Control Type	Study and Control Drugs Dose, Route, Regimen	Study Objective	# Subjects by Arm Entered / # Analyzed	Duration	Gender M/F Median age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
1A	9 (US)	1996/ Complete (2002): 226	Multicenter, randomized single-blind with OL, dose-ranging, long-term follow-up	High-dose VGB (100-148mg/kg/d) Low-dose VGB (18-36 mg/kg/d) Oral High or low-dose VGB for 14-21 d, followed by flexible dosing up to 3 yrs	To evaluate safety and efficacy of VGB in subjects younger than 2 yrs of age with new-onset IS	High-dose 108/107 Low-dose 114/114	14-21 d, with long-term follow-up of up to 3 yrs	High-dose 45 M / 61 F 0.6 yrs (0.1-1.7 yrs) Low-dose 63 M / 50 F 0.6 yrs (0.1-1.7 yrs)	M or F, age <2 yrs, diagnosis of IS for ≤3 mos, weight ≥3.5kg, no prior treatment	Proportion of subjects free of spasms for 7 consecutive days after 14 days of VGB based on CCTV EEG within 3 d of end of 7-d period during which caregiver deemed subject to be spasm-free

Table 1. Description of Clinical Efficacy Studies - Controlled Studies

Study ID	Number of Study Centers (Locations)	Study Start Enrollment Status (Date) Total Enrollment	Design Control Type	Study and Control Drugs Dose, Route, Regimen	Study Objective	# Subjects by Arm Entered / # Analyzed	Duration	Gender M/F Median age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
W019	9 (Europe, UK, Canada)	1994 Complete (1996) 40	Multicenter, randomized DB placebo-controlled, parallel-group with OL follow-up period	VGB at initial dose of 50mg/kg/d with titration allowed to 150mg/kg/d for 5 d, followed by 6 mos of OL VGB Placebo for 5d, followed by 6 mos of OL VGB Oral	(Primary) To determine the safety and efficacy of VGB, as compared to placebo, as the initial mono-therapy in children with newly diagnosed and previously untreated IS (Secondary) To provide information on the duration of response to treatment by assessing both relapse rate and time to relapse	VGB 20/20 DB phase) 16/12 (OL phase) Placebo 20/20 (DB phase) 20/16 (OL phase: subjects received VGB)	Baseline period, 2-3 d DB period, 5 d OL follow-up, 6 mos	VGB 8 M / 12 F 7 mos (5-20 mos) Placebo 11 M / 9 F 8 mos (4-17 mos)	M or F, age 1-18 mos: newly diagnosed IS with no prior treatment	Average percent change in daily spasm frequency from baseline to end of DB period.

Table 1. Description of Clinical Efficacy Studies - Controlled Studies

Study ID	Number of Study Centers (Locations)	Study Start Enrollment Status (Date) Total Enrollment	Design Control Type	Study and Control Drugs Dose, Route, Regimen	Study Objective	# Subjects by Arm Entered / # Analyzed	Duration	Gender M/F Median age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
FR03	11 (France)	1990 Complete (1994) 23	Multicenter, randomized OL, comparative, response-mediated cross-over	VGB 150 mg/kg/d for 4 weeks (if no response, then cross-over to hydro-cortisone for 4 weeks) Hydro-cortisone 15 mg/kg/d for 4 wks (if no response, then cross-over to VGB for 4 wks) Long-term follow-up optional for both groups Oral	To comparatively assess the efficacy and safety of VGB versus hydro-cortisone in infants with TS (Bourneville's disease) and suffering from newly diagnosed and untreated IS	VGB 11/11 (No subjects crossed-over to receive hydro-cortisone) Hydro-cortisone 12/11 (7 subjects crossed-over to receive VGB)	2-mos randomized period (No specific dosing data are available for the follow-up period, but some subjects were followed for ≥2 yrs)	VGB 5 M / 6 F 6.6 +/- 1.7 mos (mean) (no range given) Hydro-cortisone 6 M / 6 F 8.4 +/- 4.6 mos (mean) (no range given) Mean age at treatment initiation for total population: 7.5 +/- 3.6 mos (50-507d)	M or F, age 1 mos to ≤2 yrs confirmed diagnosis of TS (Bourneville's disease), new onset of IS with no prior treatment	Proportion of subjects with total (not partial) disappearance of IS

CCTV EEG = closed-circuit television electroencephalograph; d = day; DB = double-blind; F = female; IS = infantile spasms; M = male; mos = months; OL = open-label; TS = tuberous sclerosis; UK = United Kingdom; US = United States; VBG = Vigabatrin; wks = weeks; yrs = years

4.3 Review Strategy

Review of individual study reports for the three controlled studies, the publications from these studies, the clinical summary, and the submitted integrated summary of efficacy

4.4 Data Quality and Integrity

None of the three pivotal studies submitted were designed to support the approval of an NDA. As discussed in detail in sections 1 and 6 of this review, there are significant flaws in the design and/or execution of these studies.

4.5 Compliance with Good Clinical Practices

Adequate compliance with Good Clinical Practices.

4.6 Financial Disclosures

The Sponsor indicates that Studies W019 and FR03 were completed prior to February 2, 1999, the effective date of 21 CFR Part 54 requiring a Financial Disclosure certification. The Sponsor indicates that the only investigator with financial information to disclose is Dr. Elterman and that the other investigators of Study 1A have no financial information to disclose. Dr. Elterman states that he is an officer of a not-for-profit Texas corporation (The Pediatric Epilepsy Research

Foundation) that may receive royalty payments from the Sponsor based upon sales from vigabatrin. He further states that as a researcher he would be eligible for funding from this not-for-profit corporation. In the opinion of this reviewer, Dr. Elterman's status is not significantly likely to introduce bias into the results of Study 1A.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

See Clinical Pharmacology review.

5.2 Pharmacodynamics

See Clinical Pharmacology review.

5.3 Exposure-Response Relationships

See Clinical Pharmacology review.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The effectiveness of vigabatrin in the treatment of IS is supported in this application by the 3 controlled studies (Studies 1A, W019, and FR03). In addition, and provided as supporting data, are 2 uncontrolled studies (Studies 3325 and 3E01) and other controlled and uncontrolled studies from the literature.

These studies used one of the 2 available formulations—tablet or sachet. Given the increased ease of use in the intended population, the Sponsor is seeking approval of the sachet formulation for IS based on the results of all studies. The tablet and sachet formulations are bioequivalent.

6.1.1 Methods

In the 3 controlled studies (Studies 1A, W019, and FR03), a total of 275 subjects received vigabatrin and were evaluable for efficacy. These subjects were all younger than 2 years of age (at the time of study enrollment) and of either sex. All the controlled studies excluded subjects who had been previously treated with drugs known to have efficacy in the treatment of spasms.

Initiation doses of vigabatrin evaluated in these studies ranged from 18 to 150mg/kg/day, were subject to protocol-allowed titration, and were increased to a maximum dose of 369.5mg/kg/day in the long-term follow-up periods.

6.1.2 General Discussion of Endpoints

All 3 controlled studies assessed the effect of vigabatrin therapy on cessation of spasms, either based on clinical evaluations or on clinical evaluations plus video EEG. Secondary endpoints included:

- Time to response (with "response" generally defined as cessation of all spasms and/or a sustained spasm-free period)
- Outcome of subjects during long-term follow-up
- Frequency of spasm clusters
- Physician global assessment of vigabatrin efficacy
- Psychomotor development

Subgroup analyses included age at onset of IS, use of AEDs at baseline, duration of IS, and disease etiology (symptomatic or cryptogenic).

6.1.3 Study Design

Study 1A –

In this high/low-dose comparator study of 221 subjects, high-dose vigabatrin (target of 100 to 148mg/kg/day) was compared to low-dose vigabatrin (target of 18 to 36mg/kg/day).

The primary efficacy endpoint was the proportion of subjects achieving spasm cessation for 7 consecutive days beginning within the first 14 days of therapy and confirmed via closed-circuit television (CCTV) EEG monitoring within 3 days of the seventh day of spasm freedom.

In the high-dose group, 17/107 (16%) of subjects had complete cessation of spasms compared with 8/114 (7%) of subjects in the low-dose group (p=0.0375). Importantly, spasm cessation required verification by CCTV EEG within 3 days of the seventh day of spasm freedom. For logistical reasons, most subjects were not able to obtain CCTV EEG within the specified 3 days. In sensitivity analysis of the primary endpoint, as the CCTV EEG monitoring date was extended beyond 3 days, both the total number of responders in each treatment group and the separation between high and low dose continued to increase. By day 9, the response rates were 26% and 11% for high and low dose, respectively (p=0.0025). Relaxing the EEG timing criterion to allow confirmation at a subsequent clinic visit, rather than only within 3 days, resulted in cessation rates for the high- and low-dose treatment groups of 31% and 13% respectively (p=0.0014.)

Multiple secondary analyses were performed in Study 1A. In a comparison of the proportions of subjects in high-dose and low-dose treatment groups who became spasm-free significantly greater in the high-dose treatment group (68%) compared with the low-dose treatment group (52%) (p=0.0126). Time-to-response analysis revealed a clear separation (p=0.0016) between treatment arms beginning within a week of vigabatrin exposure. The median time to spasm cessation was 6 weeks in the high-dose treatment group and 13 weeks in the low-dose treatment group.

Subgroup analyses were also performed in Study 1A. In the comparison of the proportion of subjects classified by etiology who were spasm-free for 7 consecutive days and remained spasm-free for the duration of the study period, the response rates of the 3 IS etiology groups differed significantly (p=0.0031), but in each etiology subgroup a greater spasm cessation rate was seen with high dose vigabatrin compared to the low dose vigabatrin (p=0.53). Baseline AED use had no effect on high- vs low-dose treatment outcomes (p=0.93), in other words the effect of high- vs low-dose vigabatrin was maintained regardless of baseline AED use. In addition, use of concomitant AEDs after day 14 had no effect on response rates when examining percent of subjects who were spasm-free for 7 consecutive days and remained spasm-free through the duration of the trial. Lastly, physician global assessments increased from mild to moderate improvement over a 3-month period (p=0.008) and the high-dose group had significantly higher scores than the low dose group overall (p=0.0285).

Study W019 –

This controlled study used a placebo control and defined the primary efficacy endpoint as the average percent change in spasm frequency over a 2-hour sampling window each day to the final 2 days of the double-blind period. The difference in reduction of spasms between vigabatrin and placebo was not statistically significant 54.4% vs 41.5% (p=0.562). Unfortunately the sampling window of 2 hours per day was poorly chosen since 1) it provided an inadequate observation window to detect spasms and 2) it assumed constancy of spasms at the same time each day; therefore treatment effects could not be properly discerned. However, when a more clinically appropriate and more rigorous measure of spasm frequency over 24 hours was used, also in the double-blind phase of the study, the percent reduction in spasms in the vigabatrin group was 68.9% compared with 17.0% in the placebo group. This difference was statistically significant (p=0.030). An additional secondary endpoint was complete spasm cessation as defined by having 0 or 1 spasms which achieved a significant difference 45% vs 15 % (p=0.036). vigabatrin elicited a greater reduction in the duration of clusters than placebo at the end of the double-blind phase (p=0.023). Lastly, investigator overall assessment of efficacy in the double-blind phase showed a highly significant difference between groups (p=0.001).

In general, subjects treated with placebo or hydrocortisone who did not respond to these treatments ultimately achieved cessation of spasms after switching to vigabatrin. In the controlled studies, the time to response with vigabatrin was short, generally occurring within the first 2 to 4 weeks of therapy. In evaluations of vigabatrin efficacy during long-term follow-up phases of the studies (ranging from 3 months to >2 years), spasm-free status was maintained for the majority of subjects; a small number of subjects experienced relapse of spasms, which

generally occurred approximately 1 to 5 months after initial achievement of spasm-free status. In Study 1A, most subjects who relapsed became spasm-free again (28/39). In those subjects, spasm-freedom was attained with vigabatrin dose adjustments and/or with the addition of other AEDs.

Study FR03 –

In this study using an active control (hydrocortisone), the primary efficacy endpoint was the proportion of subjects in each group with a total disappearance of spasms. Results showed that 100% of vigabatrin -treated subjects vs 36% of hydrocortisone-treated subjects achieved spasm control and/or cessation (p=0.001). Subjects could be crossed over to the other treatment group after 1 month in the case of inefficacy or intolerance to the first treatment. None of the subjects who initially received vigabatrin crossed over. Seven of the hydrocortisone treated subjects crossed over to vigabatrin because of intolerance (1) or lack of control (6), and all 7 achieved complete spasm cessation with vigabatrin. The mean time to response with vigabatrin treatment was 4.0 ± 5.1 days vs 12.8 ± 11.9 days with hydrocortisone treatment. This comparison slightly missed statistical significance (p=0.058). Taking into account all subjects who received vigabatrin as first or second-line treatment, mean time to spasm control was statistically significantly different (p=0.01) at 3.48 ± 4.08 days vs 12.8 ± 11.9 days. The predefined secondary endpoint of EEG pattern variation following treatment disclosed an improvement after 8 weeks of treatment in nearly all subjects receiving vigabatrin. Other secondary endpoints of well-being, behavior, and psychomotor development disclosed marked improvements in association with vigabatrin treatment.

Uncontrolled Studies

In the 2 uncontrolled studies, spasm cessation was assessed in 2 different manners (spasms and spasm clusters). In Study 3325, complete cessation of spasms was achieved in 47% (20/43) of subjects in the evaluation phase and 67% (22/33) of subjects in the long term phase. In Study 3E01 complete cessation of spasm clusters was observed for 68% (131/192) of subjects. The incidence of relapse on vigabatrin was 21% in Study 3E01 and 15% in Study 3325. Long-term treatment with vigabatrin (ranging from 3 months to >2 years) resulted in continued spasm control for the majority of treated subjects.

6.1.4 Efficacy Findings

Primary Efficacy Endpoint(s)

The primary and secondary efficacy results across the 3 controlled clinical studies are discussed and compared in the subsections below.

The Sponsor's Table 15 provides an overall summary of the efficacy results from these studies.

Table 15. Results of Efficacy - Controlled Studies

Study	Treatment Arm/Dose	Number Analyzed	Primary Endpoint	Key Secondary Endpoints	Long-term Follow-Up
1A	High-dose VGB 100-148 mg/kg/d	107	Proportion of subjects free of spasms by caregiver assessment and CCTV EEG confirmation within 3 days of 7 days of clinical spasm-freedom: 16% for high-dose VGB group versus 7% for low-dose VGB, p=0.0375.	Proportion of subjects free of spasms for 7 consecutive days and remained spasm-free: 68.2% for the high-dose group vs 51.8% for the low-dose group; p=0.0126.	Follow-up ranged from 2 wks to 3 yrs. 171 subjects became spasm-free. 59 relapsed (high dose 11 and 28 low). 28 became spasm-free again and remained spasm-free
	Low-dose VGB 18-36 mg/kg/d	114	Sensitivity analysis of demonstrated increasing separation between high- and low-dose as CCTV EEG confirmation window expanded (N=28 high and N=12 low p=0.0025).	Proportion of subjects in 3 IS etiology groups free of spasms for 7 consecutive days and remained spasm-free: 74% of symptomatic-TS, 50% of symptomatic-other and 72% of cryptogenic; p=0.0031.	
W019	VGB 50-150mg/kg/d	20 (DB phase) 12 (OL phase)	Percentage reduction in average frequency of spasms (assessed during 2-h monitoring window) from baseline to end of DB period: 54.4% for VGB, 41.5% for placebo; p=0.562.	Percentage reduction in average frequency of spasms (assessed during 24-h monitoring window) from baseline to end of DB period: 68.9% for VGB, 17.0% for placebo; p=0.030. Improvement in mental development based on Denver testing in 7 of 25 subjects and no worsening in any subjects.	Follow-up was up to 6 mos. 22/25 demonstrated decrease of at least 70% in spasm count with VGB treatment by Week 24 compared to baseline
	Placebo	20 (DB phase) 16 (OL phase)			

Table 15. Results of Efficacy - Controlled Studies

Study	Treatment Arm/Dose	Number Analyzed	Primary Endpoint	Key Secondary Endpoints	Long-term Follow-Up
FR03	VGB 150mg/kg/d	11 (first 4 wks) 14[a] (long-term)	Proportion of subjects with total disappearance of IS on VGB 11/11 vs hydrocortisone 4/11; p=0.001. Time to response, 4.0±5.1 days versus hydrocortisone 12.8±11.9; p=0.058. Seven subjects from initial hydrocortisone group crossed over to VGB: all 7 had total disappearance of IS after receiving VGB. No VGB subjects crossed over to hydrocortisone.	Improvement in EEG, physician's global assessment, and psychomotor development was observed for subjects treated with VGB. Statistically significant differences in improvement were seen in general well-being (11/11 VGB versus 5/11 hydrocortisone, p=0.0124) and behavior (10/10 VGB versus 4/11 hydrocortisone, p=0.0039). There was also a trend favoring VGB in seizure-frequency severity scores (11/11 VGB versus 7/11 hydrocortisone, p=0.0902).	Follow-up was >2 years. Long-term VGB: 3/14 relapsed; 11/14 had partial seizures.
	Hydrocortisone 15mg/kg/d	11 (first 4 wks) 4 (long-term)	Proportion of subjects with total disappearance of IS: 4/11. Time to response, 12.8±11.9 days.		Long-term hydrocortisone: 0/4 relapsed; 3/4 had partial seizures.

[a] Includes 5 subjects who initially received hydrocortisone in the first 4 weeks and crossed over to receive VGB for the second 4 weeks.

CCTV = closed-circuit television; d = day; DB = double-blind; EEG = electroencephalograph; h = hour; IS = infantile spasms; OL = open-label; VBG = Vigabatrin; wks = weeks.

The primary efficacy endpoints of the 3 controlled studies were as follows

• **Study 1A** - The proportion of subjects who were free of spasms for 7 consecutive days beginning within the first 14 days of vigabatrin therapy. Subjects considered spasm-free must have remained free of spasms according to caregiver response to direct questioning regarding spasm frequency, and had no indication of spasms or hypsarrhythmia during 8 hours of CCTV EEG recording that included at least 1 sleep-wake-sleep cycle that was performed within 3 days of the 7-day spasm-free period.

• **Study W019** - The average percent change in daily spasm frequency, assessed during a predefined 2-hour window, from baseline to the end of the double-blind study period, where end of the double-blind study period was defined as the final 2 days of the period.

• **Study FR03** - The proportion of subjects with a total disappearance of IS.

The primary endpoints for Study 1A and Study FR03 were similar in that they were based on the proportion of subjects free of spasms, whereas the endpoint for Study W019 was based on change in spasm frequency. However, a secondary endpoint for Study W019 was based on cessation of spasms. The results for all 3 studies on proportion of subjects achieving spasm-free status are shown in Sponsor's Table 16.

Table 16. Proportion of Subjects in Controlled Studies Achieving Spasm-free Status

Study Number Dose Groups	Percent of Subjects Spasm-free n/N (%)	Time Frame of Spasm Cessation Evaluation	*p*-value
1A			
High-dose VGB	17/107 (16)	First 2 weeks of study	0.0375[a]
Low-dose VGB	8/114 (7)		
W019			
VGB	7/20 (35)	Final day of double-blind	0.063[b]
Placebo	2/20 (10)	period (5-8 days)	
FR03			
VGB	11/11 (100)	End of first 4 weeks	0.001[c]
Hydrocortisone	4/11 (36)	of study	

[a] *p*-value based on chi-square test.
[b] *p*-value based on Mantel-Haenszel test.
[c] *p*-value based on chi-square test with Yates's correction for small samples.

The Sponsor argues that all 3 studies indicate that vigabatrin was successful in eliminating spasms. Variable percentages of cessation were obtained in the 3 studies, due to design or ascertainment differences.

Study 1A - In this largest study, 16% of high-dose and 7% of low-dose vigabatrin groups achieved spasm-free status within the first 2 weeks by clinical and CCTV EEG confirmation. The primary efficacy endpoint required spasm freedom within 2 weeks as ascertained by the caregiver, and an 8-hour CCTV EEG confirmation within 3 days of spasm cessation. Even in the advanced epilepsy centers which performed this study it was not possible to attain this standard due to inadequate numbers of video EEG beds and other logistical issues, so investigators obtained video EEGs as close to the 3 days as possible. Relaxing the EEG timing criterion to allow confirmation at a subsequent clinic visit, rather than only within 3 days, resulted in cessation rates for the high- and low-dose treatment groups of 31% (33/107) and 13% (15/114), respectively (Chi-Square test, Chi Square [1] = 10.2, p=0.0014.)

To further explore the sensitivity of cessation rates to timing of the video EEG, analyses were performed for a variety of EEG visit windows. As the visit window broadened not only did the

total number of responders increase but also the separation in cessation rates between groups increased. At all times the difference between high and low-dose groups was statistically significantly different.

Study W019 - The analysis of the primary efficacy endpoint (change in spasm frequency) using the specified 2-hour monitoring window showed that overall percentage reduction in spasms in the vigabatrin group was 54.4% compared with 41.5% in the placebo group. This treatment difference was not statistically significant (p=0.562). The short observation window was the significant limitation of this approach given the presence of both large variations in the total number of spasms and variations in the distribution of the spasms throughout the day. Additionally, another limitation was the evaluation time point early in the course of therapy (8 days). In the secondary efficacy analysis of spasm frequency using a 24-hour monitoring window, also in the double-blind phase of the study, the differences between the treatment groups were much greater than for the 2-hour window. The overall percentage reduction in spasms in the vigabatrin group in this analysis was 68.9% compared with 17.0% in the placebo group; this difference was statistically significant (p=0.030).

Study FR03 - Response was defined as total disappearance of IS after one month of treatment. All subjects who received vigabatrin in this study were responders (i.e., the 11 who received vigabatrin first plus 7 who received vigabatrin after crossing over from hydrocortisone therapy). Four subjects who were initially randomized to hydrocortisone were responders on that therapy.

Secondary Efficacy Endpoint(s)

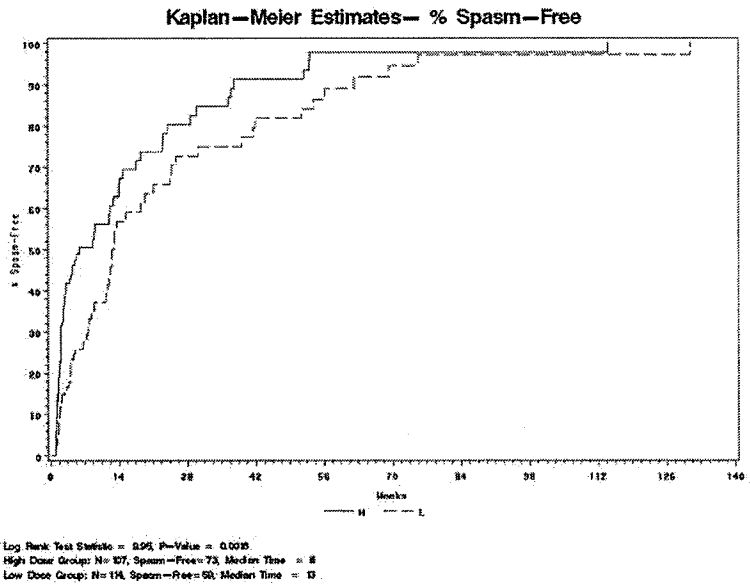
The results of secondary efficacy analyses of endpoints similar in 2 or more of the controlled studies are summarized in the following subsections.

Time to Response

All 3 controlled studies examined time to response, which was generally defined as cessation of all spasms and/or a sustained spasm-free period. Overall, the time to response with vigabatrin was short and generally occurred within the first 2 to 4 weeks of therapy.

Study 1A - The first secondary response analysis was defined as spasm cessation for 7 consecutive days during the study period with and without video EEG confirmation; this was examined with respect to 2 endpoints: remaining spasm-free and achieving spasm-freedom regardless of subsequent maintenance. For the first endpoint, there was a clear separation between the high- and low-dose vigabatrin groups in the Kaplan-Meier curves (p=0.0016), showing a greater response in the high-dose group Figure 4. The separation of curves is evident beginning at 2 weeks of vigabatrin exposure. The high-dose subjects attained median spasm-freedom by 6 weeks, which was 7 weeks before the low-dose group.

Figure 4. Kaplan-Meier Curves Comparing Treatment Groups on Time to Spasm Cessation for 7 Consecutive Days and Remained Spasm-free During Study Period via Secondary Criteria



Study W019 - Secondary efficacy parameters included percent reduction of spasms and percent complete cessation of spasms, and were measured from baseline to final 2 days or final day, in other words a day to day analysis was not performed therefore time to response was not able to be determined. Subgroup analysis of the double blind period revealed that 35% of subjects attained complete cessation of spasms within 5 days which was not statistically significant compared to placebo (10%). There was a statistically significant reduction in spasms by day 4 to 5 (68.9% versus 17% p=0.030) indicating that reduction of spasms was beginning within 3 to 4 days after initiation of vigabatrin. The investigators attempted to capture this by examining reduction of spasm to 1 per day by day 5 (45% versus 15% p=0.036). In the subgroup analysis of the open label phase, response was defined as a spasm-free period of continuous 4 weeks or more on monotherapy. Fifteen of 36 subjects responded; of these, 9 of 15 (60%) did so within 2 weeks of the initiation of treatment. The mean (SD) time to response was 1.5 (1.1) weeks (range, 0 to 4 weeks). Therapeutic success, defined as the complete absence of spasms in the final 12 weeks of the open-label phase in subjects taking no other antispasm medication, was also assessed. Eleven subjects could be classified as therapeutic successes with vigabatrin as first-line monotherapy. Time to response for therapeutic successes was the same as that for all responders (i.e., mean of 1.5 weeks). Taken in sum by several measures (percent reduction or complete cessation), efficacy was attained in days to weeks.

Study FR03 - The analysis based on the groups initially receiving vigabatrin first (N=11) and hydrocortisone first (N=11) showed a total cessation of spasms of 4.0±5.1 days for vigabatrin (all 11 patients responding) and 12.8±11.9 days for hydrocortisone (in the 4/11 patients responding) (p=0.058). Seven of the subjects who initially received hydrocortisone during the first 4 weeks of

the study were crossed over to receive vigabatrin the second 4 weeks. When these subjects were combined with the 11 subjects who received vigabatrin first, the total number of subjects achieving total cessation of spasms on vigabatrin therapy was 18, compared with 4 subjects in the hydrocortisone group. The overall mean (± SD) time to cessation of spasms was 3.48±4.08 days in first or second line treatment with vigabatrin.

Long-term Follow-up

Relapse rates were similar between the controlled (23%) and uncontrolled studies (20%), despite variations in study designs and protocol-defined endpoints. Based on these data, approximately 20% of patients in clinical practice would be expected to relapse, most of whom should be expected to regain control of spasms.

All 3 controlled studies employed a long-term follow-up period during which subjects could receive open-label vigabatrin. Among other variables, recurrence of seizures other than IS, use of concomitant AEDs, and/or relapse on vigabatrin therapy were assessed. (These variables are discussed separately in the following sections.)

Study 1A - Once the initial 14-day evaluation period was completed, and after a possible additional 7-day fixed dose segment if spasm-freedom was attained, the subject could enter a flexible dosing period of at least 2 weeks up to 3 years. Dosing could be adjusted up or down at investigator's discretion, but the dose could not be altered by more than 25 to 50mg/kg/day. During this flexible dosing period, the mean dose of vigabatrin was 144 and 127mg/kg/day for the high and low-dose groups, respectively. Over the duration of the entire study, subjects received an average of 138.7 ± 46.2mg/kg/day and 121.5 ± 65.9mg/kg/day in the high- and low-dose groups, respectively. The distribution of duration of exposure to vigabatrin is illustrated in Table 17.

Table 17. Distribution of Dosing Duration – Study 1A

	High-dose N=107	Low-dose N=114
Mean (SD) (mg/kg/day)	138.7 (46.2)	121.5 (65.9)
Range	38-338	18-364
Median	131	119
Distribution of dosing duration:	n(%)	n(%)
1 week or more	106 (99.1)	114 (100.0)
2 weeks or more	105 (98.1)	114 (100.0)
3 weeks or more	105 (98.1)	113 (99.1)
1 month or more	100 (93.5)	113 (99.1)
2 months or more	90 (84.1)	106 (93.0)
3 months or more	84 (78.5)	96 (84.2)
6 months or more	75 (70.1)	86 (75.4)
9 months or more	72 (67.3)	81 (71.1)
12 months or more	58 (54.2)	67 (58.8)
15 months or more	42 (39.3)	53 (46.5)
18 months or more	35 (32.7)	47 (41.2)
21 months or more	27 (25.2)	37 (32.5)
24 months or more	22 (20.6)	32 (28.1)
27 months or more	12 (11.2)	27 (23.7)
30 months or more	10 (9.4)	24 (21.1)
33 months or more	7 (6.5)	15 (13.2)
36 months or more	5 (4.7)	11 (9.7)
39 months or more	3 (2.8)	6 (5.3)
42 months or more	0 (0.0)	2 (1.8)
45 months or more	0 (0.0)	1 (0.9)
48 months or more	0 (0.0)	1 (0.9)
51 months or more	0 (0.0)	1 (0.9)
54 months or more	0 (0.0)	1 (0.9)
57 months or more	0 (0.0)	0 (0.0)

SD = standard deviation

Subjects with an Up-titrated Dose

Table 18 shows the response rates for subjects whose dose was increased after 14 days of vigabatrin therapy (i.e., responders as defined by the secondary efficacy criteria, allowing relapse). When vigabatrin dosage was increased, slightly more subjects in the high-dose group (38%) compared to the low-dose group (34%) were responders. Slightly more subjects in the low-dose group (11.3%) compared to the high-dose group (9.5%) were not responders when vigabatrin dosage was increased. The same percentage of subjects in both groups (high-dose, 1%; low-dose, 1%) who did not receive increased vigabatrin dosage was non-responders. The

titration range in the high-dose group of responders (N=84) was 54 to 207mg/kg/day; in the low-dose group of responders (N=74) the range was 32 to 158mg/kg/day.

Table 18. Up-titrated Dose (Responder vs Non-Responder) – Study 1A

Randomization Dose	Was the Subject's Dose Uptitrated?	Was the Subject a Responder?[a]	Subjects n (%)
High	No	No	2 (0.9)
High	Yes	No	21 (9.5)
High	Yes	Yes	84 (38.0)
Low	No	No	2 (0.9)
Low	No	Yes	13 (5.9)
Low	Yes	No	25 (11.3)
Low	Yes	Yes	74 (33.5)

[a] to that dose increase

Use of other AEDs and effect on spasm cessation rates

Table 19 shows the frequencies of post-baseline AED use ever reported for a subject. In both the high- and low-dose treatment groups, phenobarbital had the highest frequency of use post-baseline (in 46 (43%) high-dose and 35 (31%) low-dose subjects). The second most prevalent AED prescribed in the high-dose group was clonazepam, noted in 21 (20%) subjects. The second most prevalent AED prescribed in the low-dose group was topiramate, noted in 23 (20%) subjects.

Table 19. Post Baseline AED Usage - Study 1A

Post-Baseline AED Usage		
AED	High-dose N=107	Low-dose N=114
adrenocorticotropic hormone	10 (9.3)	15 (13.2)
benzodiazepine	0 (0.0)	1 (0.9)
carbamazepine	17 (15.9)	15 (13.2)
clonazepam	21 (19.6)	19 (16.7)
clorazepate	3 (2.8)	1 (0.9)
diazepam	7 (6.5)	4 (3.5)
fosphenytion	0 (0.0)	1 (0.9)
gabapentin	1 (0.9)	0 (0.0)
lamotrigine	11 (10.3)	16 (14.0)
levetiracetam	0 (0.0)	1 (0.9)
lorazepam	8 (7.5)	8 (7.0)
magnesium chloride	0 (0.0)	1 (0.9)
methylprednisolone	1 (0.9)	2 (1.8)
midazolam	1 (0.9)	1 (0.9)
oxcarbazepine	1 (0.9)	1 (0.9)
pentobarbital	0 (0.0)	1 (0.9)
phenobarbital	46 (43.0)	35 (30.7)
phenytoin	6 (5.6)	6 (5.3)
prednisolone	1 (0.9)	3 (2.6)
prelone	1 (0.9)	2 (1.8)
primidone	1 (0.9)	1 (0.9)
pyridoxine	8 (7.5)	9 (7.9)
tiagabine hydrochloride	1 (0.9)	0 (0.0)
topiramate	18 (16.8)	23 (20.2)
valproic acid	10 (9.3)	10 (8.8)
zonisamide	2 (1.9)	3 (2.6)

The relationship between vigabatrin dose and use of AEDs in the flexible dosing period was also examined. (These analyses did not adjust for use of other AEDs at baseline.) One hundred and 7 subjects received AEDs after 14 days and prior to 3 months: 49 subjects in the high-dose group, 5 subjects in the low-dose group and 53 subjects in the low to high-dose group. (The low to high-dose category comprises those subjects who were randomized to the low- during the initial 14 days.) Subjects who received other AEDs after the initial 14 days had the following cessation rates:

High dose:	69% cessation (34/49)
Low dose:	40% cessation (2/5)
Low-to-high dose:	53% cessation (28/53)

Subjects who did not receive other AEDs after the initial 14 days had the following cessation rates:

High dose:	67% cessation (39/58)
Low dose:	86% cessation (12/14)
Low-to-high dose:	40% cessation (17/42)

The use of other AEDs did not seem to interact with dosing categories in their effects on spasm cessation, that is, persistent spasm-freedom was not influenced by the presence of other AEDs. It is important to note that in the flexible-dosing period, these vigabatrin dose categories, rather than predicting cessation, are determined by the subject's cessation status and the investigators' decisions to modify dose. For example, the cessation rates in the low-dose category, either with or without other AEDs, generally reflect the investigators' decisions not to increase vigabatrin dose in those subjects whose spasms were controlled on the low dose.

Study W019 –
In Study W019, there was 6-month open-label observation period with visits at 4, 8, 16, and 24 weeks. Twenty-five of 36 subjects who entered the open-label phase had spasm data at week 24. Of these 25 subjects, 22 demonstrated a decrease in their spasm count of at least 70% compared with baseline as measured by weekly counts. The remaining 3 subjects all had an increased spasm count compared with baseline; these 3 subjects had all received vigabatrin plus other antispasm medication during the study. A total of 15 subjects were classified as responders to vigabatrin (defined as at least 4 weeks of spasm freedom), which represents 38% of all subjects and 42% of those entering the open phase. Of the 15 responders, only 1 was classified as having hypsarrhythmia at the end of the study due to the absence of a follow-up EEG. Eleven of the 36 were considered therapeutic successes, defined as no spasms in the last 12 weeks of the open-label period and on vigabatrin monotherapy. The percentages of subjects (N=36) with improvement in the open-label period investigator's assessment of spasms were 65% (marked improvement), 12% (moderate improvement), and 6% (minimal improvement). Seventy-six percent of subjects (26/36) were considered by the investigator to have benefited from their treatment as either vigabatrin monotherapy or in combination with other AEDs. For the investigator's assessment of seizures other than spasms during the open-label period, the percentage of subjects (N=36) marked "not applicable" (meaning this percentage of subjects had no other seizures during the open-label follow-up) was 69% (22/36); the remaining subjects were classified as having marked improvement (9%), moderate improvement (3%), minimal improvement (6%), no change (9%), or worsened (3%).

Study FR03 –
In Study FR03, only subjects who were followed for at least 2 years (14/18 vigabatrin subjects and 4/4 hydrocortisone subjects) were included in the analysis of data from the long-term follow-up. Mean duration of follow-up was 2.41 years in the vigabatrin group and 2.13 years in the hydrocortisone group. The occurrence of partial seizures was reported for 11/14 vigabatrin subjects and for 3/4 hydrocortisone subjects during the follow-up period. These seizures generally occurred within the first 6 months following the end of the initial study. Following the occurrence of partial seizures, concomitant antiepileptic therapy had to be initiated in most subjects (carbamazepine, clobazam, and/or stiripentol). Monotherapy was maintained in 3/14 vigabatrin subjects and in 1/4 hydrocortisone subjects.

Relapse

All 3 controlled studies reported data on "relapse," which was generally defined as return of spasms after achievement of spasm-free status. Overall, the number of subjects with relapse was very small during the long-term follow-up periods of these studies [39/171 subjects (22.8%) in Study 1A, 3/15 subjects (20.0%) in Study W019, and 3/14 subjects (21.4%) in Study FR03]. In subjects who did relapse, most re-achieved spasm-free after vigabatrin dose adjustments and/or with concomitant AEDs. Relapse occurred at a range of approximately 1 to 20 months after initial achievement of spasm-free status. Other factors possibly impacting relapse (concomitant medication or extrinsic seizure precipitants, e.g., infections or fever) were not reported.

Study 1A - Of the 25 subjects attaining spasm-freedom according to the primary efficacy analysis (spasm-free for 7 consecutive days beginning within the first 14 days and with CCTV EEG confirmation within 3 days of the seventh day of spasm-freedom), 2/17 in the high-dose group and 2/8 in the low-dose group relapsed. The mean time to relapse was 162 days (range of 53 to 270 days) in the high-dose group and 45 days (range of 31 to 58 days) in the low-dose group.

Of the 48 subjects attaining 7 consecutive days of spasm-freedom within the first 14 days with CCTV EEG confirmation at any time (i.e., not within the 3 days specified in the primary efficacy variable), 2/33 in the high-dose group and 3/15 in the low-dose group relapsed. The mean time to relapse was 162 days (range of 53 to 270 days) in the high-dose group and 46 days (range of 31 to 58 days) in the low-dose group.

Of the 71 subjects attaining 7 consecutive days of spasm-freedom within the first 14 days with or without CCTV EEG confirmation, 5/43 (12%) in the high-dose group and 13/28 (46%) in the low-dose group relapsed. The mean time to relapse was 87 days (range of 31 to 270 days) in the high-dose group and 88 days (range of 29 to 334 days) in the low-dose group.

Thirty-nine (23%) of the 171 subjects who became spasm-free for 7 consecutive days during the course of the study, with or without CCTV EEG confirmation, relapsed, 11/84 (13.1%) in the high dose group, 28/87 (32.2%) in the low dose group. Twenty-eight (72%) of the 39 subjects who relapsed obtained subsequent spasm-free status while 11 (28%) who were in the high-dose

group. Twenty-two (79%) of the 28 subjects who achieved spasm-freedom again remained spasm-free for the remainder of their follow-up.

Among subjects who relapsed the average time from initial spasm-free status to relapse was 111 days and the median was 50 days, ranging from 14 to 605 days. Twenty subjects had their vigabatrin dose increased 1 to 625 days after their relapse. Fifteen subjects had their vigabatrin dose decreased 8 to 601 days after their relapse. Four subjects did not have sufficient dose data past the relapse date to assess any change.

Study W019 - There was 6-month open-label observation period with visits at 4, 8, 16, and 24 weeks. Relapse was evaluated at 24 weeks. A total of 15 subjects were classified as responders to vigabatrin during the open-label period (with "responder" defined as a spasm-free period of 4 weeks or more). Of these 15 subjects, 3 relapsed and were not considered therapeutic successes (defined as the complete absence of spasms in the final 12 weeks of the open-label phase in subjects taking no other anti-spasm medication).

Study FR03 – This study had a cross-over design, with subjects not attaining spasm control being placed in the alternate therapy. Eighteen subjects who were followed for at least 2 years were included in a long-term assessment. The vigabatrin group included 9 subjects who attained spasm-freedom with vigabatrin as their initial treatment and 5 subjects who had to be crossed over to vigabatrin after hydrocortisone inefficacy. The hydrocortisone group included 4 subjects who were being maintained on this drug. Relapse was observed in 3 of the 14 subjects who received vigabatrin as either their first therapy or after being crossed over to vigabatrin after failure on hydrocortisone. Relapse occurred after a mean period of control of spasms of 3.7 months (range, 3 to 5 months). No relapse was reported in the 4 hydrocortisone subjects who responded to steroids as the first drug. Statistical analyses were not performed owing to the small sample size of the hydrocortisone group and no information regarding the clinical course of these subjects was provided.

Spasm Cluster Frequency

Spasm cluster frequency was evaluated in Study 1A and in Study W019. Both studies showed a decrease in spasm cluster frequency in subjects treated with vigabatrin.

Study 1A –
The median number of spasm clusters per day decreased from baseline at each visit through month 3 in both groups, with the median count lower in the high-dose group compared with the low-dose group at each visit. The mean numbers of clusters also show a decrease and are both larger and more variable than the median numbers, due to large counts observed in a small number of subjects. At baseline, approximately 50% of subjects in both high- and low-dose groups were having zero to 5 seizures per day; more than 30% in both groups were having 5-10 seizures per day. By week 2 the median numbers of clusters had decreased by half in the high-dose group, versus an approximate 25% reduction in the low-dose group. By 1 month, median clusters in the high-dose group had decreased to 0.5 and by month 2, to zero, while at each of these times the low-dose group had improved but far less than the high-dose group, however this

difference was not statistically significant (p=0.6425). Table 20 summarizes the distributions of clusters per day from baseline to month 3.

Table 20. Distributions of Clusters per Day - Study 1A

Visit	Dose	Mean Clusters	SD	Median Clusters
Baseline	High-dose	5.6	7	3.5
	Low-dose	5.8	7.2	3.6
Week 2	High-dose	6.8	31.7	1.6
	Low-dose	6.6	15.6	2.4
Month 1	High-dose	3	7.4	0.5
	Low-dose	3.9	8.8	1.5
Month 2	High-dose	2.8	12.1	0
	Low-dose	3	7	0.5
Month 3	High-dose	3.4	18.4	0
	Low-dose	1.6	5.3	0

SD = standard deviation

Study W019 - The results of the analyses on spasm clusters (frequency and duration) were similar to those of overall spasm frequency (primary efficacy variable) in that no statistically significant differences between the vigabatrin and placebo groups were observed for the 2-hour monitoring window for either cluster frequency or duration. For the 24-hour window, 13 (65%) of subjects in the vigabatrin group achieved 40% or greater reduction in cluster frequency compared with 8 (42%) subjects in the placebo group (p=0.068). In the analysis of the duration of clusters, no difference was found at the 2 hour window between the 2 treatment groups. The reduction in duration of clusters over a 24-hour period was greater in vigabatrin treated subjects than placebo. More vigabatrin subjects achieved a 70% or greater reduction in cluster duration than placebo and more placebo subjects had no reduction or increase in cluster duration (p=0.023). This reduction in clusters is shown in Table 21.

Table 21. Percentage Change in Average Duration of Clusters (over Final 2 Days) - Double-Blind Phase (Intent-to-Treat) - Study W019

	Placebo		VGB		Total		*p*-Value
% Improvement	**n**	**%**	**n**	**%**	**n**	**%**	
2 hour							
Missing	4		6		10		
>=70	9	56	8	57	17	57	
40-69	0	0	2	14	2	7	
1-39	1	6	1	7	2	7	
<=0	6	38	3	21	9	30	
Total	20	100	20	100	40	100	1.000
24 hour							
Missing	2		1		3		
>=70	4	22	8	42	12	32	
40-69	2	11	5	26	7	19	
1-39	3	17	3	16	6	16	
<=0	9	50	3	16	12	32	
Total	20	100	20	100	40	100	0.023

Electroencephalography

All 3 controlled studies generally required hypsarrhythmia or modified hypsarrhythmia as an entry criterion then used subsequent EEG recordings as part of their evaluation of vigabatrin efficacy. Overall, in those receiving vigabatrin, EEG assessments documented the elimination of hypsarrhythmia, the electrographic characteristic of IS. Furthermore EEGs also confirmed the elimination of hypsarrhythmia more quickly in the higher dose regimens.

Study 1A - Investigators noted that attainment of CCTV EEGs within the protocol-mandated 3-day window was, at times, impossible for a variety of reasons- the low numbers of available video monitoring beds, transportation or other family issues and a range of other barriers. Standard clinical practice does not entail CCTV EEG monitoring, and if performed, it is usually in cases of non-response to verify diagnosis. Routine EEG or EEG with the addition of sleep phase is usual standard of care to confirm clinical observation of efficacy, if confirmation is required. Thus, analysis was performed to determine efficacy outcomes with various sensitivities. Relaxing the EEG timing criterion to allow confirmation at a subsequent clinic visit, rather than only within 3 days, resulted in cessation rates for the high-and low-dose treatment groups of 31% (33/107) and 13% (15/114), respectively (.2 test, .2 [1] = 10.2, p=0.0014.)

To further explore the sensitivity of cessation rates to timing of the video EEG, analyses were performed for a variety of EEG visit windows. As the visit window broadened not only did the total number of responders increase but also the separation in cessation rates between groups increased. This responder analysis is presented in Table 22.

Table 22. Responder Analysis - Sensitivity to EEG Visit Windows - Study 1A

	Responders			
EEG visit window[a]	High-dose n	Low-dose n	Total # of Responders	χ^2 test p-Value
0,3[b]	17	8	25	0.0375
0,4	20	8	28	0.0091
0,5	22	9	31	0.0067
0,6	22	11	33	0.0229
0,7	25	12	37	0.0106
0,8	26	12	38	0.0067
0,9	28	12	40	0.0025
0,10	28	12	40	0.0025
-1,3	18	8	26	0.0238
-1,4	21	8	29	0.0055
-1,5	23	9	32	0.0041
-1,6	23	11	34	0.0147
-1,7	26	12	38	0.0067
-1,8	27	12	39	0.0042
-1,9	29	12	41	0.0015
-1,10	29	12	41	0.0015
-2,3	19	8	27	0.0148
-2,4	22	8	30	0.0033
-2,5	24	9	33	0.0024
-2,6	24	11	35	0.0093
-2,7	27	12	39	0.0042
-2,8	28	12	40	0.0025
-2,9	30	12	42	0.0009
No visit window	33	15	48	0.0014

[a] The values of the visit window are relative to the day 7 of the 7-day spasm-free period. Negative values correspond to visits occurring before the end of the period. For example, -1,3 represents the window from 1 day before to 3 days after last day of the end of the 7-day spasm-free period.
[b] The 0,3 window is that of the primary endpoint definition.

Study W019 - An EEG was performed at baseline and at the end of the double-blind and open-label phases to detect the proportion of subjects demonstrating hypsarrhythmia. The EEG was to be of long duration and was to include a period of sleep. At the end of the double-blind phase (Day 8), the majority of subjects in both treatment groups had hypsarrhythmia still evident: 19/20 (95%) placebo subjects and 16/20 (80%) vigabatrin subjects; this difference between treatment groups was not statistically significant (p=0.342). The main endpoint of the open-label phase was response as defined by spasm-free period of 4 weeks or more. Fifteen of 36 subjects who completed the open phase responded with 4 or more weeks of spasm-freedom and 14 of those had no hypsarrhythmias on EEG. The fifteenth subject did not have an EEG performed at the end of the study. At the end of the open-label phase, subjects were classified as having therapeutic success when a complete absence of spasms was noted during the final 12 weeks of the study on vigabatrin monotherapy. Eleven of 36 subjects had a therapeutic success and while 1 subject again had missing EEG data, the remaining 10 had no hypsarrhythmia. Thus by either criteria of efficacy, "response" or "therapeutic success," absence of hypsarrhythmia corresponded with elimination of spasms.

Study FR03 – An EEG was obtained at baseline and after 8 weeks of treatment. In the subjects treated initially with vigabatrin, 3 of 11 had hypsarrhythmia present before treatment and in all 3, hypsarrhythmia and spasm cessation occurred following 8 weeks of treatment. In the hydrocortisone group, the influence of hydrocortisone was more difficult to evaluate since most subjects (7/11) crossed over to the vigabatrin group after the initial 4 weeks of treatment; the effect of each drug taken separately was therefore impossible to assess.

All 3 studies reinforced the importance of EEG assessment and demonstrated that clinical spasm-freedom corresponded to absence of hypsarrhythmia. Stated differently, EEG assessment is important in the determination of response and elimination of hypsarrhythmia corresponds with complete response.

Physician Unblinded Global Assessment

All 3 controlled studies employed some type of physician unblinded global assessment of efficacy. In general, most subjects treated with vigabatrin had favorable physician global assessment results.

Study 1A - Mean unblinded physician global assessment scores increased from "mild improvement" to "moderate improvement" over a 3-month period (p=0.0008). The high-dose group had significantly higher scores than the low-dose group over time (p=0.0285). By week 2, the high-dose group attained higher scores than the low-dose group (5.9 versus 5.3, SE=0.2, 0.2). This relative difference was maintained throughout the study period.

Study W019 - The investigator's unblinded overall assessment of efficacy (double-blind phase) showed statistically significant differences between the placebo and vigabatrin treatment groups in favor of vigabatrin (p<0.001). Sixteen (80%) subjects had marked or moderate improvement with vigabatrin versus 3 (15%) of subjects on placebo. Of note, 4 (20%) subjects worsened under placebo therapy and no (0%) subjects worsened on vigabatrin under the 5-day double-blind period.

Study FR03 - General unblinded assessment by the physician of seizure-frequency severity was markedly improved in 11/11 vigabatrin -treated subjects which correlated highly with "marked" improvement in well-being in 9/11 and "moderately or markedly" improved behavior in 10 of these subjects. This correlation was not uniformly present in the hydrocortisone-treated subjects, even for those in whom seizure frequency improved. That is, in some subjects treated with hydrocortisone, seizure frequency showed "marked" improvement but both general well-being and behavior worsened. During the first treatment period, 6/11 hydrocortisone-treated subjects remained unchanged or worsened in general well-being and 5/11 showed "moderate or marked" improvement. Behavior was unchanged or worsened in 7/11 and moderately or markedly improved in 4/11 hydrocortisone-treated subjects, again in discordance between seizure frequency-severity and behavior. In addition, an improvement in general well-being and behavior was experienced by hydrocortisone subjects after crossing over to vigabatrin -treatment. Statistical analyses of the physician global assessments were performed using Fisher's exact test to compare the 2 treatments in the first treatment period. Given the small numbers of subjects,

the response categories were aggregated to improvement (marked or moderate) versus no improvement (unchanged or worse). Statistically significant differences in improvement were seen in general well-being (11/11 vigabatrin versus 5/11 hydrocortisone, p=0.0124) and behavior (10/10 vigabatrin versus 4/11 hydrocortisone, p=0.0039). There was also a trend favoring vigabatrin in seizure-frequency severity scores (11/11 vigabatrin versus 7/11 hydrocortisone, p=0.0902).

Psychomotor Development (Unblinded Assessments):

Study W019 - Psychomotor development was assessed by means of the Denver developmental test. Denver tests were to be performed at baseline and at the end of the open phase thereby allowing sufficient time to demonstrate response to treatment. Seven of 25 subjects (28%) receiving vigabatrin who were tested scored normally on the Denver test at the end of the study; all 7 were classified as therapeutic successes (defined as the complete absence of spasms in the final 12 weeks of the open-label phase in subjects taking no other antispasm medication). Three subjects who were suspect at baseline became normal at end of study. All subjects who had a normal Denver test by the end of study had responded to vigabatrin monotherapy. No subjects had normal Denver tests in the non-responder group. Five subjects were untestable, and 6 had incomplete testing. Of the untestable subjects, none were responders. This is consistent with the need to have complete response, that is, elimination of spasms and hypsarrhythmia, to improve psychomotor development. Unfortunately, 6 subjects had missing baseline or end of study tests, including both responders and non-responders. This precluded a more robust analysis of therapeutic effect on development. No subjects rated as normal at baseline worsened, i.e., were rated as suspect, at the end of the study. This demonstrates that vigabatrin did not lead to worsening of mental development. These findings suggest but don't establish the importance of achieving complete spasm control in order to allow normal development. They also suggest that patients who did not respond to therapy did not attain normal development.

Study FR03 - Psychomotor development was assessed with the Brunet Lézine test (a French adaptation of the Gesell test validated for the assessment of the psychomotor development of children during the first 30 months of life). All patients were to have received evaluation before and after treatment. Five of 11 subjects who were initially treated with vigabatrin and 6 of 11 subjects who initially received hydrocortisone had testing before and after treatment. Under initial treatment with vigabatrin, all who underwent this test twice had an improvement in developmental quotient, which ranged from modest to substantial. Under hydrocortisone, only 4 subjects were maintained on hydrocortisone (and not crossed over to vigabatrin) and only 3 of the 4 were tested before and after treatment; those subjects exhibited a stable or improved developmental quotient. This study suggests that improvement of developmental quotient occurred following response to vigabatrin treatment and also that no worsening of development quotient occurred with vigabatrin treatment.

Sponsor's Summary of Efficacy Parameters (6.16)

The results of efficacy parameters assessed in the 3 controlled studies of vigabatrin are summarized by the Sponsor as follows with Reviewer notes in bold italics:

• The short-term treatment evaluation periods ranged from 5 to 28 days in these studies. The proportion of subjects achieving complete cessation of spasms with vigabatrin therapy during these evaluation periods ranged from 11% to 100%. High-dose vigabatrin (100 to 148mg/kg/day) was shown to be statistically significantly more effective in achieving spasm cessation than low-dose vigabatrin (18 to 36mg/kg/day).
Reviewer Note:
As discussed above, there are concerns about the design, interim analyses, and the statistical analysis plan of the largest study (1A) that leave the statistical significance of its primary outcome in doubt. The primary outcome of Study W019 was not significant. Study FR03 was an open label study that provides supportive but not pivotal evidence of efficacy.

• Vigabatrin was more effective than placebo or hydrocortisone in spasm control and/or cessation. In general, subjects treated with placebo or hydrocortisone who did not respond to these treatments ultimately achieved cessation of spasms after switching to vigabatrin.
Reviewer Note:
As discussed above, these conclusions have not been definitively established.

• The time to response with vigabatrin was short and generally occurred within the first 2 to 4 weeks of therapy.
Reviewer Note:
This appears to be true.

• During long-term follow-up (ranging from 3 months to >3 years), spasm-free status was maintained for the majority of subjects, with few subjects experiencing relapse of spasms. Relapse occurred approximately 1 to 43 months after initial achievement of spasm-free status. Subjects in some studies were able to maintain spasm-free status on vigabatrin monotherapy during long-term follow-up, with or without titrated withdrawal of other therapies.
Reviewer Note:
These studies continued vigabatrin treatment for a period of years, leading to safety concerns especially permanent progressive visual field deficits that may lead to blindness. It remains an unanswered question as to whether it is possible to stop spasms with relatively short-term vigabatrin therapy (up to several months) and then to discontinue vigabatrin using other AEDs as needed. Such an approach might reduce the risk of retinal toxicity.

• Even though a somewhat greater spasm cessation rate was observed in high-dose subjects who did not receive other AEDs compared with high-dose subjects who did receive AEDs in Study 1A, in general, the use of other AEDs as adjunctive therapy at baseline or during long-term follow-up did not seem to alter the efficacy of vigabatrin.
Reviewer Note:
This appears to be true.

• Subjects with symptomatic IS, particularly those with tuberous sclerosis, had higher rates of response than subjects with cryptogenic IS.
Reviewer Note:

This appears to be true.

• All 3 controlled studies used EEG recordings as part of their evaluation of vigabatrin efficacy. Overall, results of EEG assessments documented electrographic evidence of elimination of the electrographic characteristics of the syndrome in those receiving vigabatrin with a clear separation in response between subjects taking higher vs lower doses.
Reviewer Note:
This appears to be true. Only Studies 1A and W019 used CCTV-EEG to confirm cessation of spasms reported by the caregiver. While the correlation between hypsarrhythmia and spasm is not absolute, the improvement of EEG is a reasonable secondary outcome.

• Although data were more variable for evaluations of physician global assessment and subject psychomotor development, results typically showed good improvement in both areas. Numbers were inadequate for quantitative evaluation of developmental quotient; however, qualitative evaluations were noted in patients treated with vigabatrin and it is likely the improvement is a consequence of complete control of IS.
Reviewer Note:
These unblinded studies suggest but do not establish that early elimination of spasms improves the long-term neurodevelopmental outcomes of IS patients.

6.1.5 Clinical Microbiology

No issues.

6.1.6 Efficacy Conclusions by Reviewer

The usual standard for NDA approval is not met.

The Elterman Shields study (1A) originated as a compassionate use program. It is only partially single blind. The possible bias inherent in the treating physicians' knowing the randomization and the caretakers knowing the dosage (and possibly inferring the randomization) is compensated only in part by the mandatory confirmations of spasm cessation by video EEG sessions which in turn were reviewed by blinded EEG reviewers. Thus we have a low dose/high dose study with adequate numbers of subjects and a reasonable endpoint. The enrollment size being quite large was a function of compassionate outreach rather than statistical requirement. The outcome is highly suggestive of efficacy. Unfortunately, the limited blinding, the several unprespecified interim analyses, the lack of a final statistical analysis paln until months after study completion, and the marginal statistical significance (contingent on the analysis method used) result in a study that does not meet the usual Agency criteria for a pivotal study supporting NDA approval.

The Appleton study (W019) has the best design: double blind and placebo controlled. The problems are the wrong primary endpoint, too few patients, and too short a treatment period.

These shortcomings could very well explain why the outcome is not significant. While it is reasonable to reanalyze the data with more appropriate outcome measures, this constitutes a post hoc analysis. Post hoc analyses are prone to be fishing expeditions looking for the particular endpoint or treatment period that would favor the agent under study. However, it may be too cynical to say that choosing a post hoc endpoint that corresponds to what almost every other study chose as its apriori endpoint and a post hoc treatment period length that corresponds to what almost every other study chose as its apriori treatment period length is the same as choosing the one endpoint or treatment length that by post-hoc observation made the data look significant. Nevertheless, showing significant efficacy on the basis of a post hoc endpoint and post hoc treatment period length does not meet the usual criteria for a pivotal study.

The Chiron Dumas study (FR03) is an open label study that is most appropriately considered as confirmatory data rather than a pivotal study. Depending on whether one judges the hydrocortisone dose to be adequate and whether one considers oral hydrocortisone to be likely as effective as ACTH (ACTH itself not being approved for this indication at point in time), one could say that hydrocortisone was an active control or a pseudo-placebo. In either event, the vigabatrin appears superior in the TS-IS population studied in this open label population. This supports the subpopulation observation from the Elterman/Shields study that tuberous sclerosis patients appeared to respond in higher percentages than IS patients due to other etiologies.

In light of these conclusions, a discussion of issues for an advisory committee meeting and subsequent regulatory action is given in section 9 of this review.

7 INTEGRATED REVIEW OF SAFETY

A separate review of the overall safety data of this NDA has been written by Dr. Gerard Boehm.

A separate review of the data on visual field defects has been written by Dr. Ronald Farkas.

The Assessment of Intramyelinic Edema (IME) and MRI abnormalities are discussed in this review below in section 7.1.12 Special Safety Studies

7.1.12 Special Safety Studies

Assessment of Intramyelinic Edema (IME) and MRI Abnormalities Attributable to Vigabatrin Therapy

Background

Safety concerns regarding intramyelinic edema (IME) attributable to vigabatrin arose originally from the results of animal toxicology studies, which demonstrated vacuolization of cells in specific regions of the brains of animals administered vigabatrin chronically and subchronically.

In light microscopic histopathologic specimens, vacuolization was seen in brain stem, cerebellum, basal ganglia and anterior commissure of rats. The distribution of vacuoles in the dog is similar, except that the fornix is prominently involved in dogs. On ultrastructural examination, the vacuoles were seen to be within myelin laminae, splitting the intraperiod line, hence the lesion was termed intramyelinic edema (IME).

The lesion appeared within 4 weeks of starting daily oral administration, progressed to a plateau and then did not progress thereafter even if vigabatrin administration was continued. The IME resolved within 3 months of discontinuation of vigabatrin. There were no long-term histopathological findings in dogs after vigabatrin discontinuation, but astrocytosis and mineralization was seen in some rodents at the last timepoint examined. Importantly, IME in animals completely correlated in onset and resolution with prolongation of evoked potential (EP) latencies and with high T2 signal on MRI. These latter findings led to the application of these techniques to monitor children and adults treated with vigabatrin for CPS for any evidence of IME.

IME could not be elicited in monkeys. While this may have been due to low bioavailability of vigabatrin, serum levels corresponded to exposures in humans administered doses of 3-4 g/day and CSF levels exceeded CNS exposures measured clinically.

In response to the animal findings, clinical trials of vigabatrin conducted by the prior NDA 20-427 sponsor in over 400 adults and 200 children with CPS included prospective surveillance with multimodality EP and with MRI. Contemporaneous review of the original EP and MRI reports as well as subsequent central review of the original EP tracings and MRI images by subspecialty experts provided no evidence of IME in these populations. The absence of IME in monkeys and humans on histologic examination and the lack of electrophysiological or imaging evidence of IME in humans led to the tentative conclusion that IME did not occur in primates.

The absence of IME in monkeys and humans on histologic examination and the lack of electrophysiological or imaging evidence of IME in humans at that time led to the tentative conclusion that IME did not occur in primates.

Evidence of Possible IME in Infants after Vigabatrin for Infantile Spasms (IS):

This conclusion was challenged, however, when Dr. Philip Pearl reported MRI signal changes, consistent with IME, in 3 infants treated with vigabatrin for IS. This again raised the question of whether vigabatrin could induce IME in humans and, if so, whether there are clinical accompaniments or sequelae. This concern was reinforced by the reports of 10 additional cases of MRI abnormalities associated with vigabatrin captured through post-marketing safety surveillance and by a report of 6 possible cases in a draft manuscript provided to the Sponsor by Dr. Olivier Dulac of Necker-Enfants Malades University Hospital, Paris, France.

In response to the information from Dr. Pearl, the Sponsor assembled an expert review panel composed of senior pediatric epileptologists and neuroradiologists on 21 Feb 2007 with a goal of

determining future actions. The advisory group concluded: 1) that the MRI lesions were not definitively attributed to vigabatrin; 2) such abnormalities were unlikely to have clinical sequelae in infants; and 3) that a retrospective study would serve to define incidence and prevalence of such abnormalities.

Retrospective Study of Five Centers:

The Sponsor then initiated a retrospective review at 5 international centers with long-term experience in the use of vigabatrin in IS and with ongoing IRB/EC approved studies allowing dissemination of data. From these 5 institutions, clinical data and MRI reports from 213 children treated with vigabatrin for IS were reviewed. The goal of this review was to establish study parameters for a retrospective epidemiologic study with blinded review of MRI images.

Table 1. Retrospective Review of Infant MRI Data

Site Identifier [N=5]	Institution	Patients with MRI Data Included in Briefing Document [N=213]
002 Bourgeois	Children's Hospital Medical Center, Boston, MA	1
003 Carmant	Hopital Ste. Justine, Montreal, Que.	89
004 Chiron	Hopital Enfants Malades, Paris, France	35
005 Thiele	Massachusetts General Hospital, Boston, MA	34
007 Westall	Hospital for Sick Children, Toronto, Ont.	54
Source Data: Table 3, 5_22_2007 Briefing Document		

Of these 213 patients, 204 had MRI reports available for review. Of the 294, 42 patients were identified with T-2 abnormalities regardless of preexisting or underlying pathologies. These were classified as shown in the Sponsor's Table 14.

Table 14. Relationship of MRI Finding to VGB	
Attributable Relationship of MRI Finding to VGB	**Definition**
Likely related (N=23)	Typical topographic distribution involving bilateral deep grey matter structures and occurred while on VGB
Questionable relationship (N=13)	When the MRI abnormality was atypical in terms of topography but occurred while on VGB, when a typical MRI abnormality occurred while off VGB, when an underlying pathology could explain the MRI abnormality or when the timing of exposure to VGB in relation to the MRI was unknown
Unrelated (N=10)	When only the MRI abnormality was present on a baseline MRI or when the MRI abnormality was atypical in terms of topography or occurred while off VGB
Source Data: Table 15, 5_22_2007 Briefing Document	

In conclusion, 23 of 204 patients from this5 institution retrospective review showed typical MRI signal abnormality suggestive of vigabatrin effect. However only 2 of them had baseline MRIs, and consequently some patients may have had pre-existing MRI abnormalities. Twelve of 23 patients had complete or partial resolution of these MRI signal abnormalities on subsequent MRI (7 patients still on and 5 patients off vigabatrin). Eleven patients did not have any subsequent MRI to evaluate evolution of these MRI signal abnormalities. No patients had persistent stable or progressive MRI signal abnormalities on subsequent MRI. **Based on these data, an estimated incidence of 10% to 20% of patients with MRI abnormalities in those vigabatrin-treated infants with IS was assumed for the purposes of planning additional trials.**

In addition, the 3 abnormal MRI cases from Dr Pearl were included in the ISS submitted to NDA 22-006 on 08 March 2007. The Agency, in response to the 08 March 2007 submission, requested additional data to address the findings of MRI signal changes.

Type A Meeting of June 6, 2007:

The Sponsor completed the 5 Center retrospective review and shared these data with the Agency during a Type A meeting on June 6, 2007. The retrospective review of 213 children identified 23 (10.8%) children with abnormalities similar in appearance and distribution of that reported by Dr. Pearl.

During the Type A meeting, it was agreed that a retrospective, epidemiological review of MRI examinations obtained in infants treated for IS, both with vigabatrin and with other therapies, would be carried out to obtain a more precise estimate of the incidence and prevalence of the imaging abnormalities in infants **(Study OV-1019).** In addition, **the Agency and the Sponsor agreed that a new, blinded review of the MRI data from prior clinical trials of vigabatrin in older children and adults with CPS would also be conducted.**

Infants assessed in Retrospective Epidemiologic Study of IS (Study OV-1019):

The retrospective epidemiologic study of IS (Study OV-1019) was designed to determine whether vigabatrin causes MRI signal changes in this population and, if so, their incidence and prevalence. Given the irregular timing of MRI examinations, the analysis compared the prevalence and incidence during vigabatrin treatment with other treatments for IS and was not based on patient years of exposure.

For **Study OV-1019**, 10 sites in the US and Canada provided clinical data and MRI images of 205 infants treated for IS, either with vigabatrin or with other therapies. The MRI images were reviewed by 2 pediatric neuroradiologists (with adjudication) masked to subject identity and treatment, to determine the presence of pre-specified abnormalities, namely increased T2 or FLAIR signal or restricted diffusion not readily explainable by a well-characterized pathological process.

The results of Study OV-1019 showed that vigabatrin exposure has a clear and statistically significant association with an increased frequency of the pre-specified MRI abnormalities compared to non-vigabatrin treated infants with IS. The incidence of such abnormalities was 36% in vigabatrin-exposed subjects, compared to 5.9% in vigabatrin non-exposed subjects (p=0.031).

The results of **Study OV-1019** suggested a dose effect, in that subjects exposed to =125 mg/kg/day vigabatrin had an incidence of 41.7% of pre-specified MRI abnormalities, whereas subjects exposed to <125 mg/kg/day had a lower incidence of 33.3%. However, this difference did not achieve statistical significance, (p=0.099).

In **Study OV-1019**, the prevalence of pre-specified MRI abnormalities in vigabatrin -exposed subjects was 21.5%, compared to 4.1% in the vigabatrin-naïve subjects (p<0.001). This is consistent with prior estimates of the prevalence of vigabatrin-associated MRI abnormalities of 10-20%. Results of **Study OV-1019**, as well as the observations of Pearl, and clinicians in France and Finland also indicate that the MRI abnormalities are transient, at least in the majority of cases, and they are more likely to be found in infants exposed to high-doses (=125 mg/kg/d) rather than low-dose vigabatrin.

In the Pearl abstract, the pre-publication paper of Desgeurre, and in the Sponsor's reviews and study, there is no evidence for clinical sequelae. In 3 Finnish children, descriptions of abnormal motor movements coincident with the findings of MRI abnormalities led to an EMEA review. In these cases, the abnormal movements resolved following discontinuation of vigabatrin. Therefore, although the data are far from definitive, no evidence of long-term clinical sequelae of the MRI abnormalities has been identified. The EMEA concluded that the risk benefit balance remained acceptable and no change in the indication of vigabatrin in initial therapy for the treatment of IS was warranted. An amendment to the Undesirable Effects section of the Summary of Product Characteristics was added, stating "Cases of cytotoxic oedema or related abnormal MRI findings/increase in signal intensity have been reported" and "Movement disorders, including dystonia, dyskinesia and hypertonia have in rare cases been seen, either alone or in single cases in association with abnormalities in an NMR".

In conclusion, vigabatrin treatment of infants with IS induces MRI abnormalities of hyperintense T2 signals. The diagnosis of IME is based on histopathology and to date, no tissue, either from autopsy or biopsy has been available to correlate with MRI findings. Nevertheless, it is likely that the T2 signal hyperintensities represent IME. It is possible that these imaging abnormalities are associated with clinical abnormalities of motor function, predominantly increased tone and dystonia, in some infants. However, the MRI abnormalities appear to be transient as have been the motor abnormalities seen in a few infants and thus do not appear to be associated with long-term clinical sequelae. A prospective study is proposed to better define the clinical implications, if any, of these imaging findings.

Children and Adults with CPS:

To explore the possible association of vigabatrin exposure and MRI abnormalities in children and adults treated with vigabatrin for CPS, the Sponsor undertook a repeat review of the MRI images obtained in clinical trials conducted by the prior NDA 20-427 sponsor in these populations. The goal was to determine if there was any evidence for an association of vigabatrin exposure and MRI abnormalities in these populations.

The MRI images to be reviewed were those that had been already evaluated by the prior NDA 20-427 sponsor, the results of which were submitted to NDA 20-427 on 29 May 1997. The MRI scans in these earlier studies were obtained prospectively and specifically to look for evidence of IME. In this new repeat review, masked neuroradiologists identified all MRI abnormalities consistent with edema, i.e., high T2 or FLAIR signal or diffusion restriction, not explainable by a pathological process readily diagnosed radiographically (e.g., prior ischemia). Therefore, many cases with non-specific, age-related "small vessel ischemic" white matter disease were included in the pre-specified abnormality category. In other words, this was a conservative approach meant to capture all potential abnormalities. The sponsor points out that one limitation of this methodology is that it may overestimate the frequency of abnormalities. Additionally, the Sponsor notes that an overestimation biasing against vigabatrin is inherent in the analysis of prevalence and incidence since the analysis uses total patient numbers as opposed to patient years of exposure. The rationale was to use the most sensitive approach to search for any possible drug effect.

The Sponsor concluded that there were no statistically significant differences in either the prevalence or incidence of pre-specified MRI abnormalities between the vigabatrin-exposed and the non-exposed subjects. Among those subjects who had MRI examinations during treatment, pre-specified MRI abnormalities were seen in 14.2% of vigabatrin-exposed subjects compared to 13.1% of non-exposed subjects ($p=0.579$). The incidence of pre-specified MRI abnormalities in vigabatrin-exposed subjects was 10.8% compared to 8.0% in the non-exposed group ($p=0.437$). When analyzed by age group, the differences between treatment groups are small, vary in direction and are not statistically significant.

Sponsor's Overall Assessment of Benefit to Risk Ratio:

In infants with infantile spasms, MRI abnormalities occur at increased frequency in association with vigabatrin therapy, however, no obvious clinical sequelae of moment nor any long-term sequelae have been identified. Since vigabatrin demonstrates significant efficacy in both elimination of spasms and re-attainment of developmental milestones and given that IS carries a high mortality and severe morbidity risk, the benefit of vigabatrin therapy in many patients with IS outweighs the risks described in this report.

Reviewer Note:
As noted elsewhere in this review, due to flaws in Studies 1A and W019, efficacy in eliminating the spasms has not been demonstrated by usual Agency criteria; the open label long-term follow-up to these studies is encouraging but is not designed to demonstrate efficacy in improving long-term developmental status.

I agree that no obvious clinical sequelae have been demonstrated. Given the spectrum of severity of the IS syndrome and its various underlying etiologies, it is difficult to be sure if the MRI abnormalities have clinical correlations. Although occurrence of these MRI findings are not an absolute contraindication to using vigabatrin in the MRI population, the MRI findings (which seem to be indicative of IME) remain a safety concern in weighing the benefit to risk ratio for vigabatrin.

In children and adults with refractory complex partial seizures, no evidence exists for a causal relationship between vigabatrin therapy and MRI abnormalities. As there is no demonstrated risk in this population, the benefit/risk profile of vigabatrin in CPS is not impacted by the potential for MRI abnormalities.

Reviewer Note:
The absence of MRI lesions in the adult and child (over age 3 years) studies suggests that the risk for IME is largely limited to the immature human brain. However, there may be exceptions to this. The benefit to risk ratio should include consideration of these MRI findings.

In contrast to the proposed IS indication, the NDA studies for the proposed indication of complex seizures indicate efficacy. The weighing of benefit to risk ratio should however include the consideration that there are multiple alternative therapies approved for complex partial seizures.

As discussed in the Type A meeting with the Agency, the Sponsor plans to conduct a post-marketing prospective study of children with IS to provide additional data on potential long-term clinical consequences of MRI signal abnormalities. Since these abnormalities are seen in children irrespective of treatment modality, this study would examine children treated with vigabatrin as well as other therapies. The protocol synopsis can be found in the Risk Map.

Sponsor's Overall Conclusions:

• There is a causal relationship between vigabatrin treatment of infants for IS and the occurrence of MRI signal changes (abnormal T2 and FLAIR signal). These changes occur in a characteristic anatomical distribution, with symmetric involvement of globus pallidus, thalamus, brainstem and deep cerebellar nuclei.

Reviewer's Note:
These MRI changes are presumed to represent IME. This seems likely but has not been definitively established as discussed above.

• There is likely a dose relationship of vigabatrin-induced MRI changes in infants. Infants taking higher doses are likely at greater risk for the development of MRI changes than those patients treated with lower doses (<125 mg/kg/day).

Reviewer's Note:
The dose relationship is not statistically significant. In any event, the "higher doses" are well within the currently used and recommended dose range for IS.

• The MRI abnormalities are generally transient, whether or not vigabatrin is continued.

Reviewer's Note:
This appears to be the case although it also appears that vigabatrin was discontinued in most cases when the MRI abnormalities were noted.

• Whether clinical manifestations accompany the process causing the MRI changes is unknown; it is possible that there are motor signs in some infants.

Reviewer's Note:
The proposed post-marketing prospective study might help resolve this if vigabatrin is marketed.

• Whether there are long-term sequelae of the pathological process producing the MRI abnormalities is also unknown, but there are no data at this time to support the occurrence of long-term clinical consequences.

Reviewer's Note:
The uncertainty over the possible long-term consequences requires that this concern be considered in weighing the relative benefit to risk of vigabatrin therapy for IS.

• MRI signal abnormalities are not a consequence of the treatment of children above 3 years of age and adults with CPS with vigabatrin.

Reviewer's Note:
It is not clear that age 3 is an absolute cutoff beyond which there are no risk or MRI signal abnormalities with whatever pathologic and clinical correlations exist. Although the risk

seems more remote than in the infant population, it must still be considered in weighing the relative benefit to risk of vigabatrin therapy for CPS.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

See section 1.3.4 and Clinical Pharmacology review.

8.2 Drug-Drug Interactions

See section 1.3.5 and Clinical Pharmacology review.

8.3 Special Populations

As discussed above, subgroup analysis of Study 1A and the results of the open label Study FR03 suggest but do not establish that vigabatrin may be more effective in stopping spasms when the underlying etiology is tuberous sclerosis.

8.4 Pediatrics

The proposed indication, infantile spasms, is a pediatric syndrome.

8.5 Advisory Committee Meeting

Pending on January 7-8, 2009.

9 OVERALL ASSESSMENT

The two controlled studies (1A Elterman/Shields and W019 Appleton), which are single and double blind in design respectively, provide the best opportunity for demonstrating efficacy for vigabatrin in eliminating the spasms of IS. These two studies are strongly suggestive but not definitive for establishing efficacy in eliminating the spasms. (The third controlled study [FR03: open label] and the two uncontrolled studies are also consistent with efficacy but are supportive data rather than efficacy trials).

However and unfortunately, as discussed in detail above, both studies 1A and W019 have significant flaws in design and analysis. As a result, the usual standard for NDA approval is not met.

Is it nonetheless possible to argue for an approval with limited distribution based on the urgent need for an approved therapy for infantile spasms?

The argument for such an approval could be made as follows. The status quo is unacceptable. There is no approved treatment for IS in the United States. Although most American patients are currently treated with ACTH gel (approved for endocrine testing and for the exacerbation of multiple sclerosis indication but not approved for the IS indication), a significant number of American patients are treated with vigabatrin. The sources (various other countries) and perhaps the quality of the drug currently used in the United States are variable. There are no approved dosage and monitoring procedures despite serious safety concerns about retinal toxicity. Although one would prefer to wait for a better designed pivotal efficacy trial of vigabatrin, such a trial is unlikely to be done. Therefore, it can be argued that the status quo would be improved if vigabatrin were to be available by a strictly controlled and monitored system of limited distribution.

The argument against such an approval in the absence of the usual criteria for efficacy is that the usual standards for efficacy should be met and that significant safety concerns (visual field deficits and intramyelinic edema) exist that are not adequately defined and/or detectable by monitoring. Furthermore, a proposal to market vigabatrin to treat the IS population would be more compelling if, in addition to stopping spasms, there was evidence demonstrating or strongly suggesting that stopping the spasms improves the long-term neurodevelopmental prognosis for the affected infants. Although one may believe and certainly would hope that long-term developmental prognosis improves if spasms can be stopped early-on in IS, the evidence is not convincing. This raises the concern that the long-term use of vigabatrin (as currently proposed) may add the additional burden of permanent vision impairment/blindness or possible deficits from the IME to an already developmentally disabled population without an over-riding benefit to offset this risk. Indeed, the lack of a method to monitor the appearance and progression of a visual field deficit in the infant population and the limited understanding of the IME phenomenon in the infant population makes the usual approach to considering a benefit-to-risk ratio difficult to impossible. The approval of vigabatrin on the basis of less than definitive evidence of efficacy may also have an unintentional impact on the practice of medicine. Currently, most American patients are treated with ACTH gel (approved for other indications but not for IS). ACTH gel may or may not be more efficacious or safer. However, if vigabatrin becomes the only approved therapy, the practice of prescribing might shift away from ACTH gel toward vigabatrin without an adequate evidence-based rationale.

The opinion of the Advisory Committee may be helpful in weighing the merits of these opposing arguments. This reviewer cannot recommend outright approval but would suggest consideration of a strictly limited and carefully monitored program of distribution with mandatory patient registry (limited to patients with documented infantile spasms), mandatory monitoring procedures, and mandatory safety and efficacy reporting. This would provide a uniform drug

substance in the United States and provide a mechanism for comprehensive post-marketing data. Such post-marketing data might also address the still unanswered question as to whether relatively short-term vigabatrin therapy (less than 6 months) to eliminate the spasms followed by another AED as needed might be as effective in preventing relapse or the occurrence of other seizure types and might be less likely to result in significant retinal toxicity.

9.1 Conclusions

The usual standard for NDA approval is not met.

9.2 Recommendation on Regulatory Action

Refer to Advisory Committee. Consideration should be given to limited distribution of vigabatrin for the treatment of infantile spasms (IS) as discussed above.

The design and results of the three primary efficacy studies submitted in support of this application do not meet the usual Agency standards for establishing efficacy of a new drug. In addition, there are two safety concerns that are difficult to address in the IS population: retinal toxicity and MRI-signal changes. The retinal toxicity producing a permanent progressive peripheral field deficit cannot be adequately assessed in the IS patient population and could result in total blindness. There are also vigabatrin-induced MRI signal changes occurring in about 20% of infants less than age 3 years that may correspond to the intramyelinic edema (IME) observed in the preclinical rat and dog model and which may or may not have a clinical correlation. These safety concerns make the usual consideration of the benefit to risk ratio of vigabatrin therapy problematic.

However, given the inherent difficulties of studying the efficacy and safety of vigabatrin therapy for IS and the lack of any currently approved treatment for IS, the appropriateness of approving vigabatrin for IS for limited distribution on the basis of the preponderance of existing evidence in the absence of a definitive demonstration of efficacy should be reviewed by an Advisory Committee.

9.3 Recommendation on Postmarketing Actions

Pending Advisory Committee meeting.

9.3.1 Risk Management Activity

Pending submission of REMS plan by Sponsor and pending Advisory Committee meeting.

9.3.2 Required Phase 4 Commitments

Pending Advisory Committee meeting.

9.3.3 Other Phase 4 Requests

Pending Advisory Committee meeting.

9.4 Labeling Review

Pending Advisory Committee meeting.

9.5 Comments to Applicant

Pending Advisory Committee meeting.

CLINICAL REVIEW

Application Type	NDA
Submission Number	022-006
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Reviewer Name	Gerard Boehm, MD, MPH
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Established Name	Vigabatrin
(Proposed) Trade Name	Sabril
Therapeutic Class	Antiepileptic
Applicant	Ovation
Priority Designation	P
Formulation	Powder for Oral Solution
Dosing Regimen	BID
Indication	Infantile spasms
Intended Population	Pediatric

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EXECUTIVE SUMMARY

1.1.1 Safety

This review considers the overall safety data presentations in the vigabatrin Infantile Spasms (IS) NDA, excluding visual field defects and MRI abnormalities. Data on visual field defects were reviewed by Dr, Ronald Farkas and Intramyelinic Edema (IME)/MRI abnormalities were reviewed by Dr. Phillip Sheridan, in separate memos.

Vigabatrin is an orally administered irreversible inhibitor of gamma-aminobutyric acid transaminase. Ovation submitted an NDA seeking approval for vigabatrin for the treatment IS. There are currently no FDA approved treatments for IS. In addition to the vigabatrin IS NDA, Ovation also submitted a separate amendment to a previously submitted NDA seeking approval for the treatment refractory complex partial seizures (CPS) in adults. The safety data from the CPS NDA amendment are reviewed in a separate document.

Vigabatrin has a long and complicated regulatory history including numerous regulatory submissions, 3 advisory committee meetings, and a sponsor change. FDA put the vigabatrin CPS development program on hold in the 1980s due to the finding of IME in several animal species. After resuming development, the sponsor submitted the vigabatrin CPS NDA to FDA in 1994. The Division completed its review in 1995 and the application was found not approvable, due mainly to deficiencies in the presentation of safety data. The sponsor submitted an amendment to the NDA that addressed the deficiencies and vigabatrin received an approvable letter in 1997. The sponsor subsequently withdrew the application, prior to vigabatrin approval in the US, due to the finding of permanent visual field defects in a notable percentage of treated patients. Ovation acquired the rights to vigabatrin from Aventis and submitted CPS NDA amendment and the IS NDA that is the focus of this review.

Vigabatrin is currently approved for use in over 50 countries. Vigabatrin was first approved in the United Kingdom in 1989. Vigabatrin is approved in most countries in the European Union as well as Canada and Mexico. Approved indications include monotherapy for the treatment of Infantile Spasms (IS) and for the treatment of partial epilepsy in subjects who have not responded adequately to other antiepilepsy drugs.

Vigabatrin related IME was a major preclinical safety finding. IME, manifested as microvacuolization in the brain, has been identified in mice, rats, dogs, and less consistently in monkeys. These findings led to a clinical hold for the CPS development program and 3 advisory committee meetings. Another preclinical finding of note was retinal degeneration observed in albino rats but not in pigmented species.

The current vigabatrin IS submission includes pooled safety data from 3 controlled IS studies, and one uncontrolled IS study. Ovation also presents safety data from subjects <3 years old from non IS studies, and data from a retrospective study of IS patients. The vigabatrin IS safety

database includes 325 IS subjects and 21 non IS subjects < 3years old. The retrospective study included 250 IS patients and these data were not integrated with the data from the prospective studies.

In addition to the data for IS subjects, Ovation's CPS NDA amendment includes safety data for subjects exposed to vigabatrin. The CPS NDA amendment includes Integrated data analyses of pooled data from 80 epilepsy trials, including over 4,000 vigabatrin exposed subjects dating back to the original NDA.

The number of patients exposed to vigabatrin in the IS safety database clinical trials falls short of ICH guidelines. The IS NDA submission includes safety data for 346 subjects exposed to vigabatrin in the combined controlled and uncontrolled trials. Ovation reported that 172 subjects were exposed to vigabatrin for more than 6 months, 120 were exposed for more than 1 year and that 75 subjects lacked sufficient data to determine the duration of exposure. The ICH Guidance recommends that 1,500 subjects be exposed with 300-600 subjects exposed for 6 months, and 100 exposed for 1 year (at relevant doses, with reasonable exposure to the highest proposed dose). If one includes the exposure during the entire development program, the number of vigabatrin exposed subjects exceeds ICH guidelines.

The designs of the submitted IS studies preclude reliable assessment of drug related AEs in the IS NDA. The paucity of controlled comparative data and short durations of the controlled periods of the small number of submitted trials do not provide sufficient opportunity to identify drug related events. One can rely on comparative safety data from the adult safety database although one must consider that extrapolation of these data from use in treating adults and children with seizure disorders to use in infants with IS is not optimal. Narrative summaries of serious adverse events or AEs leading to discontinuation were generally of poor quality and often containing insufficient information to characterize the event.

The reported causes of death in the clinical trial subjects in the IS NDA were sudden death, pneumonia, pulmonary hemorrhage and cardiac arrest.

The most common SAEs among vigabatrin clinical trial subjects in the IS NDA were pneumonia (3.2%, n=11), status epilepticus (3.2%, n=11), pyrexia (1.7%, n=6), convulsion (1.5%, n=5), bronchospasm (1.2%, n=4), viral infection (1.2%, n=4), and gastroesophageal reflux disease (1.2%, n=4). There were no SAEs of acute hepatic failure, acute renal failure, pancreatitis, aplastic anemia, rash, Stevens Johnson syndrome, Toxic epidermal necrolysis, or hypersensitivity reported for these studies.

Twenty-two vigabatrin clinical trial subjects in the IS NDA discontinued for an AE. The AEs leading to discontinuation of more than one subject were status epilepticus (n=3), convulsion (n=2), infantile spasms (n=2), and pneumonia (n=2).

Common AEs that occurred in vigabatrin clinical trial subjects in the IS NDA were somnolence, sedation, lethargy, convulsions, vomiting, constipation, diarrhea, irritability, insomnia, pyrexia, nasal congestion, rash, and decreased appetite.

As noted above, the small size of the safety database and the paucity of data from controlled phases of clinical trials precluded identification of drug related events in IS studies. Data from the adult CPS NDA amendment identified a number of vigabatrin related findings and those events are summarized below.

Vigabatrin use was associated with edema adverse events. In analyses of pooled controlled trial data from the adult CPS submission, the risk of edema was higher among vigabatrin subjects compared to placebo subjects. Dose response analyses of controlled trials data suggested an increasing risk of edema peripheral and generalized edema with increasing vigabatrin dose but not other edema related adverse events. Edema adverse events were not classified as SAEs and infrequently led to discontinuation. The edema AEs did not appear to be related to cardiac, renal or hepatic AEs and did not appear to be associated with increased creatinine, low serum albumin, or proteinuria.

Evidence from the adult CPS submission supports an increased risk for depression with vigabatrin and insufficient evidence to support an increased risk of suicidal behavior. Data from 12 pooled controlled studies document an increased risk for depression related SAEs among vigabatrin subjects, although the number of SAEs was relatively small. In addition, data from these trials suggest an increased risk for depression AEs leading to discontinuation among vigabatrin subjects compared to the subjects randomized to other treatments. There did not appear to be a clear dose response for depression related AEs.

Vigabatrin was associated with increased risk of peripheral neuropathy signs and symptoms in the adult CPS submission. In the original NDA, risks for parathesia and hyporeflexia adverse events were 3 times higher among vigabatrin subjects compared to placebo subjects. Vigabatrin studies were not designed to systematically evaluate peripheral neuropathy and did not include nerve conduction studies, quantitative sensory testing or skin or nerve biopsy.

There have been cases of liver injury resulting in death or transplant in patients treated with vigabatrin but it is not clear if vigabatrin is causally related to these cases. Concomitant medications, and prolonged duration of vigabatrin use prior to liver injury, make it difficult to assess the role of vigabatrin in these events. There were no identified cases of transaminase elevations >3x ULN with total bilirubin >2.0mg/dL in the vigabatrin development program, and there was no increased risk of transaminase outliers among vigabatrin subjects in an analysis of pooled controlled trial data. These laboratory results must be interpreted in light of the understanding that vigabatrin causes *decreases* in serum transaminases.

Vigabatrin was associated with an increased risk for a number of CNS AEs including somnolence, sedation, coordination abnormalities and confusional state. The occurrence of these events could impair a patient's ability to perform tasks such as driving or operating machinery.

Lab data suggest that vigabatrin subjects experienced declines in hemoglobin and hematocrit that were not seen in subjects that received placebo. Despite these laboratory findings, vigabatrin subjects did not appear to experience high frequencies of concerning clinical events. A search of

the development program identified only 2 vigabatrin subjects that experienced unexplained declines in hemoglobin below 8g/dL and or hematocrit below 24%. In addition, there appeared to be few post marketing reports of anemia adverse events. The sponsors did not collect sufficient information to classify the observed anemia events.

Vigabatrin causes reductions in serum transaminases (ALT>AST), presumably through its effect as a transaminase inhibitor. In one analysis, 94% of subjects had a 60-100% maximum decrease in their ALT compared to baseline and 4% had an ALT result of 0. The magnitude of the declines appeared to be dose related.

Vigabatrin use is associated with weight gain. Data from controlled trials demonstrated that vigabatrin treated subjects had a higher mean increase in weight from baseline than did placebo treated subjects. In addition, vigabatrin subjects had a higher risk of gaining >=7% of baseline body weight. In the Integrated database, 10.2% (415/4077) of vigabatrin subjects had a weight increased AE. The long term impact of vigabatirn associated weight gain on cardiac disease or blood pressure outcomes is not known.

Due to the small number of analyzed ECGs, lack of specified timing in relation to dose, and lack of pre-specified measurement methodology, Ovation's analyses of ECGs collected during vigabatrin clinical trials are insufficient to assess the effect of vigabatrin on cardiac repolarization. Preclinical data did not appear to suggest an effect of vigabatrin on ion channels or repolarization.

Recommendations

Any ongoing or planed vigabatrin clinical trials should incorporate monitoring of hemoglobin, hematocrit, serum iron, transferrin, ferritin, reticulocyte count, red cell morphology, red cell indices, haptoglobin, urine hemoglobin, and erythropoietin.

Any ongoing or planned vigabatrin clinical trials should incorporate hematologic testing during post-treatment washout in order to assess rate of recovery from reduction of hemoglobin and hematocrit.

Ovation should conduct a thorough QT study in humans. This could be conducted as a phase IV commitment.

If approved for pediatric indications, Ovation should collect data that address the effect of vigabatrin on growth and development.

Ovation should closely follow up any spontaneous reports of liver injury. Follow up should include complete description of the case, outcome information, lab test results, biopsy results, and post mortem test results. In addition, Ovation should submit any serious liver injury cases as 15-day reports.

Ovation should incorporate the labeling language that will be requested by the Division.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

Ovation identified four deaths from studies included in their integrated safety database for the infantile spasms NDA (ISS, p.76). The mortality risk among the infantile spasms subjects was 1.2% (4/346). Three deaths were from study 1A. I summarize these deaths below.

1A/911 Cause of death: sudden death
This was a sudden death occurring in a 7-1/2-month-old, 6.4 kg, African American female child with symptomatic Aicardi's Syndrome, sickle cell trait, and a history of clonic and tonic-clonic seizures. She initiated vigabatrin therapy on March 21, 1997. The subject had been receiving phenobarbital at baseline but this was abruptly discontinued due to change in caregiver. The subject was seen by the pediatrician for a well-baby checkup and age-appropriate immunizations on the day prior to death. The physician reported that she was more alert, interactive, and "much better" seizure-wise compared to baseline. At the time of death she had been on vigabatrin therapy for 74 days and was receiving a vigabatrin dose of 195 mg/kg for 3 consecutive weeks. On ——— at 1:30 pm, the infant's caregiver put her down for a nap. When the caregiver attempted to wake the infant at 3:30pm, the infant was not breathing. The infant was taken to a local hospital and given vigorous cardiopulmonary resuscitation but could not be revived. The child had no intercurrent illness and did not receive pertussis immunization. An autopsy was performed; however, repeated attempts to obtain the report were unsuccessful. The sponsor believes this death would be considered a SUDEP (Sudden Unexplained Death in Epilepsy) (*Aicardi's syndrome is an X-linked disorder that includes agenesis of the corpus callosum, cystic intracerebral anomalies, infantile spasms, mental retardation, lacunar chorioretinopathy, and vertebral body abnormalities).* b(6)

1A/461 Cause of death: pneumonia
This subject had been off vigabatrin for three weeks at the time of onset of the adverse event. This subject was a 10-3/4 month 5 kg old female with infantile spasms and Miller-Dieker Syndrome, a genetic disorder associated with lissencephaly, microcephaly, severe mental deficiency, seizures, and frequent infections. She had begun vigabatrin therapy on August 8, 1997. Due to lack of efficacy, vigabatrin was tapered and discontinued with the last dose given on November 13, 1997. At this time, she started clonazepam, 0.5 mg bid. Lamictal® therapy was started for seizure control on November 20, 1997. She was hospitalized on ——— with a diagnosis of upper lobe pneumonia. "Do Not Resuscitate" orders were written at least 24 hours prior to her death. Supplemental oxygen was discontinued the evening of ——— as agreed upon by her parents and the attending physician. She continued to receive feedings per a gastrostomy tube, antibiotics, and acetaminophen for comfort measures until she died on ——— No autopsy was performed.

1A/559 Cause of death: pulmonary hemorrhage secondary to pulmonary angiomatosis
This death occurred in a 3-month-old, 4.2 kg female with a history of severe encephalopathy of unknown etiology with onset of IS at 5 weeks of age. The infant also had a history of another unclassified seizure type. Vigabatrin treatment was initiated in June 12, 1997 and the dose was increased to a maximum dose of 750 mg without obvious improvement. The infant was also receiving an unspecified dose of chloral hydrate in addition to vigabatrin. She was initially treated with vitamin B6, but the spasms continued. Once on vigabatrin, her spasms decreased from 3 per day to 1-2 per day; however, startle seizures increased and she had development of a new seizure type during which she stared and was unresponsive. She was also diagnosed with cortical blindness. Metabolic studies and an MRI were normal. The infant was in hospice care and had developed increasing spasm activity the weekend prior to her death. At midnight on the day before her death, she began to bleed from the mouth and expired 2 hours later. At the

time of death she was receiving a dose of 148.8 mg/kg vigabatrin and had been on this dose for 3-1/2 weeks. Autopsy findings showed the infant died from a pulmonary hemorrhage secondary to pulmonary angiomatosis. Plexuses of large abnormal muscularized vessels with focal subintimal fibrosis were present next to the right and left bronchi of the lungs, which raises the possibility of arteriovenous shunting. Left ventricular hypertrophy in the heart is additional evidence that there was an abnormal hemodynamic state.

The sponsor identified one death in a subject from study W019. I provide the sponsor's summary for that death below.

W019/103 Cause of death: Cardiac arrest
This female aged six months, commenced vigabatrin therapy in August 1995. She suffered bronchitis and otitis media leading to hospitalization in November 1995 and then pneumonia in December 1995. The patient was treated with cefaclor for obstructive bronchitis in September 1995 and with Augmentin in December 1995. On — this patient suffered mild bronchitis and a cardiac arrest leading to death; this was considered to be related to a heart disorder (possibly related to a previous infection). The patient had completed the study; her death occurred two days after the end of the study. The patient's notes record that at the final study visit it was noted that the patient had had chronic obstructive bronchitis which had been treated by a local pediatrician. There were a number of respiratory conditions reported as adverse events for this patient during the study The patient was treated with various antiepilepsy medications during the study: the dose of vigabatrin at the end of the study was 100 mg/kg/day, which was reduced to 50mg/kg/day.

In addition to the 4 deaths from the studies included in the integrated safety database, the sponsor identified 4 deaths in subjects from study 3E01 (retrospective study not included in the integrated safety database). The mortality risk for this trial was 1.6% (4/250). Two deaths occurred after stopping vigabatrin; the first death (patient 07-07-07 pneumonia, septic shock) occurred 7 months after stopping vigabatrin and a second death (patient 08-02-01, interstitial pneumonia, CMV infection) occurred over 2 months after stopping vigabatrin treatment. Below I provide the narrative summaries for the 2 study 3E01 deaths that occurred on vigabatrin treatment. b(6)

Patient 02-02-02: Patient was male (d.o.b.: — having an age of IS onset of 29 months (date: — IS etiology was reported as related to an unclear progressive deterioration of the brain, similar to leucodystrophy. Patient received an initial dose of VGB of 40mg/kg/day that was titrated over a 14-day period to a dose of 200mg/kg/day. Treatment with VGB improved the condition of the child, but did not completely stop the spasms. No other anti-epileptic medication was added. After four months of receiving VGB treatment, the patient was found dead in the morning by his parents (date: — . The child was aged 33 months. The patient's physician reported that the child had been getting progressively weaker and weaker (the condition said to be similar to spinal muscular atrophy).

Patient 11-03-22: Patient was female (d.o.b.: — and presented with IS 5.5 months after birth (date: — IS etiology was said to be related to septo-optic dysplasia. Patient was treated with VGB at an initial dose of 40mg/kg/day that was titrated over a five-day period to a steady-state dose of 80mg/kg/day. At this dose the patient had complete cessation of IS. On — hus after 11 months of VGB treatment, with IS still controlled, at the age of 17 months the child was found dead. The cause was reported to be bronchopneumonia.

The limited number of deaths and the lack of deaths during the brief controlled segments of the clinical trials preclude any quantitative assessment of mortality risk by treatment. None of the reported causes of death appeared unexpected given the subjects' underlying diseases.

Post Marketing Death Reports

Ovation provided a Safety Update for the IS NDA that included pediatric post marketing data from 3/97-2/29/08. Ovation identified 11 post marketing reports describing 12 deaths in patients aged less than 12 years. For these pediatric deaths, the included patients ranged in age from 9 days to 11 years and 3 were males and 4 were females (5 unknown sex). Ovation provided line listings with limited information about these events. Four reports included insufficient detail to characterize the causes of death. Two patients were found dead in bed (one noted to be taking cisapride). The reported causes of death for the remaining subjects were SSPE, sepsis/pneumonia, congenital heart malformation, underlying metabolic disorder, recurrent pulmonary infections, and respiratory insufficiency/septicemia.

7.1.2 Other Serious Adverse Events

Ovation reported that 23% (79/346) of vigabatrin subjects in the integrated safety database experienced one or more SAEs (p.77). The SAEs reported by at least 1% of subjects in the integrated safety database were pneumonia (3.2%, n=11), status epilepticus (3.2%, n=11), pyrexia (1.7%, n=6), convulsion (1.5%, n=5), bronchospasm (1.2%, n=4), viral infection (1.2%, n=4), and gastroesophageal reflux disease (1.2%, n=4) (Source Table 4.1.5.1). I read the narratives for the 11 subjects with SAEs of pneumonia and the 4 subjects with SAEs of bronchospasm. These narratives provide very little information aside from documenting the event and subjects' daily doses of vigabatrin. I provide an example of such a narrative below.

Subject 1A-310 This Caucasian male born on was enrolled on 28Apr97 weighing 6.9 kilograms. The subject was assigned to the high-dose group and began vigabatrin on 28Apr97 for infantile spasms. Vigabatrin was dosed at 125 mg/day, and finally increasing to 1625 mg/day on 01Jun97. On 15Feb99, the subject experienced an SAE described as pneumonia (seriousness criteria unknown), which lasted an unspecified length of time. No action was taken, and the subject recovered from the event with no sequelae. The relationship to study drug was judged as not related. On 23Mar99, the subject experienced another SAE described as pneumonia (seriousness criteria unknown), which lasted 8 days. No action was taken, and the subject recovered from the event with no sequelae. The relationship to study drug was judged as not related. No concomitant AEDs or other medications were reported.

For the 6 subjects with SAEs of pyrexia, the narratives provided no explanation for the event for 3 subjects and documented associated infections (pneumonia, UTI, cystitis, otitis media, and viral gastroenteritis) for 3 subjects.

I examined table 4.1.5.1 to look for SAEs of particular concern. There were no SAEs of acute hepatic failure, acute renal failure, pancreatitis, aplastic anemia, rash, Stevens Johnson syndrome, Toxic epidermal necrolysis, or hypersensitivity reported for these studies. Three SAEs of "death" were among the deaths identified above (1A-461, 1A-559, and 1A-911). Ovation identified 3 SAEs of respiratory arrest, one SAE of respiratory failure, and one SAE of proteinuria/glomerulonephritis. I provide information from the narratives for these events below.

Respiratory Failure

Subject 1A/103 This 2 year and 8- month old Caucasian male, weight 12.7 kilograms, with a history of infantile spasms, complex partial seizures, partial seizures with generalization, tonic seizures and myoclonic seizures experienced respiratory failure. The subject had been on vigabatrin for approximately two years when the

respiratory failure occurred. Vigabatrin dose was 1500mg/day at the time of the event. The subject was admitted for respiratory insufficiency secondary to tonsillar enlargement and a tonsillectomy and adenoidectomy. The investigator assessed the event of respiratory failure as not related to vigabatrin. Severity was not provided; no action was taken. The outcome was "other." Concomitant medications included Topamax 62.5mg TID. The subject terminated from the study because he was "spasm free" with last dose of drug on 22Dec1998.

Respiratory arrest

Subject 1A/112 (CND) This Caucasian female born on —— was enrolled on 09Oct96 at Site 1 weighing 6.4 kilograms. The subject was assigned to the low-dose group and began vigabatrin on 14Oct96 for infantile spasms. Vigabatrin was dosed at 250 mg/day, increasing to 375 mg/day on 30 Oct96, to 625 mg bid on 08Jan98, and finally decreased to 500 mg bid on 11Mar98.

On —— the subject experienced an SAE described as respiratory arrest, ending on the same day. Non-drug therapy was administered (details not provided), outcome was listed as recovered with no sequelae, and the relationship to study drug was judged as not related. Seriousness criteria for the SAE was not specified. However an adverse event of mild drug hypersensitivity was also reported on 2 occasions on 12Feb97; one of these events was life-threatening (but not reported as an SAE). Both events continued to study completion. The investigator assessed the events as not reasonably attributed to vigabatrin. Treatment was 'Other,' but no details were provided.

Concomitant AEDs included clonazepam and topiramate. Other reported concomitant medications included albuterol, Auralgan otic, baby lax, Bactroban, Cefzil, Decadron, Donatussin, Murine eye drops, Mylanta, Phenergan, Poly-DM, Tylenol, and Ventolin.

Subject 1A-209 This Caucasian male born on —— was enrolled on 25Sep96 weighing 9.5 kilograms. The subject was assigned to the low-dose group and began vigabatrin on 27Sep96 for infantile spasms. Vigabatrin was dosed at 250 mg/day, increased to 1250 mg/day on 25Oct96, to 1750 mg/day on 23Nov96, to 2500 mg/day on 03Feb97, and finally decreased to 2000 mg/day on 21Nov97. This subject experienced several SAEs during the study including pneumonia, ear infection, hydrocephalus, gastrointestinal disorder, b(6)

On —— he experienced an SAE lasting 2 days while hospitalized described as cardio-respiratory. The outcome was recovered with no sequelae and the relationship to study drug was assessed as not related. He had 2 temporally related AEs including severe cardiorespiratory arrest for 2 weeks on —— Treatment was 'Hospitalization', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He also had severe ventriculoperitoneal shunt malfunction for 2 weeks on —— Treatment was 'Hospitalization', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. Although the 2 adverse events resulted in hospitalization, they were not reported as SAEs by the investigator.

On ——, he experienced an SAE described as respiratory arrest, ending the same day, and was hospitalized. The outcome was recovered with no sequelae and the relationship to study drug was assessed as not related. There were no related AEs.

Subject 1A-658 This male (Race = 'Other') born on was enrolled on 15Jul97 weighing 7.25 kilograms. The subject was assigned to the high-dose group and began vigabatrin on 17Jul97 for infantile spasms. Vigabatrin was dosed at 750 mg/day, decreasing to 500 mg/day on 04Jan99, and finally to 250 mg/day on 02Dec99.

On ——, he experienced an SAE described as respiratory arrest lasting 1 day and was hospitalized. He recovered with no sequelae and the relationship to study drug was assessed as not related. He also had moderate convulsion for 1 week on —— with seriousness listed as 'Life-Threatening', but treatment was 'None'. The outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributed to vigabatrin.

Concomitant AEDs included phenobarbital and lorazepam. There were no other concomitant medications reported.

Proteinuria/Glomerulonephritis

Subject 1A/269 (ZSK) This Caucasian male born on — was enrolled on 23Apr99 weighing 10.4 kilograms. The subject was assigned to the low-dose group and began vigabatrin on 23Apr99 for infantile spasms. Vigabatrin was dosed at 1500 mg/day until decreased to 500 mg/day on 21Apr00.

On 25Aug99, he experienced an SAE (seriousness criteria unknown) described as decreased blood albumin lasting 1 day. He recovered from the SAE with no sequelae and the relationship to study drug was judged as unlikely. There were no related AEs.

On 25Aug99, he experienced an SAE (seriousness criteria unknown) described as proteinuria lasting 1 day. He recovered from the SAE with no sequelae and the relationship to study drug was judged as not related. He had 3 related AEs including proteinuria of unknown intensity on 22Apr99 continuing to study completion. Treatment was 'Other' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He also had mild kidney biopsy on 25Aug99. Treatment was 'None', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He had mild hypoalbuminemia on 25Aug99 continuing to study completion. Treatment was 'Other' and the investigator assessed the AE as not reasonably attributable to vigabatrin.

On — he experienced an SAE described as focal glomerulonephritis continuing to study completion. The relationship to study drug was judged as not related. He had 5 related AEs including moderate nephrotic syndrome on — continuing to study completion. Treatment was 'Hospitalization' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He also had mild hypertension for less than 1 week on 01Mar00. Treatment was 'Other', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He had moderate peripheral edema for 1 week on — Treatment was 'Hospitalization', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He had moderate nephrogenic anemia on — continuing to study completion. Treatment was 'Other', and the investigator assessed the AE as not reasonably attributable to vigabatrin. He had moderate anemia for 2 weeks on — Treatment was 'Other', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. Although there were 2 adverse events resulting in hospitalization (nephrotic syndrome and peripheral edema), these were not reported as an SAE by the investigator.

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On — he experienced an SAE (seriousness criteria unknown) described as infusion site swelling lasting 5 days. He recovered from the SAE with no sequelae and the relationship to study drug was judged as not related. There were no related AEs.

On 03May00, he experienced an SAE (seriousness criteria unknown) described as metabolic disorder lasting 1 day. He recovered from the SAE with no sequelae and the relationship to study drug was judged as not related. He had 2 related AEs including moderate vomiting for less than 1 week on — Treatment was 'Hospitalization', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He had markedly reduced dietary intake for less than 1 week on —). Treatment was 'Hospitalization', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. The 2 adverse events resulting in hospitalization were not reported as an SAE by the investigator.

Concomitant AEDs included phenobarbital, prednisolone, methylprednisolone, furosemide, and clorazepate. Other concomitant medications included albumin iv, amoxicillin, aspirin, captopril, cefotaxime, Epogen, general anesthesia, albumin iv 25%, Lasix iv, sedation iv, Kayexalate, Mylicon, Pedialyte, Pepcid, prednisone, Solu-Medrol, calcium carbonate, Tranxene, Tylenol, Xylocaine, and Zithromax.

No adverse events from study 3E01 (retrospective study not included in the integrated safety database) were designated as serious adverse events.

Post marketing SAE reports
Ovation stated that from 3/97-2/29/08 they identified 209 post marketing reports with 350 SAEs. Among these reports, 37 were for children <3 years old and 19 were for children 3 to 12 years old. For the <3 year old group, brain edema (n=3), encephalopathy (n=3), and nuclear magnetic resonance imaging brain abnormal (n=7) were the only events reported more than twice. For the 3-12 year old group, visual field defect (VFD) (n=6) was the only event reported more than twice (Safety update, 4/25/08, Table 1.12.1a). There was one SAE of face edema, one of angioedema, and one of rash. There were no SAEs of hepatic failure, aplastic anemia, anemia, or Stevens Johnson syndrome.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In the 3/14/08 response to Division questions, Ovation noted that 62% (216/346) of the subjects in the safety population for the IS NDA discontinued a trial prematurely. The most common reasons for discontinuation was other[1] (22%, 77/346), lack of efficacy (19%, 67/346), administrative reasons (10%, 35/346), protocol violation (4%, 13/346) and adverse event (3%, 12/346) (Source Submission dated 3/14/08, pp.13-6). A table summarizing the disposition of subjects by study type and location (Table 11.1) is included in an appendix to this review.

7.1.3.2 Adverse events associated with dropouts

Ovation reported that 6.4% (22/346) of vigabatrin subjects in their overall safety database discontinued from a trial due to adverse events. I list those subjects and the events leading to discontinuation in the following table.

Subject	Age (mos)	Sex	Adverse Event(s) Leading to Withdrawal
1A/171	7	M	Sedation
1A/206	7	F	Faecaloma
1A/213	10	M	Status epilepticus
1A/263	8	F	Otitis Media
1A/280	12	M	Convulsion, Rash
1A/303	6	F	Gastrointestinal infection, Post-operative infection
1A/352	11	F	Pneumonia, Status epilepticus
1A/401	13	M	Infantile spasms
1A/406	5	M	Hypertension, Infantile spasms
1A/411	14	M	Somnolence
1A/461	7	F	Pneumonia
1A/472	5	F	Convulsion
1A/481	1	F	Status epilepticus
1A/502	11	M	Irritability

[1] In their 5/07/08 response to Division questions, Ovation noted that other included the following: became spasm free, n=64; changed to Sabril from Canada, n=4; study closure, n=5; medication no longer available, n=2; to start felbamate, n=1; VFD risk, n=1.

1A/559	1	F	Death, Pulmonary hemorrhage
1A/660	8	F	Blood alkaline phosphatase increased
1A/911	5	F	Death
3325/407332623	8	M	Dystonia
3325/407332628	5	M	Developmental coordination disorder
3325/407332647	4	M	Weight increased
3325/407332656	5	F	Hypertonia, Insomnia
0332/40733231	23	M	Hyperkinesia

In this relatively small collection of events, there did not appear to be clusters of similar adverse events leading to discontinuation.

Two adverse events from study 3E01 (retrospective study not included in the integrated safety database) led to discontinuation. Patient 07-06-05 discontinued for myclonic status and patient 08-02-01 discontinued vigabatrin for irritability. The narrative for patient 08-02-01 noted that the patient died 2 months after discontinuing vigabatrin and the cause of death was CMV infection (3E01 Study report, p.50).

7.1.4 Other Search Strategies

Ovation did not conduct any additional analyses to assess particular toxicities.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In study 1A, the largest source of safety data in the NDA (222 of the 346 subjects), adverse events were elicited through open ended questions and were captured on an AE sheet in the CRF. The AE sheet captured information on the onset and cessation dates, intensity, seriousness, action taken, outcome, opinion of investigator on causality, and description of the event. During the randomized single blind phase of this trial, subjects were seen at the week 2 visit, where any AEs were recorded. During the open label phase, subjects were seen at months 1, 2, 3, 6, 9, 12, 18, 24, 30, and 36. Subjects were also to be seen for follow up 2 weeks and 3 months after final dose.

Studies W019, FR03, and 3325, (total 103 exposed IS subjects) had AE sheets in their CRFs. Investigators elicited AEs through open ended questions and AE sheets captured the event, dates of onset and cessation, severity, opinion about causality, action taken, and outcome. Study W019 assessed subjects on each of the first 8 days and then at weeks 4, 8, and 16. Study FR03 assessed subjects at weeks 2, 4, 6, and 8. Study 3325 assessed subjects weekly.

Ovation categorized adverse events as treatment related when the investigator recorded in the CRF the relationship to study drug as "suspected", "probably", "certain", "definite", or "highly probable" (NDA ISS submission, Appendix 2, p.197).

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Using the data sets submitted with the NDA and those submitted on 2/12/08, I examined the coding of adverse event verbatim terms to preferred terms for studies 1A, W019, FR03, and 3325. The coding appeared appropriate and there were no egregious examples of splitting similar events, lumping unrelated events, or incorrect coding. The coding of verbatim terms should have allowed for accurate analyses of adverse events in the IS study subjects.

7.1.5.3 Incidence of common adverse events

Ovation reported that in the IS controlled trials, 85% (221/261) of vigabatrin treated subjects experienced one or more adverse events (NDA ISS submission, p.42). The adverse events reported by at least 5% of vigabatrin treated subjects are listed below.

Infections and Infestations - upper respiratory tract infection (40.61%), otitis media (31.03%), viral infection (16.86%), pneumonia (11.11%), ear infection (9.20%), sinusitis (6.13%), bronchitis (5.75%)

Nervous System Disorders - somnolence (16.48%), sedation (15.33%), lethargy (5.75%), convulsion (5.36%)

Gastrointestinal Disorders - vomiting (14.18%), constipation (11.49%), diarrhea (10.73%)

Psychiatric Disorders - irritability (16.86%), insomnia (9.58%)

General Disorders and Administration Site Conditions - pyrexia (20.69%)

Respiratory, Thoracic, and Mediastinal Disorders - nasal congestion (7.28%)

Skin and Subcutaneous Tissue Disorders - rash (8.05%)

Metabolism and Nutritional Disorders - decreased appetite (6.51%)

In study 3E01, the retrospective study not included in the integrated database, 33 patients (13.2%, 33/250) experienced 42 adverse events. The reported AEs were somnolence (n=15), hyperkinesia (n=8), insomnia (n=5), hypotonia (n=4), nervousness (n=3), agitation (n=1), asthenia (n=1), coma (n=1), laryngitis (n=1), myoclonus (n=1), diarrhea (n=1), and weight increased (n=1) (Source Study report 3E01, p.47).

7.1.5.4 Common adverse event tables

For AEs in controlled IS trials, Ovation provided Table 8. The information in Table 8 is of limited value in terms of assessing AE risk by treatment because trial FR03 (cross-over study) had data for only 12 hydrocortisone and 18 vigabatrin subjects and W019 had data for only 20 vigabatrin and 20 placebo subjects, and the treatment period was 5 days. Table 8 also provides

the data from trial 1A (a low dose/high dose comparative trial with a 14-21 days single blind phase) for all vigabatrin subjects combined, offering no comparative value. Despite the limitations noted above, the data from FR03 and W019 provide the only available comparative data from table 8. I provide the AE risks by treatment from these trials below.

Adverse Events Occurring during Trial FR03 and the Controlled Phase of Trial W019				
	FR03		W019	
Event	Hydrocortisone (n=12) % (n)	Vigabatrin (n=18) % (n)	Placebo (n=20) % (n)	Vigabatrin (n=20) % (n)
Any System Organ Class				
Any Event	83.3% (10)	33.3% (6)	35% (7)	35% (7)
Infections and Infestations				
Any Event	16.7% (2)	11.1% (2)	15% (3)	10% (2)
Upper Respiratory tract infection	0	0	5% (1)	0
Bronchitis	0	0	0	5% (1)
Infection	0	5.6% (1)	0	0
Rhinitis	0	0	10% (2)	5% (1)
Bronchiolitis	0	5.6% (1)	0	0
Oral candidiasis	8.3% (1)	0	0	0
Laryngitis	8.3% (1)	0	0	0
Rhinovirus infection	0	5.6% (1)	0	0
Nervous System Disorders				
Any Event	33.3% (4)	16.7% (3)	10% (2)	20% (4)
Somnolence	8.3% (1)	5.6% (1)	5% (1)	20% (4)
Hypotonia	0	0	5% (1)	0
Depressed level of consciousness	8.3% (1)	0	0	0
Hyperkinesia	8.3% (1)	5.6% (1)	0	0
Opisthotonus	8.3% (1)	5.6% (1)	0	0
Gastrointestinal Disorders				
Any Event	33.3% (4)	0	10% (2)	5% (1)
Vomiting	8.3% (1)	0	5% (1)	0
Constipation	0	0	0	5% (1)
Diarrhea	0	0	5% (1)	0
Abdominal pain	8.3% (1)	0	5% (1)	0
Abdominal distension	8.3% (1)	0	0	0
Dyspepsia	8.3% (1)	0	0	0
Psychiatric Disorders				
Any Event	58.3% (7)	22.2% (4)	0	0
Irritability	8.3% (1)	0	0	0
Insomnia	8.3% (1)	0	0	0
Agitation	33.3% (4)	11.1% (2)	0	0
Sleep disorder	16.7% (2)	0	0	0
Abnormal behavior	0	5.6% (1)	0	0
Restlessness	0	5.6% (1)	0	0
Affective disorder	8.3% (1)	0	0	0
Decreased activity	8.3% (1)	0	0	0
General Disorders and Administration Site Conditions				
Any Event	16.7% (2)	0	5% (1)	0
Pyrexia	0	0	5% (1)	0

Hunger	16.7% (2)	0	0	0
Skin and Subcutaneous Tissue Disorders				
Any Event	0	0	10% (2)	0
Rash	0	0	5% (1)	0
Erythema	0	0	5% (1)	0
Eye Disorders				
Any Event	8.3% (1)	0	0	0
Conjunctivitis	8.3% (1)	0	0	0
Investigations				
Any Event	25% (3)	0	0	0
Weight increased	25% (3)	0	0	0
Vascular Disorders				
Any Event	16.7% (2)	0	0	0
Hypertension	16.7% (2)	0	0	0
Endocrine Disorders				
Any Event	16.7% (2)	0	0	0
Cushingoid	16.7% (2)	0	0	0

Source: Table 8, NDA Submission, pp.44-50.

Somnolence occurred more frequently among vigabatrin subjects compared to placebo subjects in study W019. The small number of events and subjects limits the usefulness of this analysis.

7.1.5.5 Identifying common and drug-related adverse events

Given the small size of the IS safety database and the IS study designs, it is difficult to identify drug related adverse events. Identification of drug related adverse events generally relies on comparative analyses from randomized double blind placebo controlled trials.

Ovation's NDA presentation included Table 10, which listed the AEs commonly occurring (in at least 2% of subjects) in the overall IS safety population along with the risks for those events. I include this table as an appendix to this review. Many of the most commonly reported events (>10%) were infection-related and included Upper respiratory tract infection (31%, 107/346), Otitis media (24%, 84/346), Pyrexia (16%, 56/346) and Viral infection (13%, 45/346). The commonly reported, non infection related AEs were Somnolence (15%, 53/346), Irritability (14%, 45/346), Sedation (12%, 41/346), and Vomiting (11%, 39/346).

The IS section of proposed labeling includes a table of the AEs occurring in at least 5% of subjects during trial W019 and a comparison of "treatment related" AEs in the low dose and high dose groups during the controlled portion of trial 1A. I provide those tables below.

Table 2. Treatment-Emergent Adverse Events Occurring in ≥5% of Patients (Study W019)

Body System Event	VGB [N=20] %	Placebo [N=20] %
Nervous System Disorders		

Table 2. Treatment-Emergent Adverse Events Occurring in ≥5% of Patients (Study W019)

Body System Event	VGB [N=20] %	Placebo [N=20] %
Somnolence	40	20
Infections and Infestations		
Ear infection	5	0
Psychiatric Disorders		
Irritability	5	0

Table 3. Treatment-Related Adverse Events Occurring in ≥2% of Patients (Study 1A)

Body System Event	VGB Low Dose [N = 114] %	VGB High Dose [N = 108] %
Nervous System Disorders		
Sedation	14	13
Somnolence	9.6	12
Lethargy	0	2.8
Psychiatric Disorders		
Irritability	7	5.6
Insomnia	4.4	4.6
Sleep disorder	4.4	1.9
Gastrointestinal Disorders		
Constipation	3.5	2.8
Metabolism and Nutrition Disorders		
Increased appetite	2.6	0.9

7.1.5.6 Additional analyses and explorations

Given that the majority of study subjects within the IS NDA database are <2 years old, examination of AE risks stratified by age is unhelpful.

Ovation provided Appendix 4 Table 4.1.8 that stratified AE risks by sex. In the table below, I identify the AEs occurring in at least 2% of either males or females and where the relative risk was at least 2 times greater when comparing males to females.

Adverse Event	Males n=176	Females n=168
Infections and Infestations		
Urinary Tract Infection	1.7% (3)	6.0% (10)
Gastroenteritis viral	0.6% (1)	6.6% (11)

Rhinitis	2.3% (4)	4.8% (8)
Roseola	1.7% (3)	3.6% (6)
Respiratory syncytial virus infection	1.1% (2)	3.6% (6)
Croup infections	2.8% (5)	1.2% (2)
Nervous System Disorders		
Status epilepticus	2.3% (4)	5.4% (9)
Febrile convulsion	1.1% (2)	2.4% (4)
Infantile spasms	2.8% (5)	0
Hemiparesis	0	2.4% (4)
Psychiatric Disorders		
Sleep disorder	3.4% (6)	1.2% (2)
Crying	0	2.4% (4)
General Disorders and Administration Site Conditions		
Adverse drug reaction*	4.0% (7)	1.8% (3)
Respiratory, Thoracic, and Mediastinal Disorders		
Rhinorrhea	0.6% (1)	4.8% (8)
Pneumonia aspiration	2.8% (5)	0.6% (1)
Upper respiratory tract infection	2.8% (5)	0.6% (1)
Aspiration	0	3.0% (5)
Respiratory disorder	0.6% (1)	2.4% (4)
Respiratory distress	2.3% (4)	0
Skin and Subcutaneous Disorders		
Eczema	2.8% (5)	1.2% (2)
Dermatitis diaper	1.1% (2)	2.4% (4)
Metabolism and Nutritional Disorders		
Feeding disorder	1.1% (2)	3.6% (6)
Increased appetite	2.8% (5)	0.6% (1)
Eye disorders		
Hypermetropia	1.1% (2)	2.4% (4)
Investigations		
Weight increased	2.3% (4)	0
Blood and Lymphatic System Disorders		
Neutropenia	2.3% (4)	1.2% (2)
Ear and Labyrinth Disorders		
Ear disorder	1.1% (2)	3.0% (5)

Other notable events Constipation Males 11.9% (21), females 6.6% (11)
* The preferred term Adverse drug reaction generally subsumed adverse events that were likely due to concomitant medications.

Without placebo comparator data we cannot determine if the observed differences in risk by sex in these vigabatrin subjects reflect differences in the background risk for these events or are due to a drug sex interaction.

Ovation provided Table 14 that stratified AE risks by race, but this table is of limited value. Ovation reported that 57% (197/346) of study subjects were Caucasian and 24% (87/346) were of unknown race leaving only 27 subjects classified as black and 39 subjects classified as other. Due to these small numbers of individuals in the different race strata the analyses of AE risk by race does not allow for robust examinations of drug race interactions.

Ovation examined AE risks for evidence of dose response. Ovation examined dose response in study 1A. Study 1A was a randomized parallel group single blind study comparing low dose (18-36mg/kg/day) and high dose (100-148mg/kg/day) vigabatrin for the treatment of IS.

Subjects randomized to the low dose group were divided into 2 groups on the basis of weight. Subjects weighting 3.5-7kg were administered 125mg/day and subjects weighing 7.1-14kg were administered 250mg/day (resulting dose range 18-36mg/kg/day).

Subjects in the high dose group were divided into 5 groups on the basis of weight. Subjects received the following treatments based ion their weight:

• Subjects 3.5 to 5.0 kg were started on 125 mg for the first 3 days of the study, then were increased to 250 mg on day 4, and then to 500 mg on day 7.
• Subjects 5.1 to 7.5 kg were started on 125 mg for the first 3 days of the study, then were increased to 375 mg on day 4, and then to 750 mg on day 7.
• Subjects 7.6 to 10.0 kg were started on 250 mg for the first 3 days of the study, then were increased to 500 mg on day 4, and then to 1000 mg on day 7.
• Subjects 10.1 to 12.5 kg were started on 375 mg for the first 3 days of the study, then were increased to 750 mg on day 4, and then to 1500 mg on day 7.
• Subjects 12.6 to 14.0 kg were started on 375 mg for the first 3 days of the study, then were increased to 750 mg on day 4, and then to 1750 mg on day 7.

Subjects who remained spasm free during the first 14 days of the fixed dose phase continued in the fixed dose phase for an additional 7 days and then were entered into the flexible dose phase. Subjects who were not spasm free by day 14 of the fixed dose phase were entered into the flexible dose phase which lasted from 2 weeks to 3 years.

Through the first 14 days of trial 1A, 51% (58/114) of the low dose subjects experienced 1 or more AEs compared to 48% (52/108) of the high dose subjects (NDA ISS submission, p.144). Ovation reported that sedation and somnolence were the most common adverse events during the first 14 days of treatment. In the low dose group, the risk for sedation was 15% compared to 12% in the high dose group. In the low dose group, the risk for somnolence was 10% and was 12% in the high dose group (NDA ISS submission, p.144).

I reviewed the study report for study 1A to examine the risks by dose group for the remaining adverse events. Table 14.4 listed all AEs by dose group occurring within the first 14 days of treatment. The results did not provide robust evidence of increased risks for adverse events in the high dose group compared to the low dose group and in fact the AE risks were comparable for the low and high dose groups.

Ovation did not examine AE risks stratified by concomitant medications (to look for drug-drug interactions) or by concomitant disease (to look for drug-disease interactions).

7.1.6 Less Common Adverse Events

Ovation's Table 11 provides a listing of the AEs occurring in <2% of the overall IS safety population. I include that table as an appendix to this review.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Trials in the IS safety database required laboratory testing including hematology, chemistry and urinalysis testing. The sponsor summarized results that were presented in the study reports. The sponsor conducted no pooled analyses of laboratory results. The laboratory results presented in the study reports were limited. Study 1A reported only limited laboratory outlier analysis results. Study W019 did not require laboratory testing during the double blind phase and only tested subjects at baseline and the end of week 24 (end of open label phase) (Source study report W019, p.63). In the study report for FR03, the sponsor reported that not all lab data were collected by investigators, precluding statistical analyses of these data. The sponsor only reported that no clinically relevant change was seen in the available data (Source Study report FR03). Study 3225 included comparisons of baseline and latest recorded median lab test results.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The sponsor separately summarized laboratory results from IS studies 1A, W019, FR03, and 3325. For the non-IS, studies with pediatric patients (300, 314, 332, 345, and WIT01) Ovation only reported that the studies were very small, demonstrated no apparent treatment related trends, and could not support definitive conclusions (NDA ISS, p. 90)

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

The study report for 1A did not include analyses focused on measures of central tendency. The Division requested mean change analyses for study 1A. Ovation noted that lab values were not collected during the blinded phase of the trial, when subjects were randomized to low or high dose vigabatrin. Lab data are available only for the open label phase of the trial, which allowed flexible dosing. When Ovation presented the results from the open label phase, the results were grouped by high dose and low dose, reflecting the original randomization, and for all subjects combined. Since the classification by dose does not necessarily reflect the dosing that the subject received at the time of the lab test, I present the combined data results below.

Subjects in study 1A experienced mean declines in AST and ALT. At month 1, the mean change from baseline for AST was -10.2 U/L and for ALT was -17.7 U/L. There did not appear to be marked additional declines among surviving subjects during months 3-30. At month 1, the mean change from baseline for ALP was 15.6 U/L. For months 2-24, surviving subjects experienced

mean declines in ALP (range -5.0 at month 18 to -13.5 at month 24). (Source 5/16/08 Response to Questions, pp.23-25).

At month 1, subjects in study 1A experienced a mean decline in hematocrit of -0.65% and hemoglobin of -0.33g/dL. For the remaining months of the study, the surviving subjects experienced mean increases and deceases in hematocrit and hemoglobin compared to baseline (Source 5/16/08 Response to Questions, pp.41-44). For platelets, study subjects consistently experienced mean decreases for all study months with the largest mean decline compared to baseline at month 24 (-56.7 $x10^3$, n=39) (Source 5/16/08 Response to Questions, pp.52-53).

Study FR03 included no statistical analyses of lab data.

For study W019, the study report provided mean changes from baseline to end of study (week 24). The end of study results were from the open label phase. I provide select mean change results from study W019 in the following table.

Select Mean Change from Baseline Results from Study W019

Laboratory Test	n	Mean change from baseline
Hemoglobin (g/dL)	24	-0.1
Hematocrit (%)	21	-3.2
RBC ($x10^{12}$/L)	20	-0.2
WBC ($x10^9$/L)	24	0.5
Platelets ($x10^9$/L)	24	-43.6
ALT (IU/L)	21	-13.8
AST (IU/L)	23	-6.3

Source Study report W019, pp.137-8.

For study 3325, the study report provided comparisons of median tests at baseline and for the last recorded result. I provide those results in the following table.

Median Baseline and Last Recorded Results from Study 3325

Laboratory Test	Median Baseline (n)	Median Last Recorded (n)
Hemoglobin (g/dL)	12.1 (34)	11.8 (33)
Hematocrit (%)	38.5 (33)	38 (33)
WBC (x1000/mL)	8.8 (34)	9.4 (33)
Platelets (x1000/mL)	409 (34)	452 (33)
ALT (IU/L)	14 (27)	4 (31)
AST (IU/L)	17 (27)	17 (32)
Sodium (mmol/L)	139 (31)	139 (34)
Creatinine (mcmol/L)	40 (31)	41 (33)

Source Study report 3325, p.38.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

For study 1A, the sponsor identified of the percentage of subjects with lab result outliers after 1 month of treatment. The study report for 1A noted that of the 145 subjects with normal

hemoglobin at baseline, 18 (12.4%) had a low outlier result after 1 month of vigabatrin treatment and of the 147 subjects with a normal hematocrit at baseline, 8 (5.4%) had a low result after 1 month of vigabatrin treatment. For ALT, of the 117 subjects with a normal result at baseline, 8 (6.8%) had a low outlier after 1 month. No subjects had a low outlier for AST. At baseline, 106 subjects had normal ALP, one subject had a low ALP and 48 subjects had high ALP. Of the 106 subjects with normal ALP at baseline, 17 developed high outliers at month 1. At baseline, 76 subjects had normal platelet counts, one subject had a low platelet count and 66 subjects had high platelet counts. Of the 76 subjects with normal platelet counts at baseline, 2 developed low outliers at month 1 (Source: Study report 1A, p.362-374).

There was no outlier analysis of lab data for study W019, FR03 or 3325.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Ovation did not identify marked outlier lab results. Ovation did identify adverse events related to lab results from the Safety Population (n=346). Those results are listed below.

- Hematology - anemia (7 subjects; 2.02%), neutropenia (6 subjects; 1.73%), iron deficiency anemia (2 subjects; 0.58%), white blood cell count increased (2 subjects; 0.58%).
- Clinical chemistry - blood alkaline phosphatase increased (8 subjects; 2.31%).
- Urinalysis - hematuria (3 subjects; 0.87%), white blood cells urine positive (2 subjects; 0.58%), proteinuria (2 subjects; 0.58%).

Ovation noted that none of these events were SAEs. One lab result related AE, blood alkaline phophatase increased, led to discontinuation from a trial. The narrative for that event is provided below.

Study 1A/Subject 660

A 7-month old multi- racial female experienced elevated alkaline phosphatase while on vigabatrin. Subject received first dose of low-dose vigabatrin therapy on 02Aug1997 and last dose on 26Sept1997. The event started on 03Sept1997. The investigator assessed the event as mild in intensity, not serious, and reasonably attributable to study medication. Study drug was discontinued prematurely due to the event and, as indicated on the study termination page, due to lack of efficacy since the subject continued to have spasms at the maximum allowed dose of vigabatrin. The event of elevated alkaline phosphatase resolved on 25Sept1997. Medical history included microcephaly, right gaze preference, questionable left homonymous hemianopsia, does not sit, left hemiparesis, severe delayed development, and recurrent diaper rash. Concomitant anticonvulsant medications included phenobarbital, Klonopin, and ACTH. Other concomitant medication information not provided.

I reviewed the subject's CRF and found that she had a baseline ALP of 245. After 1 month of vigabatrin, her ALP was 1498 and a repeat ALP 6 days later was 1752. The subject did not have elevations of total bilirubin or transaminases and calcium and phosphorus were normal. The ALP was not fractionated and GGT was not collected in this study. Vigabatrin was stopped and repeat ALP approximately 2 weeks later was 384.

7.1.7.4 Additional analyses and explorations

Ovation provided no additional lab data analyses.

7.1.7.5 Special assessments

Ovation conducted no special assessments using data from the IS studies. A review of lab data related to hepatotoxicity is presented in the adult CPS NDA Amendment review.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Trials in the IS safety database required capture of vital signs including blood pressure, heart rate, respirations and weight. The sponsor did not provide in the NDA a summary of vital sign results. The sponsor did not include analyses of vital sign results in the study report for study 1A. The study report for W019 summarized change from baseline results for blood pressure and heart rate at the end of the double blind phase and the open label phase, but did not summarize outlier results. In the study report for FR03, the sponsor reported only that no abnormal change of height or weight was reported during the study. In the study report for 3225, the sponsor only provided growth curves with height and weight plotted before and after vigabatrin treatment and commented that there did not appear to be an influence of vigabatrin on natural growth (Source study report 3325, p.32).

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Ovation provided no analyses of vital sign data in the IS NDA submission. I reviewed vital sign data from the individual IS study reports and requested additional vital sign analyses from Ovation.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Neither the ISS nor the study report included vital sign analyses for study 1A, the Division asked Ovation to provide this information. Ovation provided their response in a 4/23/08 submission. In the first 2 weeks of study 1A, subjects were randomized to low dose or high dose vigabatrin. After those 2 weeks, subjects continued in the open label phase where their doses of vigabatrin could be changed. During the first two weeks, there did not appear to be notable differences when comparing the low and high dose groups for vital signs mean changes from baseline. I provide the vital sign mean changes from baseline at week 2 for the low dose and high dose groups in the table below.

Vital Sign Mean Changes from Baseline at Week 2, Study 1A

Vital sign parameter	Treatment	Mean change from baseline to week 2
Diastolic Blood Pressure (mmHg)	Low dose (n=90)	-0.4
	High dose (n=74)	-0.5
Systolic Blood pressure (mmHg)	Low dose (n=102)	-0.6
	High dose (n=94)	2.9
Heart Rate (bpm)	Low dose (n=108)	-0.7
	High dose (n=98)	0.4
Respiratory rate	Low dose (n=86)	-0.6
	High dose (n=80)	0.5

Source Tables 5.2-5.4, 4/23/08 submission

At the end of the double blind phase of study W019, the mean change from baseline for diastolic BP was similar for vigabatrin (3.5mm Hg, n=17) and placebo (3.1mm Hg, n=15) subjects. Placebo subjects experienced a mean drop in systolic BP (-3.6mm Hg) and vigabatrin subjects experienced a mean increase (2.3 mm Hg). Placebo subjects experienced a mean increase in heart rate (4.9 bpm) but vigabatrin subjects experienced a slight decrease in mean heart rate (-0.6 bpm) (Source Study report W019, pp.896-7). At the end of the open label phase, study subjects experienced increases in mean systolic and diastolic BP (6.4 mmHg for both) and a mean decrease for heart rate (-4.6 bpm) (Source Study report W019, p.145).

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

None of the IS study reports included analyses of vital sign outlier results. The Division requested an outlier analysis of vital sign data from study 1A. In their 4/23/08 submission, Ovation provided an outlier vital sign analysis for Study 1A that defined outlier values as those >2 SD from the mean. The Division requested additional vital sign outlier analyses for Study 1A that used specific cutoff values. Those cutoff values are listed below.

Pulse

Age	Low	High
1-12 months	<100	>160
>12 months	<80	>110

Systolic Blood Pressure

Age	Low	High
1-12 months	<70	>110
>12 months	<74	>110

Diastolic Blood Pressure

Age	Low	High
1-12 months	<50	>70
>12 months	<55	>75

Respirations

Age	Low	High

1-12 months	<30	>60
>12 months	<24	>40

Ovation provided the results of their analyses in their 5/16/08 submission. Week 2 results from those analyses are summarized below. Week 2 includes data from subjects receiving randomized low or high dose vigabatrin. The remainder of the study allowed flexible dosing and so they lack comparative value.

Vital Sign Outlier Results, Study 1A, Week 2			
	High Dose	Low Dose	Combined
Pulse (BPM)			
N	82	85	167
Low outlier	1.2% (1)	4.7% (4)	3.0% (5)
High Outlier	2.4% (2)	9.4% (8)	6.0% (10)
Systolic Blood Pressure (mm Hg)			
N	66	81	147
Low outlier	3.0% (2)	8.6% (7)	6.1% (9)
High Outlier	19.7% (13)	12.3% (10)	15.6% (23)
Diastolic Blood Pressure (mm Hg)			
N	37	49	86
Low outlier	24.3% (9)	24.5% (12)	24.4% (21)
High Outlier	16.2% (6)	16.3% (8)	16.3% (14)
Respirations (resp/min)			
N	46	55	101
Low outlier	17.4% (8)	21.8% (12)	19.8% (20)
High Outlier	(0)	4.1% (2)	3.5% (3)

In general, outlier risks were either similar for the two vigabatrin dose groups or higher among the low dose group. There was a slight increase high outlier risk for systolic blood pressure for the vigabatrin high dose group compared to the low dose group.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Ovation did not identify marked outlier vital sign results or adverse events related to vital signs from the Safety Population (n=346). Two subjects from the IS safety population discontinued for vital sign related AEs. Subject 1A/406 discontinued for infantile spasms and hypertension. The hypertension in this case was felt to be due to ACTH. I provide that narrative for this event below.

Study 1A/Subject 406

b(6)

This 6- month old Caucasian male, weight 8.16 kilograms, with a history of infantile spasms due to encephalopathy, experienced infantile spasms (increased) while on vigabatrin. Subject had been on vigabatrin for 28 days prior to the event. The subject was hospitalized on — due to the event of infantile spasms, which continued despite vigabatrin therapy at the maximum dose of 1250 mg/day at the time of the event. The investigator assessed the causality as possibly related to vigabatrin with severity not indicated. On — the subject experienced mild hypertension related to ACTH administration. As a result of the increase in infantile spasms and the hypertension, the vigabatrin dose was tapered to discontinuation with last dose of drug on — The subject recovered from the infantile spasms on — nd from the hypertension on — Concomitant medications at the time

of the events included ACTH 0.375 cc IM BID from 18Feb1997 to 25Feb1997, 0.375 cc IM QD from 26Feb1997 to 06Mar1997 and Decadron 4 mg IM from 31Jan1997 to 3Feb1997, albuterol 2mg/5cc 1.5cc q6 hours prn. Medical history included prenatal history of maternal hypertension with hospitalization for 3 days and bed rest from 32 weeks to term. Caesarean section was performed after 28 hours of labor.

This subject had a baseline BP of 109/51 and a visit 3 (2/3/97) BP of 113/72. The CRF did not provide a BP result from around the date of discontinuation (2/29-3/3/97). A BP recorded 4 months after discontinuation was 93/77.

Subject 3325/407332647 discontinued for weight gain. I provide that narrative below.

Study 3325/Subject 407332647
This 4 year-old male with a history of West syndrome, simple partial seizures, tonic seizures, and complex partial seizures experienced weight increase while on vigabatrin. Subject received first dose of vigabatrin on 31Mar1989 and last dose on 18Dec1989. The event of weight increase occurred on 26Apr1989. The investigator assessed the event as moderate in intensity, and probably related to study drug. The study drug was stopped on 03May1989 for approximately one month, and was re-started due to persistence of spasms. The subject recovered from the event. Medical history included: severely abnormal axial hypotonia, moderately delayed (ocular contact +). Concomitant medications included phenobarbital, diazepam, carbamazepine, and phenytoin.

The subject's CRF documented a baseline weight of 5.7 kg that increased to 6.6 kg on April 26, 1989 and led to discontinuation. Vigabatrin was restarted, as noted above, and by 12/28/89 the subject weighed 9.8kg.

7.1.8.4 Additional analyses and explorations

Ovation provided no additional analyses of vital sign data.

7.1.9 Electrocardiograms (ECGs)

None of the NDA IS studies recorded ECGs.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

The IS NDA did not include a summary of ECG testing. A complete summary of the available ECG data in adults is provided in the CPS NDA Amendment Review.

7.1.10 Human Carcinogenicity

In a 5/7/08 submission, Ovation identified the incident cancer diagnoses in the vigabatrin development program. In the IS studies, two cancers were diagnosed. Study 1A subject 175, a 2 month old female was diagnosed with neuroblastoma 18 days after starting vigabatrin. Study 1A subject 475, a 13 month old female, was diagnosed with angiosarcoma after 9 months of vigabatrin treatment. One other pediatric cancer was diagnosed in the vigabatrin development program. Study 097-332 subject 40733203, a 9 year old male had an adverse event of "excision of an occipital hole tumor" after 7 months of vigabatrin treatment.

7.1.11 Special Safety Studies

Safety studies examining visual field changes in vigabatrin treated patients are reviewed by Dr. Ronald Farkas and data related to IME are being reviewed by Dr. Phillip Sheridan, both of the Division of Neurology Products.

7.1.12 Withdrawal Phenomena and/or Abuse Potential

Ovation noted that they did not examine adverse events with respect to timing of vigabatrin therapy withdrawal for the IS safety database. Ovation referred to withdrawal data derived from studies of vigabatrin in adults. Ovation noted that seizures have occasionally occurred and status epilepticus has rarely occurred in adults during the discontinuation of vigabatrin. Ovation felt that it would be prudent to recommend tapering vigabatrin when discontinuing its use. Ovation reported that none of the study reports submitted as part of the IS NDA reported withdrawal seizures.

Ovation also reported that the incidence of acute behavioral events following vigabatrin withdrawal in adults was <3%. Ovation did not characterize these events but suggested that tapering of vigabatrin may reduce the incidence of these events (Source, IS NDA ISS, p.163).

7.1.13 Human Reproduction and Pregnancy Data

Human reproduction data are not relevant to the population of patients with infantile spasms.

7.1.14 Assessment of Effect on Growth

Ovation provided no discussion of the effect of vigabatrin on growth in there is NDA submission. The Division asked Ovation to summarize data that would allow an assessment of growth in vigabatrin treated children.

In their 5/16/08 response to Division questions, Ovation identified pediatric studies that captured height and weight data. Ovation noted that CPS studies 0118, 0192, 0221, and 0294 and IS studies W019, FR03, and 1A recorded baseline and final height and weight. The protocols for these studies did not specify the methodology for measuring these parameters.
Ovation provided a table summarizing the weight and height changes in the CPS placebo controlled trials (duration 14-17 weeks). Ovation stratified the results by sex and by age (2-<12, 12-16). The results are included in the table below.

Weight and Height Mean Changes from Baseline in the CPS Placebo Controlled Trials

Sex	Vigabatrin		Placebo	
	Weight	Height	Weight	Height
2-<12 year olds				
Male n	42	6	28	7

Mean change from baseline	3.4kg	2.6cm	1.5kg	3cm
Female n	42	6	39	8
Mean change from baseline	4.1kg	2.1cm	2kg	1.1cm
>12-16 year olds				
Male n	80	10	46	12
Mean change from baseline	4.5kg	2.4cm	1.9kg	2.4cm
Female n	87	15	57	14
Mean change from baseline	4.3kg	1.9cm	1.8kg	2.4cm

The data suggest consistently greater mean increases in weight for pediatric CPS subjects exposed to vigabatrin compared to placebo. The increases in height were similar for vigabatrin and placebo subjects although these results are based on very small numbers of treated individuals. In addition, the lack of protocol specified methodology requiring careful height measurement would be expected to lead to notable inaccuracy and decrease the ability to detect drug related differences, if present.

As Ovation noted, the short duration for controlled phases of the IS studies precludes any meaningful comparative analyses of height and weight data. Ovation felt the mean weight gain for the entire treatment period (including open label) was within the range predicted by growth charts. (Source 5/16/08 Submission, pp.8-13).

7.1.15 Overdose Experience

Ovation did not present overdose information for the IS studies population in their IS NDA. Overdose data from prior vigabatrin regulatory submissions and the adult vigabatrin CPS submission documented the following adverse events: coma/semi comatose, drowsy/sleepy, vertigo, seizure, psychosis, apnea/irregular breathing, bradycardia, vomiting, confusion, agitation, status epilepticus, ataxia, delirium, concentration impaired, abnormal behavior, speech disorder, auditory hallucinations, psychosis, hypotension, hypothermia, headache, slowed thinking, irritability, tremor, oliguria, pupillary hippus, withdrawn, syncope, dehydration, and pulmonary infiltrates. (See NDA 20-427 Current Submission Review, p.76).

Ovation identified 2 pediatric subjects in the Overall Safety Population of their adult CPS submission with SAEs of overdose and one pediatric subject with an SAE of accidental overdose. Subject 0201 13870001, a 4 year old female (body weight 15.4 kgs) ingested 6g of vigabatrin (usual daily dose 0.9g/day). She was taken to an emergency department and underwent gastric lavage and was discharged home after 6 hours of observation. The narrative included no information about overdose related symptoms for this subject. Subject 0201 14100003, a 9 year old female (weight 152 pounds) ingested 12g/day for one month (usual daily dose 6g/day) due to the parents misreading the medication bottle. The narrative provided no details about symptoms but stated that the subject recovered and continued in the study. Subject 0201 13970001, a 4 year old female (body weight 15.4 kgs) ingested 30-40 500mg vigabatrin tablets (usual dose 1g/day). She was taken to an emergency department and underwent gastric lavage and was given charcoal. She was hospitalized overnight for observation. She experienced mild ataxia that resolved after several days. She continued in the study.

Ovation's proposed labeling for overdose identified many of the overdose symptoms listed above. Ovation notes that there is no antidote for vigabatrin and that measures to remove unabsorbed drug, including emesis or gastric lavage should be used. Ovation stated that charcoal does not significantly adsorb vigabatrin and that the effectiveness of hemodialysis in the treatment of vigabatrin overdose is unknown.

7.1.16 Post marketing Experience

Ovation submitted no summary of post marketing data with the IS NDA. Ovation did include in their IS NDA, periodic safety update reports that include post marketing information for all vigabatrin indications. A discussion of all post marketing information is included in the vigabatrin adult CPS NDA amendment safety review.

Ovation provided a summary of post marketing data in pediatric and IS patients in a 4/25/08 Safety Update. The Safety Update identified 1836 postmarketing reports in vigabatrin treated patients. Patient age was included in 1293 reports, and of these, 117 described events in patients aged less than 3 years old. For this group of 117 reports, 61 patients were males and 45 were females. Seventy-four of these 117 reports noted the indication for vigabatrin use. Ovation reported that 33 patients were treated for IS, 32 for generalized seizures, 3 for partial seizures, and 56 for other indications. The adverse events most commonly reported for children <3 years old were from the Nervous system. The AEs reported at least 5 times in this age group were nuclear magnetic resonance imaging brain abnormal (n=14), agitation (n=8), somnolence (n=6), and convulsion (n=5). In addition, there were 3 reports of weight increased, 2 reports of angioedema, 2 reports of peripheral edema, 2 reports of urticaria, no reports of anemia, renal failure, hepatic failure or Stevens Johnson syndrome. Ovation felt that the information in the Safety Update did not identify any new safety concerns.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Ovation cites the following four sources of safety information to support their vigabatrin application for the treatment of infantile spasms:

1) an integrated database from 3 controlled trials and 6 uncontrolled trials
2) safety information from an uncontrolled retrospective study, not included in the integrated safety database
3) postmarketing surveillance
4) published literature

Ovation further divided the integrated database into primary data for IS patients (from 3 adequate and well controlled phase III studies 1A, W019, and FR03; and one primary uncontrolled trial 3325, n=325) and secondary data for pediatric patients with refractory epilepsy (from studies

300, 314, 332, 345A, WIT01, n=21). (Source ISS, p.12) The following table summarizes the composition of the integrated database:

Table 1. Description of Study Populations in the Integrated Safety Database

Population	Study Type	Protocols Included	Treatment Groups	Subgroups Summarized (Vigabatrin Only)
Safety N=346	All	1A, W019, FR03, 3325, 300, 314, 332, 345A, WIT01	Vigabatrin	Gender[1] Race[2]
IS Subjects[3] N=325	All	1A, W019, FR03, 3325	Vigabatrin	Gender[1] Race[2]
	Controlled Non-US	W019, FR03	Vigabatrin Hydrocortisone Placebo	Gender[1] Race[2]
	Controlled US	1A	Vigabatrin	Gender[1] Race[2]
	Uncontrolled non-US	3325	Vigabatrin	Gender[1] Race[2]
Non-IS Subjects (<36 mos. of age)[4] N=21	Uncontrolled non-US	300, 314, 332, 345A, WIT01	Vigabatrin	Gender[1] Race[2]

1 Gender = male, female.

2 Race = Caucasian, Black, Other, Unknown.

3 All studies presented for the IS Subjects Population were IS studies (i.e., included only subjects with IS). However, data from Study 1A included 2 subjects >36 months of age (3.1 and 3.9 years) and 4 subjects of unknown age, and Study 3325 included 8 subjects >36 months of age (37, 46, 62, 88, 90,98, 119 and 150 months old).

4 Data from Study WIT01 included 2 subjects >36 months of age (40 months and 118 months old).

IS = infantile spasms; US = United States.

Source: Appendix 4 Table 1.2

Ovation obtained the data for the integrated database in the form of SAS data sets and data listings from the previous sponsor (Avents). Ovation also received the individual study reports for the integrated studies. Ovation acknowledged instances where the datasets and study report presentations differed (missing data in datasets, sample size differences, data on deaths, SAEs, AEs). Ovation noted that clinical laboratory data and other safety data were taken directly from the study reports. (Source ISS, p.16)

The safety data for non-Integrated study 3E01 were retrieved from the study report. Ovation provided Case Report Forms (CRFs) and patient narratives for deaths, SAEs, and AEs leading to withdrawal. In addition, Ovation provided datasets with select data for individual patients.

7.2.1.1 Study type and design/patient enumeration

Integrated Safety Database
Using data from Ovations Appendix 4, Table 3 (p.1142) I created the following table that summarizes the exposure in the NDA integrated safety database.

Exposure in the Integrated Safety Database for the Vigabatrin IS NDA		
Data Source	Number of Subjects	Subject Days of Exposure
IS studies		
Controlled Trials		
Vigabatrin	261	100890
Hydrocortisone	12	N/A
Placebo	20	100
Uncontrolled		
Vigabatrin	80	5151
Subtotal Vigabatrin IS	*325*	*105240*
Non IS Studies		
Uncontrolled		
Vigabatrin	*21*	*2464*
Total Vigabatrin	**346**	**107704**

The number of vigabatrin subjects from the different categories cannot be summed to arrive at the total due to the fact that some subjects are included in both controlled and uncontrolled studies.

Non-Integrated Safety Study 3E01
Study 3E01 reported safety data for 250 subjects.

Below I summarize details from trials included in the integrated safety database. A more complete description of these trials is included as an appendix to this review.

Studies Contributing Safety Data to the Integrated Safety Database

Study	Design	N[1]	Doses	Duration
Infantile Spasms Controlled Trials[2]				
1A	Randomized, single blind, with open label follow up	222[3]	18-36mg/kg/d (low) 100-148mg/kg/d (high)	1 week (219 subjects) to 54 months (1 subject)
W019	Randomized, double blind, placebo controlled with open label follow up	40	50mg/kg/d (initial) titrate to 150mg/kg/d	Up to 6 months
FR03	Randomized open label response mediated crossover (hydrocortisone)	18	150mg/kg/d	2 month randomized period
Infantile Spasms Uncontrolled Trial				
3325	Open label	45	50-150mg/kg/d	2d-23 months
Refractory Epilepsy Uncontrolled				
300	Open label	2	0.5-3g/d	27d-31months
314	Open label	1	titration to max dose	Up to 18 months

			of 2,3,or 4g/d	
332	Open label	4	50mg/kg/d (initial), 20-150mg/kg/day (flex dose)	4d-2.3 years
345A	Open Label	3	40-80mg/kg/d (<8 yrs old)	1-18.5 months
WIT01	Open Label	11	60-80mg/kg/d (titrate to optimal dose)	4 -6months

Source NDA Table 2
[1]Number of subjects contributing data to the integrated safety database
[2]These studies also had open label follow up extension periods
[3]One additional subject missing dose information is included in integrated analyses but was not included in analyses in the study report (Source ISS, p.21)

Study 3E01, the retrospective study not included in the integrated database, was conducted in 11 European countries and was designed to collect data on IS patients who received no other drug for IS and who were treated with vigabatrin as first line therapy.

Demographics
Integrated Safety Database
Ovation reported that the integrated safety population was nearly evenly divided in terms of sex (176 male, 168 female, 2 missing information). The mean age of study subjects was 1 year with a range of 0.1 to 12.5 years (NDA p.37).

Non-Integrated Safety Study 3E01
The sponsor reported that demographic data were available for 192/250 subjects in study 3E01. This study had a male preponderance (57%, 109/192). The sponsor did not report age data for these patients but noted that the mean age of onset of IS for these patients was 5.8 months (NDA, p.37).

7.2.1.2 Extent of exposure (dose/duration)

Integrated Safety Database

Dose
Ovation reported that the dose range for the controlled trials in the integrated safety database was 105-369.5mg/kg/day. For the uncontrolled trials, the dose range was 200-400mg/kg/day. Ovation provided a table that summarized dose data for study 1A and I include that table below.

Table 4. Average Daily Dose of Vigabatrin

Prescription Day from First Dose	High-dose	Low-Dose
Days 1-14		
N	107	114
Mean ±SD (mg/kg/day)	84.7±16.4	29.0±7.8
Range	22.2-132.1	10.5-64.7
Median	83.7	28.1

Days 15+		
N	105	114
Mean ±SD (mg/kg/day)	144±46.9	126.8±66.8
Range	53.1-346.5	18.1-369.5
Median	133.9	122.9

Duration
Ovation provided duration of exposure data in Table 3 (p.33). For the 346 subjects in the integrated database, Ovation reported that 172 were exposed to vigabatrin for more than 6 months, 120 were exposed for more than 1 year and that 75 subjects lacked sufficient data to determine the duration of exposure. I summarize duration of exposure data from Table 3 in the following table.

Duration of Exposure to Vigabatrin, Integrated Safety Database Population					
	Controlled Studies, IS		Uncontrolled Studies		Total
	Non-US	US	Non US, IS	US, non IS	
	N=38	N=223	N=80	N=21	N=346
1-14 days	20	2	0	0	7
>14-30 days	0	6	1	0	7
>30-60 days	0	23	0	0	23
>60-90 days	0	14	1	0	23
>90 days-6 mos	0	17	28	2	47
>6mos-1 year	0	40	3	9	52
>1-2 years	0	71	0	0	71
>2-3 years	0	36	0	0	36
>3-5 years	0	13	0	0	13
Missing	18	1	47	10	75

Note: Rows cannot be summed to arrive at the number provided in the total column. For this table, the exposure duration for subjects that participated in both controlled and open label phases of studies is represented in each phase separately and then represented in the "Total" column for the subjects' total exposure duration. This occurred in study W019 which included both placebo-controlled and open label phases. For example, a subject that participated in the "Controlled" phase of W019 for 13 days, and then rolled over into the "Uncontrolled" phase for 92 days, the subject is counted: in the "Controlled" column, "0-14 days" row; in the "Uncontrolled" column, ">90 days – 6 months" row; and in the "Total" column in the ">90 days – 6 months" row to represent a total duration of 105 days. (Source, 3/14/08 submission, p.12)

Combined Dose and Duration

Study 1A
In Table 6, Ovation summarized dose and duration for subjects enrolled in study 1A. For the high dose group (mean 139mg/kg/day, median 131 mg/kg /day) Ovation reported that 75 subjects were exposed for at least 6 months and 58 subjects were exposed for at least 1 year. For the low dose group (mean 122mg/kg/day, median 119mg/kg/day) Ovation reported that 86

subjects were exposed for at least 6 months and 67 were exposed for at least 1 year (Source Table 6, p.36).

IS Population
In response to a request from the Division, Ovation provided a table summarizing exposure by dose and duration for the entire IS safety population. I provide that information below (Source 3/14/08 submission).

Table 3.1: Patient Exposure to Vigabatrin by Dose and Duration (number of patients)

	Vigabatrin Dose (mg/day)									
Duration	0*	>0 to 250	>250 to 500	>500 to 1000	>1000 to 1500	>1500 to 2000	>2000 to 3000	>3000 to 4000	>4000	Unknown
≤ 1 week	174	45	45	19	13	6	1	1	1	19
>1 week to 1 month	8	29	79	50	33	16	6	0	1	9
>1 to 3 months	16	22	78	92	65	31	7	1	0	9
>3 to 6 months	4	4	10	34	43	19	10	1	0	19
>6 to 9 months	0	0	3	22	12	11	7	1	0	5
>9 months to 1 year	1	0	6	24	22	14	5	0	0	4
>1 to 1.5 years	0	1	4	9	24	17	4	2	0	4
>1.5 to 2 years	0	1	2	9	14	8	9	1	0	2
>2 to 2.5 years	0	1	6	4	7	11	8	0	0	2
>2.5 to 3 years	0	0	1	3	12	4	4	1	0	0
>3 to 3.5 years	0	0	3	3	3	4	3	0	0	0
>3.5 to 4 years	0	0	0	1	5	3	2	0	0	0
>4 years	0	0	0	2	8	5	5	0	0	0

Includes studies W019, FR03, 1A, 332.5, 300, 314, 332, 345A, WIT01.
Note: Subjects are counted at all dose levels received during the study. A single subject may be counted in multiple columns, but only one row per column.
Note: In study W019 dose information is recorded in mg/kg/day. Six subjects in study W019 do not have weight available, so the dosing cannot be converted to mg/day for consistency with other studies. The dosing information for these six subjects is excluded.
Note: In study OVATIA 16 doses (belonging to 7 subjects) were recorded in 'tablets'. Without a known formulation this cannot be converted to mg/day. The dosing information for these 16 records is excluded.
* 0 indicates off drug, not placebo.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

As noted above, Ovation included data from study 3E01 in their safety presentations but these data were not integrated with the primary data that was the basis of their analyses. Study 3E01 was a retrospective chart review of patients with IS that received only vigabatrin as their treatment for IS. Study 3E01 captured data on AEs and deaths. Ovation did not integrate data from 3E01 with the rest of the IS studies because this was a retrospective study (Source IS NDA, ISS, pp.11-12)

7.2.2.2 Postmarketing experience

Ovation provided post marketing data in a 4/25/08 Safety Update to the IS NDA. Adverse event information from that summary is included above in the relevant review sections.

Exposure
Ovation gathered post marketing exposure estimate data from Periodic Safety Update Reports written by Aventis. Ovation provided 2 tables with exposure information. Table 39 (4/25/08

Safety Update submission, p.55) summarized exposure in patient months by region for the years 1989-1994. This table provided sales data that were converted to person time (patient months) estimates using the assumed daily dose of 2g/day. The estimated person time exposure for this interval was 166,377 person years (1,996,533 patient months). Table 40 provided estimates of the number of patients exposed for each year from 1992 through 2005. These estimates were created using sales data and were based on the assumptions of an average daily dose of 2g/day and an average duration of treatment of 6 months. I converted these patient estimates to person time estimates by multiplying the number of patients by 6 months (the average estimate of use) and then dividing by 12 months (to convert to years). I then summed the person time for each year from 1995-2005 (not covered in table 39), to yield an estimated 646,800 person years of use. Summing the data from tables 39 and 40, I estimated a total of roughly 813,200 person years of use from 1989-2005.

For 1/06-6/06 Ovation estimated 14,794 person years of vigabatrin use and for 7/06-6/07 Ovation estimated 28,219 person years of use. Adding the person year estimates for 2006-6/07 (roughly 43,000 PYs) to the exposure estimate for 1989-2005 (813,200 PYs), yields an estimated person time exposure for 1989-6/07 of roughly 856,200 patient years exposure.

The exposure information from Ovation demonstrates that vigabatrin use peaked in 1998 and declined yearly since (with the exception of 2003). The first publication of vigabatrin related visual field defect cases occurred in 1997. The table below includes information from Ovation's Table 2 included in the post marketing section of their current submission and data from their response to Division questions (5/16/08).

Estimated Number of Patients Exposed from Marketed Use of Vigabatrin 1992 through 2004

Worldwide Patient Exposure / Year						
1992	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**
50,546	87,638	108,762	126,989	137,193	153,152	162,958
1999	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**
151,992	119,024	98,577	84,672	114,611	84,648	59,742
1/06-6/07*						
86,026						

Exposure was calculated based on the assumption that each patient received 2 grams (4 tablets daily) for 6 months (183 days).
*Includes 18 months of data
Source Data: PSUR No. 13, 14, 15 (Appendix 3); Safety Update Submission 4/25/08, p55.

Reports
Current submission
Ovation identified 1836 reports for the period 3/15/97-2/28/08 from the following sources: spontaneous reports (n=1487), medical literature (n=228), regulatory agencies (n=27), and unknown (n=94).

I provide demographic and indication information for the reports in the following table.

Demographic and Baseline Characteristics of Patients Described in Vigabatrin Postmarketing Adverse Event Reports	
Variable	Vigabatrin Reports[1] (N=1836) n (%)
Gender (age <3)	
Male	61 (52.1)
Female	45 (38.5)
Unknown	11 (9.4)
Gender (age 3-<12 years)	
Male	84 (51.8)
Female	71 (43.8)
Unknown	7 (4.3)
Age Groupings	
< 3 Yrs	117 (6.4)
3 to <12 Yrs	162 (8.8)
12 to <65 Yrs	968 (52.7)
>= 65 Yrs	46 (2.5)
Unknown	543 (29.6)
Race	
Asian	1 (0.1)
Caucasian	2 (0.1)
Other	1 (0.1)
Unknown	1832 (99.8)
Reported Indication for VGB Use (age<3 years)	
Infantile spasms	33 (28.2)
Partial seizures[2]	3 (2.6)
Generalized seizures, and seizures NOS[3]	32 (27.4)
Other reported indications [4]	6 (5.1)
Unknown	43 (36.7)

NOS = not otherwise specified.
1 Includes events reported between 15 March 1997 and 28 February 2008
2 Partial seizures include the following indication terms: Complex partial seizures, Frontal lobe epilepsy, Partial seizures, Simple partial seizures, Temporal lobe epilepsy.
3 Generalized seizures include the following indication terms: Convulsion, Epilepsy, Grand mal convulsion, Petit mal epilepsy, Status epilepticus.
4 Other (non-seizures) include the following indication terms: Accidental exposure, Cerebral palsy, Congenital toxoplasmosis, Drug exposure during pregnancy, Electroencephalogram abnormal, Encephalopathy, Muscle spasms, Post herpetic neuralgia, Post-traumatic epilepsy, Sturge-Weber syndrome, Tuberous sclerosis.

Source: Safety Update 4/25/08, p.57

Ovation reported that the top 5 countries with spontaneous adverse event reports were Great Britain (n=491), France (n=416), Australia (n=122), Denmark (n=91), and Canada (n=97). (Source Safety Update 4/25/08, p.56)

7.2.2.3 Literature

Ovation provided a review of the medical literature. Ovation hired NERAC Inc. to search the medical literature. The searches spanned from the inception of the individual literature databases

to 6/30/07 for the IS NDA and from 7/1/07 through 2/28/08 for the IS Safety Update. NERAC Inc. searched the following sources: US patent applications, BIOSIS,, Business News International, Chemical Business News Base, European patent applications, European patent granted, GB patent applications, International Pharmaceutical Abstracts, MEDLINE, New Product Announcements, Newsletter Index, Patent Abstracts of Japan, PCT, US patents issued, and Trade and Industry. NERAC used the following search terms: vigabatrin, infantile spasms, West syndrome, Tuberous sclerosis, and vigabatrin and prednisone or ACTH. Ovation discussed only the publications subsequent to 3/97 since earlier publications were discussed in the NDA.

Through 6/30/07
Ovation reported that the literature search identified 40 publications discussing the use of vigabatrin in IS. The 40 publications were comprised of 21 journal articles, 6 case reports, 4 review articles, and 9 other publications.

The 21 journal articles were publications of 6 open label controlled trials and 15 open label uncontrolled trials. The publication by Gaily et al did not report AE data. Lux et al reported similar AE risks for 52 IS patients treated with vigabatrin and 55 patients treated with prednisolone or tetracosactide. In a follow up of subjects from that study, Lux et al reported that 2 prednisolone or tetracosactide patients died compared to 3 vigabatrin patients. The deaths were felt to be consistent with the course of IS. Vigevano et al reported that in a randomized open label cross over study of vigabatrin and ACTH, somnolence (n=2), hypotonia (n=2), and irritability (n=1) were observed with vigabatrin and hyperexcitability, irritability and increased appetite with ACTH. In another study by Vigavano et al, the investigators reported lower AE risks with vigabatrin compared to ACTH. Hammoudi et al published results of a study looking at visual field in IS patients treated with vigabatrin. In the publications describing open label studies, a number of AEs were reported in vigabatrin treated subjects including drowsiness, somnolence, sleep disturbances, insomnia, irritability, nervousness, hyperactivity, behavioral changes, increased seizure frequency, weight gain, and edema. Villeneuve et al noted in their open label study of 70 children with IS that 2 infants died, one was a sudden death and the other was due to congenital nephritic syndrome.

Among the cited case reports, Haas Lude et al described a 6 year old female with Alexander disease and hydrocephalus who presented with uncontrolled seizures and was treated with vigabatrin. The patient developed apathy, somnolence, and sluggishness. Vigabatrin was stopped and the symptoms resolved over 2 days. Pearl published two case series of MRI changes in children treated with vigabatrin.

Among the other reports cited by Ovation, adverse events mentioned in vigabatrin treated patients included irritability, somnolence, decreased sleep, and sedation.

The four review articled identified by the search included the article by Cohen et al mentioned above examining IME in patients treated with vigabatrin, two articles about treatment of infantile spasms, and one article about vigabatrin in treating pediatric epilepsy.

7/1/07-2/28/08
Ovation reported that the Safety Update literature search identified 16 publications including 4 journal articles, 5 review articles, and 7 other publications.

The 4 journal articles presented results from open label studies of vigabatrin. The publication by Mirabella et al reported results of visual testing. Two separate publications, one by Gumus et al, and a second by Mikati et al, reported results from a study using levitiracetam to treat IS. The journal publication by Dunin-Wasowicz et al reported results from a study that used ganciclovir and AEDs to treat 22 patients with CMV and IS.

Four of the 7 "other" publications were letters to the editor in response to a review article on vigabatrin. One publication was a letter to the editor explaining the author's conclusion that ACTH is superior to steroids and VGB for IS. Desguerre et al reported on MRI signal abnormalities among 6 of 20 children with IS seen over a 2 year period. Partikian et al conducted a retrospective chart review of 130 IS patients and found that 23% (14/60) of ACTH treated patients, 15% (5/34) of vigabatrin treated patients and 33% (6/18) of patients treated with other AEDs experienced a major AE during treatment. The authors did not report all of the AEs but did note that persistent irritability led to dose reduction in 2 patients and evidence of pigmentary retinopathy led to cessation of vigabatrin in 1 child.

Ovation noted that the review article by Parisi et al concluded that vigabatrin is a potentially effective therapy for children with Tuberous Sclerosis and spasms due to focal cortical dysplasia, but for infants with spasms due to other causes, the benefits of vigabatrin use should be weighed against ophthalmologic toxicity risk. The review article by Holmes and Stafstrom summarizes clinical aspects of Tuberous Sclerosis and discusses possible mechanisms of seizures and epileptogenesis, and presents a consensus statement from the Tubersous Sclerosis Complex Working Group for future research. The article by Landmark described the targets for antiepileptic drugs in the GABAergic and glutamatergic synapses and possible sites of action for antiepileptic drugs. The other two articles (Malphrus and Wilfong, Wheeless et al) were opinion statements on the treatment of pediatric epilepsy. (Source Safety Update, 4/25/08, pp. 66-75)

7.2.3 Adequacy of Overall Clinical Experience

The exposure in the IS safety database, in terms of number of subjects, falls short of the number recommended by ICH, although when one includes the data from the entire vigabatrin development program, the exposure is adequate. Ovation presented safety data for 346 IS subjects in the IS NDA and 172 of these subjects were exposed to vigabatrin for >6months and 120 were exposed for more than 1 year. The ICH Guidance recommends that 1,500 subjects be exposed with 300-600 subjects exposed for 6 months, and 100 exposed for 1 year (at relevant doses, with reasonable exposure to the highest proposed dose). In the Integrated database presented in the CPS NDA Amendment, Ovation reports that 4,077 epilepsy subjects have been exposed to vigabatrin and have sufficient information to assess AEs. Ovation reported that 3,456 of these subjects were exposed for >6months, 2,753 subjects were exposed for >1year and 403 subjects were exposed for >5 years (Source 3/14/08 Submission, Table 2.2, p.3).

Ovation's proposed vigabatrin labeling for IS recommends a starting dose of 50 mg/kg/day and a Maximum Dose of 100-150 mg/kg/day to be administered in two divided doses. This was the dose range used in the trials included in the IS safety database.

The designs of the submitted studies preclude reliable assessment of drug related AEs in the IS NDA. The paucity of controlled comparative data and short durations of the controlled periods of the small number of submitted trials do not provide sufficient opportunity to identify drug related events. Furthermore, collection of adverse event data in this population is hampered due to the young age and inability to verbalize complaints. One can rely on comparative safety data from the adult safety database although one must consider that extrapolation of these data from use in treating adults and children with seizure disorders to use in infants with IS may not be optimal.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The cardiac in vitro and animal testing submitted as part of the adult CPS amendment, which included examination of electrical stimulation threshold or the ventricular fibrillation threshold in perfused rabbit heart preparations, long term toxicity study in dogs that included ECGs, studies of vigabatrin's effect on the hERG channel current, and follow up tests in isolated rabbit Purkinje fibers appeared adequate. Additional non clinical studies since the NDA submission designed to examine specific safety topics included visual field defect toxicity studies, and juvenile rat toxicity study looking at developmental toxicity in neonatal and juvenile development.

7.2.5 Adequacy of Routine Clinical Testing

The approach used to collect adverse event data in the IS studies appeared appropriate, with AEs recorded at each visit.

The routine lab data testing in the vigabatrin development program appeared appropriate. The lack of comparative data limits the ability to assess the relationship between vigabatrin and abnormal results.

The IS studies did not capture ECGs.

Vital sign testing in the vigabatrin clinical trials was generally adequate. One notable deficiency for vital signs was the lack of carefully measured height and weight data in children to allow assessment of growth.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Ovation explains that vigabatrin is rapidly and completely absorbed, is not metabolized to a significant extent, does not induce cytochrome P450 enzymes systems in animals and is not

protein bound. Vigabatrin is eliminated unchanged through renal excretion. A decrease in phenytoin levels of 20-30% occurs with vigabatrin. Studies of vigabatrin and carbamazepine found no effect, increases, or decreases in carbamazepine concentrations. Other antiepileptic drugs reportedly have minimal effect on vigabatrin concentrations.

As noted in Dr. Leber's Division Director's 11/18/97 memo, OCBP concluded that the sponsor's approach to studying interaction between vigabatrin and other AEDs was acceptable (Source Division Director Vigabatrin Approvable Action Memo, 11/18/97, pp.12-13).

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The most important safety issues with vigabatrin are the permanent visual field defects and MRI/IME findings. Dr. Farkas and Dr. Sheridan address these topics in their reviews. In terms of the remaining general safety, there did not appear to be any major areas neglected in the application. Additional information would be helpful in terms of vigabatrin's effect on hemoglobin and hematocrit, assessment of edema risk in IS patients, and information on vigabatrin's effect on growth.

7.2.8 Assessment of Quality and Completeness of Data

To assess the quality and completeness of the safety data I examined the agreement of the submitted safety data across the various sources submitted by the sponsor. I compared the case report forms (CRFs), narrative summaries, study report listings, and in some cases, electronic data sets for deaths, selected serious adverse events and selected AEs leading to discontinuation. I found no significant quality issues with the IS NDA safety data. In terms of completeness of data, as noted above, 75 subjects were missing data that would allow determination of duration of exposure. In addition, the narrative summaries provided very limited clinical information and in many cases it was difficult to determine the nature of the adverse event experienced by the study subject from the description in the narrative. Many examples of narratives are included above.

7.2.9 Additional Submissions, Including Safety Update

In addition to the ISS submitted with the IS NDA 022-006 (12/28/07) this review includes information from the following sources:

NDA Amendment 020-427 (vigabatrin, CPS) submitted 12/28/07.
Responses to Division questions submitted 2/11/08, 3/14/08, 4/15/08, 4/23/08, 5/1/08, 5/2/08, 5/7/08, 5/16/08, 5/23/08, 5/27/08, 6/2/08, and 6/6/08.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Identification of drug-related adverse events depends largely on comparison of adverse event risks in the drug treated population to the placebo (or other comparator) treated population from randomized trials of sufficient duration. The controlled trial data submitted for the IS treated patients do not allow for reliable assessments of drug related adverse events. Study 1A compared low dose and high dose vigabatrin and the randomized treatment period was only 14 days. Study W019 randomized subjects to either vigabatrin or placebo but the randomized treatment period was only 5 days and the study only enrolled 40 subjects. Study FR03 was a cross over design study and only enrolled 18 subjects. Relying on uncontrolled data to identify common AEs does not allow one to discriminate between events that are drug related and those that commonly occur in the population being treated (i.e. background events).

In the following sections I will identify events that appear to be drug related based on analysis of data from vigabatrin trials in indications other than IS.

7.3.1 Visual Field defects
See Dr. Farkas' review.

7.3.2 IME/MRI abnormalities
See Dr. Sheridan's review.

7.3.3 Anemia/Declines in Hemoglobin, Hematocrit
In IS studies, 2% (7/346) of vigabatrin treated subjects developed an anemia AE. None of these events were SAEs or led to discontinuation. In IS study 1A, following 1 month of vigabatrin, 12% of study subjects who had a normal hemoglobin at baseline had a low outlier for hemoglobin. Lab data also suggested small mean declines from baseline for hemoglobin and hematocrit among vigabatrin IS subjects.

In the adult CPS amendment submission, lab data suggest that vigabatrin subjects experienced declines in hemoglobin and hematocrit that were not seen in subjects that received placebo. Vigabatrin subjects experienced mean decreases in hemoglobin from baseline and had higher risks for low HGb/Hct result outliers. Analyses also suggested that these declines were dose related. Despite these laboratory findings, vigabatrin subjects did not appear to experience high frequencies of concerning clinical events. Ovation reported that 3 vigabatrin subjects (0.06%, 3/4737) from the Integrated database experienced anemia SAEs, and 3 vigabatrin subjects (0.06%, 3/4855) from the Integrated database discontinued for anemia AEs. A search of the development program identified only 2 vigabatrin subjects that experienced unexplained declines in hemoglobin below 8g/dL and or hematocrit below 24%. In addition, there appeared to be few post marketing reports of anemia adverse events. The sponsors did not collect sufficient information to classify the observed anemia events.

7.3.4 Weight gain
One vigabatrin IS subject had an AE of weight gain. Data from children enrolled in CPS trials found a greater mean increase in weight among vigabatrin treated subjects compared to placebo treated subjects.

In the adult CPS amendment submission, weight data support that vigabatrin use is associated with weight gain. Data from controlled trials demonstrated that vigabatrin treated subjects had a higher mean increase in weight from baseline than did placebo treated subjects. In addition, vigabatrin subjects had a higher risk of gaining >=7% of baseline body weight. One analysis suggested that weight increase risk was greater among female vigabatrin subjects but there did not appear to be evidence suggesting differential weight increase risk by age. In the Integrated database, 10.2% (415/4077) of vigabatrin subjects had a weight increased AE.

7.3.5 Edema
In IS studies, two vigabatrin subjects (0.6%, 2/346) had edema peripheral AEs and one subject (0.3%, 1/346) had an edema AE.

In the adult CPS amendment submission, vigabatrin use was associated with development of edema. In the Integrated Database, Ovation identified 3% (124/4077) patients with AE of edema peripheral, 0.4% (16/4077) with edema, 0.1% (5/4077) with generalized edema, 0.1% (5/4077) with localized edema, 0.1% (4/4077) with facial edema, <0.1% (3/4077) with pitting edema <0.1% (3/4077) with gravitational edema. None of these events were SAEs, and only 5 edema peripheral events and 2 edema events led to discontinuation. In analyses of pooled controlled trial data, the risk of edema was higher among vigabatrin subjects compared to placebo subjects. Dose response analyses of controlled trials data suggested an increasing risk of edema peripheral and generalized edema with increasing vigabatrin dose but not other edema related adverse events. In a separate analysis of adult subjects with edema AEs, 50 of the 215 vigabatrin subjects with edema related AEs also had a weight gain AE (only 23 of these occurred within a month of the edema related AE). The edema AEs in these subjects did not appear to be related to cardiac, renal, or hepatic AEs and did not appear to be associated with increased creatinine, low serum albumin, or proteinuria.

7.3.6 Peripheral Neuropathy
There were no reported AEs of hyporeflexia or parasthesias for the vigabatrin subjects in IS studies.

In the adult CPS database, vigabatrin subjects had increased risk for parathesia and hyporeflexia adverse events. Ovation noted that the included studies were not designed to systematically evaluate peripheral neuropathy and did not include nerve conduction studies, quantitative sensory testing or skin or nerve biopsy. In their proposed labeling, Ovation includes a Warnings and Precautions statement regarding peripheral neuropathy that provides absolute risks for peripheral neuropathy AEs among vigabatrin treated subjects from the Integrated database but includes no comparative data.

7.3.7 Liver Injury
There were no reported AEs of liver failure or liver injury among vigabatrin subjects in the IS studies.

In the adult CPS amendment submission, Ovation identified cases of liver injury resulting in death or transplant in patients treated with vigabatrin but it is not clear if vigabatrin is causally related to these cases. In the development program studies that were part of the vigabatrin safety database, one study subject died from multiorgan failure (including hepatic failure) following an episode of status epilepticus. This event was likely related to the patient's underlying medical condition and not vigabatrin. A patient with metastatic cancer developed elevated transaminases and died. A third liver failure case resulting in death involved a study subject that had been taking vigabatrin for six years prior to the event and the liver injury was temporally related to treatment with clarithromycin. A subject in a Japanese study that was not part of the vigabatrin safety database died from hepatic failure but there were insufficient details about this event to allow a determination about whether vigabatrin was causally involved.

From post marketing reports, there were four hepatic related deaths and one liver transplant. In none of the cases was a likely alternative explanation documented but all were taking multiple medications at the time of the event. Excluding cases with exposure to vigabatrin for more than 1 year prior to developing liver injury leaves 3 cases of death/transplant. The reporting rate of hepatic failure resulting in death or transplant with vigabatrin exceeds the background risk that we have relied on in the past, but liver injury risk may be elevated among patients with seizure disorders that are treated with medications that are known hepatotoxins.

Examination of available laboratory data did not identify any "Hy's law" (Transaminase 3x ULN with total bilirubin >2.0mg/dL) liver injury cases in the development program. From a pool of data from controlled trials there did not appear to be an increased risk of high transaminase outlier results for vigabatrin subjects compared to placebo. These laboratory results must be intepreted in light of vigabatrin's ability to decrease transaminases.

7.3.8 CNS Effects
Somnolence (16.5%), sedation (15.3%) and lethargy (5.8%) were among the most commonly occurring AEs in the IS controlled trials.

In the adult CPS amendment submission, vigabatrin was associated with an increased risk for a number of CNS AEs including somnolence, sedation, coordination abnormalities and confusional state. In adults, the occurrence of these events could impair a patient's ability to perform tasks such as driving or operating machinery.

7.3.9 Effects on Serum Transaminases
Subjects in vigabatrin IS trials experienced mean declines in AST and ALT from baseline.

Laboratory data from adult CPS submissions demonstrate that vigabatrin causes reductions in serum transaminases (ALT>AST), presumably through its effect as a transaminase inhibitor. In randomized controlled trials, vigabatrin treated subjects experienced mean declines in ALT and

AST that were not observed among placebo subjects. In one analysis, 94% of vigabatrin subjects had a 60-100% maximum decrease in their ALT compared to baseline and 4% had an ALT result of 0. The magnitude of the declines in transaminases appeared to be dose related. This effect could impair the ability to monitor a patient treated with vigabatrin for liver injury.
Any ongoing or planed vigabatrin clinical trials should incorporate monitoring of hemoglobin, hematocrit, serum iron, transferrin, ferritin, reticulocyte count, red cell morphology, red cell indices, haptoglobin, urine hemoglobin, and erythropoietin.

Recommendations
Any ongoing or planned vigabatrin clinical trials should incorporate hematologic testing during post-treatment washout in order to assess rate of recovery from reduction of hemoglobin and hematocrit.

Ovation should conduct a thorough QT study in humans. This could be conducted as a phase IV commitment.

If approved for pediatric indications, Ovation should collect data that address the effect of vigabatrin on growth and development.

Ovation should closely follow up any spontaneous reports of liver injury. Follow up should include complete description of the case, outcome information, lab test results, biopsy results, and post mortem test results. In addition, Ovation should submit any serious liver injury cases as 15-day reports.

Ovation should incorporate the labeling language that will be requested by the Division.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Aside from pooling to define exposure and doses, and to review adverse events, Ovation did not rely on pooled data and instead presented data from the individual studies.

7.4.2 Explorations for Predictive Factors

Ovation did provide limited "dose response" analyses using low dose and high dose group data from study 1A. Ovation provided AE risks stratified by sex but without comparator data it was not possible to determine if the observed differences in risk by sex in these vigabatrin subjects reflect differences in the background risk for these events or are due to a drug sex interaction. Ovation provided Table 14 that stratified AE risks by race, but this table is of limited value. Ovation reported that 57% (197/346) of study subjects were Caucasian and 24% (87/346) were

of unknown race leaving only 27 subjects classified as black and 39 subjects classified as other. Due to these small numbers of individuals in the different race strata the analyses of AE risk by race does not allow for robust examinations of drug race interactions. Ovation provided no analyses examining time dependency, drug disease interactions, or drug/drug interactions.

7.4.3 Causality Determination

Evidence for causality for specific adverse events is presented in section 7.3.

Appendix

Trials Contributing Safety Data to the Integrated Safety Database
Infantile Spasms

Controlled
1A was a multicenter, randomized, parallel group, single-blind study designed to evaluate the safety and efficacy of vigabatrin in subjects younger than 2 years of age with new-onset IS. The study comprised two phases, a 14- to 21-day single-blind phase where subjects were randomized to receive either low-dose (18-36 mg/kg/day) or high-dose (100-148 mg/kg/day) vigabatrin. Study drug was titrated over 7 days, followed by a constant dose for 7 days. If the patient became spasm free on or before day 14, another 7 days of constant dose was administered. During the open-label, dose-ranging, long-term follow-up (up to 3 years), the dose of vigabatrin could be increased or decreased at the discretion of the investigator. Safety was assessed by adverse events, clinical laboratory evaluations, and ophthalmologic examinations. A total of 226 subjects (0.1 to 3.9 years of age) were enrolled, and 222 subjects were analyzed for safety in the study report (114 received low-dose vigabatrin and 108 received high-dose vigabatrin). A total of 223 subjects were included in the integrated safety database. The reason for the discrepancy between 222 subjects in the CSR's safety data is that the CSR reported by treatment group (high- or low-dose vigabatrin); of the 223 subjects that received at least one dose of study drug, the data for one subject did not include a treatment arm or enough information to determine a dose group. Due to the lack of reliable data for this subject and the fact the safety data were analyzed by treatment arm, the subject was removed from the analyses for the purposes of the CSR; however, the subject's data were included in the integrated safety database, which did not report safety data by treatment group (NDA pp. 17-18 and 20-21).

W019 was a multicenter, randomized, double-blind, placebo-controlled, parallel group, in-patient study designed to evaluate the safety and efficacy of vigabatrin as first-line therapy in the treatment of newly diagnosed IS and to assess the duration of response to treatment via relapse rate and time to relapse. The study consisted of a pre-treatment (baseline) period of 2-3 days, then a 5 day double-blind treatment phase during which subjects were treated with vigabatrin (in ascending dose to 150 mg/kg/day if tolerated) or placebo (according to a predetermined randomization code). Subjects were then followed for 6 months, during which all subjects continuing in the study were treated with vigabatrin in an open-label fashion. Safety was assessed by adverse events, laboratory assessments, neurological examinations (including developmental status), physical examinations and vital signs. Forty subjects between 4 and 20 months of age were enrolled; 20 subjects received vigabatrin treatment and 20 subjects received placebo for 5 days during the double-blind phase. All 40 subjects were analyzed for safety in the study report and are included in the integrated safety database. Thirty-six subjects entered the open-label phase and received vigabatrin treatment for up to 6 months, however, only 35 subjects are included in the analysis for this period since data for one subject included in the study report were missing in the dataset for the integrated safety database. (NDA pp.18, 21).

Study FR03 was a multicenter, open-label, randomized, comparative, response-mediated, 2-month cross-over study designed to compare the efficacy and safety of vigabatrin (150

mg/kg/day without titration) and hydrocortisone (15 mg/kg/day) as first-line monotherapy in the treatment of infants with newly diagnosed IS due to tuberous sclerosis. Subjects were evaluated every 2 weeks during the study. After 1 month (4 weeks) of therapy, subjects who had an incomplete response to the first treatment or had signs of intolerance crossed over to the other treatment, whereas subjects who responded (total disappearance of spasms) were not crossed over. Hydrocortisone responders were tapered off of hydrocortisone (over a 15-day period) after 1 month of treatment in order to limit steroid induced adverse effects, whereas for vigabatrin responders, a stable vigabatrin dose was maintained throughout. At the end of 2 months (8 weeks), responders to vigabatrin could be maintained on this drug on a long-term basis. Subjects secondarily crossed over to the hydrocortisone group who were responders to this drug were to be slowly tapered off over 15 days. Safety was assessed by adverse events, clinical laboratory evaluations, and physical examinations. Twenty-three subjects were enrolled, treated, and analyzed for safety in the clinical study report (11 were randomized to vigabatrin and 12 were randomized to hydrocortisone; 7 hydrocortisone subjects crossed over to vigabatrin for the second 4 weeks of the study). The ages of the subjects ranged from 50 to 507 days. Only the data for 18 subjects were available for inclusion in the integrated database, 6 of whom were originally randomized to vigabatrin and 12 of whom were originally randomized to hydrocortisone (including the 7 who crossed over to vigabatrin) (NDA pp.18, 21).

Uncontrolled
Study 3325 was an open-label, single-center study designed to evaluate the safety and efficacy of vigabatrin in infants and children with drug-resistant infantile spasms. During a 2- to 4-week baseline phase, subjects maintained a stable dose of their usual AEDs. During a 3-month evaluation phase, vigabatrin was to be added to the usual antiepileptic medication regimen, and the dose of vigabatrin (50- 150 mg/kg/day) was optimized. During a long-term phase, subjects who had achieved >50% reduction in seizure frequency continued on long-term vigabatrin treatment. Safety was assessed by adverse events, clinical laboratory evaluations, physical examinations (including height and weight), neurologic examinations, and ophthalmologic examinations. Forty-five subjects (<2 to 12.5 years of age) were enrolled, treated, and included in the analyses of safety in the study report. Of these, 32 were infants younger than 2 years of age, and 13 were children ≥2 years of age (8 subjects were >36 months of age). All 45 subjects were included in the integrated safety database (NDA, pp.18, 22).

Refractory Epilepsy
Uncontrolled

Study 300 was an open-label, single-center, investigator-initiated study. Subjects 21 months to 58 years of age, with severe forms of epilepsy uncontrolled by conventional medication, received vigabatrin in doses of 0.5 to 3 g for 27 days to 31 months (range) as "add-on" therapy (i.e., in addition to their current antiepileptic medication). Safety was assessed by physical and neurological examinations; vital signs (blood pressure, pulse) and weight; laboratory evaluations (urinalysis, serum chemistry, hematology, plasma levels of concomitant AEDs); adverse events; and electrocardiograms (ECGs). Thirty-eight subjects (21 months to 58 years of age; mean, 16 years) were enrolled, treated, and analyzed for safety in the study report. Of these, only 2 were

younger than 36 months of age and thus are the only subjects from this study included in the integrated safety database (NDA pp. 19, 22).

Study 314 was a single-blind, single-center study in subjects 26 months to 18.3 years of age with treatment-resistant seizures (simple or complex partial seizures and/or generalized seizures) who were taking other standard AEDs. After a 2-month observation and a 1-month single-blind, add-on placebo phase (Phases 0 and I, respectively), subjects entered a 2-month fixed vigabatrin dose phase (Phase II). Vigabatrin dose was based on weight, and subjects were divided into 3 dosing categories: 1.0, 1.5, and 2.0 g/day for subjects weighing 12 - 16.9 kg, 17 - 22.9 kg, and =23 kg (received 2.0 g/day), respectively. After the fixed-dose period, subjects could enter a flexible-dose period for 2 months (Phase IIIA), an additional flexible-dose period for 2 months (Phase IIIB), and a long-term follow-up period for vigabatrin responders for 9 months (Phase IV). Safety was assessed by physical and neurological examinations; vital signs (blood pressure, pulse) and weight; laboratory evaluations (urinalysis, serum chemistry, hematology, plasma levels of concomitant AEDs); adverse events; and ophthalmologic examinations. Twenty subjects (26 months to 18.3 years of age; mean, 9.9 years) were enrolled, and of these, only one was younger than 36 months of age and was included in the integrated safety database. (NDA pp. 19, 22-23).

Study 332 was a single-blind, single-center study in subjects 2 to 15 years of age with uncontrolled epilepsy (≥4 seizures per month despite treatment with 1 to 3 other AEDs). The study comprised 5 phases: after a 1-month observation period and a 1- to 2-month single-blind, add-on placebo phase (Phases 0 and I, respectively), subjects entered a 1-month fixed dose phase (Phase II) and received vigabatrin 50 mg/kg/day as add-on therapy. After the fixed-dose period, subjects could enter a flexible-dose period for up to 6 months (Phase III) and receive add-on vigabatrin 20-150 mg/kg/day with titration of dose depending on efficacy and tolerability. The last phase (Phase IV) was a long-term continuation of vigabatrin in responders (i.e., subjects with =50% reduction in seizure frequency from placebo baseline or a clear qualitative improvement in seizure frequency and severity). Concomitant antiepileptic therapy was kept unchanged from Phase 0 until the end of Phase III. Changes were allowed during Phase IV. Safety was assessed by physical, neurological, and ophthalmologic examinations; height and weight; laboratory evaluations (serum chemistry, hematology, plasma levels of concomitant AEDs); and adverse events Sixty-six subjects (1 to 15 years of age) enrolled and of these, only 4 were younger than 36 months of age and were included in the integrated safety database (NDA pp. 19, 23).

Study 345A was an open-label, single-center study in subjects 2 to 15 years of age with any type of drug-resistant epilepsy (at least 4 seizures per month despite treatment with 1 to 3 other AEDs). Subjects older than 8 years of age received vigabatrin at an initial dose of 2 g/day (taken as a twice daily dose), and subjects younger than 8 years received vigabatrin at an initial dose of 40-80 mg/kg/day (taken as a twice daily dose). After the first month and for every month thereafter, the vigabatrin dose could be adjusted, based on side effects and amount of change in seizure frequency. Safety was assessed by physical, neurological, and mental status examinations; laboratory evaluations (serum chemistry, hematology, plasma levels of concomitant AEDs); and adverse events (NDA pp. 19-20, Thirty-three outpatients (2 to 15 years

of age) were enrolled, and of these, only 3 were younger than 36 months of age and were included in the integrated safety database (NDA pp. 19-20, 23).

Study WIT01 was a single-blind, multicenter, fixed-sequence, placebo-controlled study in subjects 2 to 12 years of age with partial uncontrolled epileptic seizures who were taking at least one other AED (but no more than 2). The study comprised 4 phases: Phase 1 was a 1- month, no additional treatment period; Phase 2 was a 1-month placebo run-in; Phase 3 was a 2-month fixed-dose phase assessing response to vigabatrin (at a dose of 40 mg/kg/day); and Phase 4 was a dose optimization and long-term efficacy and tolerance phase, beginning with 4 months of dose modification (60 mg/kg/day for 2 months and then 80 mg/kg/day for a further 2 months) to achieve titration to optimal dose, which was followed by long-term treatment and evaluation. Safety was assessed by physical and neurological examinations; laboratory evaluations (serum chemistry, hematology, plasma levels of concomitant AEDs); adverse events; and concomitant medications. Of the 49 subjects enrolled, 11 were included in the integrated safety database; however of these 11 subjects, 2 were actually older than 36 months of age (40 months and 118 months, respectively). (NDA pp. 20, 23).

Trial Not Contributing Safety Data to the Integrated Safety Database, Data Summarized Separately

Study 3E01 was a retrospective data collection in 11 European countries involving records of subjects diagnosed with IS who had been treated with vigabatrin as their first drug. Data were collected on a paper CRF from original case records. Diagnosis of IS was confirmed by EEG, magnetic resonance imaging [MRI] and/or computed tomography [CT] scans, video recordings according to the facilities, and records available. All source data were verified during on-site monitoring visits. All subject data were subsequently presented before a peer review committee to confirm diagnosis. Safety was assessed by adverse events and deaths; however, only adverse events and deaths that occurred during or immediately related to the time of vigabatrin therapy and which were considered by prescribers as being possibly related to treatment were reported. Data on 250 subjects were collected; all 250 were evaluated for safety (NDA pp. 18-19, .

Table 10. Adverse Events Occurring in >= 2% of Subjects (Safety Population)

System Organ Class Preferred Term	Vigabatrin (N=346) n (%)
Any System Organ Class	
Any Event	264 (76.30)
Infections and Infestations	
Any Event	192 (55.49)
Upper respiratory tract infection	107 (30.92)
Otitis media	84 (24.28)
Viral infection	45 (13.01)
Pneumonia	30 (8.67)
Ear infection	26 (7.51)
Bronchitis	23 (6.65)
Sinusitis	16 (4.62)
Candidiasis	13 (3.76)
Urinary tract infection	13 (3.76)
Gastroenteritis viral	12 (3.47)
Rhinitis	12 (3.47)
Infection	11 (3.18)
Influenza	10 (2.89)
Pharyngitis	10 (2.89)
Roseola	9 (2.60)
Gastroenteritis	8 (2.31)
Respiratory syncytial virus infection	8 (2.31)
Varicella	8 (2.31)
Bronchiolitis	7 (2.02)
Croup infectious	7 (2.02)
Nasopharyngitis	7 (2.02)
Nervous System Disorders	
Any Event	144 (41.62)
Somnolence	53 (15.32)
Sedation	41 (11.85)
Convulsion	15 (4.34)
Hypotonia	15 (4.34)
Lethargy	15 (4.34)
Status epilepticus	13 (3.76)
Psychomotor hyperactivity	9 (2.60)
Gastrointestinal Disorders	
Any Event	100 (28.90)
Vomiting	39 (11.27)
Constipation	33 (9.54)
Diarrhoea	30 (8.67)
Gastrooesophageal reflux disease	8 (2.31)
Flatulence	7 (2.02)
Psychiatric Disorders	
Any Event	93 (26.88)
Irritability	48 (13.87)
Insomnia	28 (8.09)
Agitation	11 (3.18)
Sleep disorder	8 (2.31)
General Disorders and Administration Site Conditions	

Any Event	89 (25.72)
Pyrexia	56 (16.18)
Unevaluable event	13 (3.76)
Adverse drug reaction	10 (2.89)
Respiratory, Thoracic and Mediastinal Disorders	
Any Event	75 (21.68)
Nasal congestion	19 (5.49)
Cough	13 (3.76)
Rhinorrhoea	9 (2.60)
Skin and Subcutaneous Tissue Disorders	
Any Event	56 (16.18)
Rash	21 (6.07)
Eczema	7 (2.02)
Metabolism and Nutrition Disorders	
Any Event	41 (11.85)
Decreased appetite	17 (4.91)
Feeding disorder	8 (2.31)
Eye Disorders	
Any Event	40 (11.56)
Strabismus	11 (3.18)
Conjunctivitis	8 (2.31)
Eye disorder	7 (2.02)
Investigations	
Any Event	36 (10.40)
Blood alkaline phosphatase increased	8 (2.31)
Blood and Lymphatic System Disorders	
Any Event	17 (4.91)
Anaemia	7 (2.02)
Ear and Labyrinth Disorders	
Any Event	12 (3.47)
Ear disorder	7 (2.02)

Table 11. Adverse Events Occurring in <2% of Subjects (Safety Population)

Infections and Infestations	Acute tonsillitis	Hordeolum	Pneumonia respiratory syncytial viral
	Adenovirus infection	Impetigo	Pneumonia viral
	Asymptomatic bacteriuria	Infected insect bite	Postoperative infection
	Bacteraemia	Infected sebaceous cyst	Respiratory tract infection
	Bronchitis acute	Infectious mononucleosis	Rhinovirus infection
	Candida nappy rash	Infusion site infection	Sepsis
	Clostridium colitis	Laryngitis	Streptococcal infection
	Conjunctivitis infective	Lobar pneumonia	Tinea infection
	Corneal infection	Localised infection	Tonsillitis
	Dental caries	Lower respiratory tract infection	Tracheitis
	Enterobiasis	Meningitis	Urinary tract infection pseudomonal
	Erythema infectiosum	Oral candidiasis	Vaginal mycosis
	Eye infection	Otitis media acute	Viral pharyngitis
	Fungal infection	Otitis media chronic	Viral rash
	Gastroenteritis rotavirus	Pharyngitis streptococcal	Viral upper respiratory tract infection
	Gastrointestinal infection	Pharyngotonsillitis	
	Hand-foot-and-mouth disease	Pneumococcal bacteraemia	
Nervous System Disorders	Balance disorder	Hemiparesis	Opisthotonus
	Clonus	Horner's syndrome	Paresis
	Coma	Hydrocephalus	Partial seizures
	Coordination abnormal	Hyperkinesia	Partial seizures with secondary generalization
	Depressed level of consciousness	Hypersomnia	Quadriparesis
	Developmental coordination disorder	Hypertonia	Simple partial seizures
	Disturbance in attention	Hypokinesia	Speech disorder
	Drooling	Infantile spasms	Speech disorder developmental
	Dystonia	Intracranial pressure increased	Subdural hygroma
	Extensor plantar response	Muscle spasticity	Syncope
	Facial nerve disorder	Myoclonic epilepsy	Tremor
	Febrile convulsion	Myoclonus	
	Grand mal convulsion	Nervous system disorder	
	Headache	Nystagmus	
Gastrointestinal Disorders	Abdominal discomfort	Gastrointestinal disorder	Retching
	Abdominal pain	Gingival pain	Salivary hypersecretion
	Dysphagia	Gingival swelling	Stomach discomfort
	Anorectal disorder	Ileus paralytic	Stomatitis

	Abdominal pain upper	Lip ulceration	Teething
	Enteritis	Mouth ulceration	Tooth discolouration
	Faecaloma	Nausea	
	Gastritis	Reflux oesophagitis	
Psychiatric Disorders	Abnormal behavior	Dissociation	Middle insomnia
	Affect lability	Eating disorder	Mood swings
	Aggression	Excitability	Posturing
	Anger	Expressive language disorder	Psychotic disorder
	Bulimina nervosa	Indifference	Restlessness
	Communication disorder	Initial insomnia	
	Conversion disorder	Listlessness	
	Crying	Mental status changes	
General Disorders and Administration Site Conditions	Asthenia	Discomfort	Oedema
	Catheter related complication	Influenza like illness	Oedema peripheral
	Cyst	Infusion site reaction	Pain
	Death	Infusion site swelling	
	Developmental delay	Malaise	
Respiratory, Thoracic and Mediastinal Disorders	Apnoea	Nasal discomfort	Respiratory distress
	Apnoeic attack	Obstructive airways disorder	Respiratory failure
	Aspiration	Pharyngolaryngeal pain	Respiratory tract congestion
	Asthma	Pleural effusion	Sinus congestion
	Bronchospasm	Pneumonia aspiration	Sleep apnoea syndrome
	Choking	Postnasal drip	Tonsillar disorder
	Dyspnoea	Pulmonary congestion	Upper respiratory tract congestion
	Epistaxis	Pulmonary hemorrhage	Wheezing
	Increased upper airway secretion	Respiratory arrest	
	Laryngeal stenosis	Respiratory disorder	
Skin and Subcutaneous Tissue Disorders	Alopecia	Fat atrophy	Rash papular
	Anhidrosis	Hypohidrosis	Scar
	Dermatitis	Ingrowing nail	Skin hypopigmentation
	Dermatitis allergic	Rash erythematous	Skin lesion
	Dermatitis diaper	Rash follicular	Urticaria
	Dry skin	Rash generalised	Urticaria localized
	Ecchymosis	Rash macular	
	Exanthem	Rash maculo-papular	
Metabolic and Nuttritional Disorders	Anorexia	Feeding problem in newborn	Increased appetite
	Dehydration	Hypernatremia	Metabolic disorder
	Diet refusal	Hypokalemia	Oral intake reduced
Eye Disorders	Amaurosis	Conjunctival haemorrhage	Myopia
	Amblyopia	Eye inflammation	Optic atrophy
	Astigmatism	Eye irritation	Optic nerve disorder

	Blepharitis Blindness cortical Cataract	Eyelid ptosis Hypermetropia Mydriasis	Retinal disorder Visual acuity reduced
Investigations	Alanine aminotransferase increased Biopsy kidney Blood albumin abnormal Blood albumin decreased Blood corticotrophin abnormal Blood potassium decreased Body temperature increased Cytoscopy	Diagnostic procedure Gamma glutamyltransferase increased Hepatic enzyme increased Liver function test abnormal Neurological examination abnormal Protein total decreased Pupillary light reflex tests abnormal Red blood cell count decreased	Red blood cell count increased Urine analysis abnormal Visual tract testing abnormal Weight decreased Weight increased White blood cell count increased White blood cells urine positive
Injury, Poisoning and Procedural Complicaitons	Arthropod bite Cephalhaematoma Drug toxicity Excoriation Fall Feeding tube complication Femoral neck fracture Femur fracture	Head injury Hip fracture Injury Joint dislocation Mouth injury Near drowning Post procedural pain Shunt occlusion	Skin laceration Surgical procedure repeated Thermal burn Upper limb fracture Vaccination complication Ventriculoperitoneal shunt malfunction
Musculoskeletal and Connective Tissue Disorders	Back pain Exostosis Hip deformity Kyphoscoliosis	Muscle twitching Muscle spasms Muscular weakness Musculoskeletal discomfort	Musculoskeletal stiffness Neck pain Osteopenia Scoliosis
Blood and Lymphatic System Disorders	Iron deficiency anemia Leukocytosis	Monocytosis Nephrogenic anemia	Neutropenia Thrombocythemia
Ear and Labyrinth Disorders	Deafness Hypoacusis	Middle ear effusion Tympanic membrane disorder	Tympanic membrane hyperaemia
Immune System Disorders	Allergy to arthropod bite Drug hypersensitivity Food allergy	Hypersensitivity Immunisation reaction Milk allergy	Seasonal allergy
Surgical and Medical Procedures	Brain operation Brain tumor operation	Fundoplication Gastrintestinal tube insertion	Surgery

	Drug delivery device implantation	Hospitalization	
Cardiac Disorders	Atrioventricular block second degree Bradycardia Cardiac arrest	Cardio-respiratory arrest Tachycardia Cyanosis	Ventricular extrasystoles Ventricular tachycardia Wolff-Parkinson-White syndrome
Congenital, Familial and Genetic Disorders	Bronchial cyst Cleft palate Cryptorchism	Epidermal naevus Hip dysplasia Talipes	Tuberous sclerosis
Renal and Urinary Disorders	Glomerulonephritis focal Glycosuria Haematuria	Ketonuria Lekocyturia Nephrolithiasis	Proteinuria
Vascular disorders	Aortic stenosis	Infarction	Hypertension
Endocrine disorders	Cushingoid	Hypercorticoidism	Diabetes insipidus
Hepatobiliary Disorders	Hepatic cyst	Hepatomegaly	
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Angiosarcoma	Rhabdomyoma	Neuroblastoma
Reproductive System and Breast Disorders	Perineal pain	Vaginal disorder	

Table 11.1
Disposition of Subjects
(Safety Population)

	IS Subjects					Non-IS[2]	
	Controlled				Uncontrolled	Uncontrolled	
	Non-US			US	Non-US	Non-US	
Status	Vigabatrin	Hydrocortisone	Placebo	Vigabatrin	Vigabatrin	Vigabatrin	Total Vigabatrin
Safety Population [1]	38 (100.0%)	12 (100.0%)	20 (100.0%)	223 (100.0%)	80 (100.0%)	21 (100.0%)	346 (100.0%)
Completed Study	37 (97.37%)	5 (41.67%)	20 (100.0%)	27 (12.11%)	60 (75.00%)	17 (80.95%)	129 (37.28%)
Unknown Status	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.45%)	0 (0.00%)	0 (0.00%)	1 (0.29%)
Discontinued	1 (2.63%)	7 (58.33%)	0 (0.00%)	195 (87.44%)	20 (25.00%)	4 (19.05%)	216 (62.43%)
Adverse Event(s)	0 (0.00%)	4 (33.33%)	0 (0.00%)	9 (4.04%)	2 (2.50%)	1 (4.76%)	12 (3.47%)
Lack of Efficacy	1 (2.63%)	2 (16.67%)	0 (0.00%)	51 (22.87%)	15 (18.75%)	2 (9.52%)	67 (19.36%)
Protocol Violation	0 (0.00%)	0 (0.00%)	0 (0.00%)	13 (5.83%)	1 (1.25%)	0 (0.00%)	13 (3.76%)
Failed to Meet Entry Criteria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lost to Follow-Up	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (1.35%)	0 (0.00%)	1 (4.76%)	4 (1.16%)
Voluntarily Withdrew	0 (0.00%)	0 (0.00%)	0 (0.00%)	7 (3.14%)	2 (2.50%)	0 (0.00%)	8 (2.31%)
Administrative Reasons	0 (0.00%)	0 (0.00%)	0 (0.00%)	35 (15.70%)	0 (0.00%)	0 (0.00%)	35 (10.12%)
Withdrawn by Investigator	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Death	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Other	0 (0.00%)	1 (8.33%)	0 (0.00%)	77 (34.53%)	0 (0.00%)	0 (0.00%)	77 (22.25%)

Includes studies W019, FR03, 1A, 3325, 300, 314, 332, 345A, WIT01.
Note: Subjects who participated in the crossover study FR03 are summarized under both treatments if the subject received both treatments. Each treatment phase was treated separately, and subjects recorded as discontinued during the randomized phase may still have continued into the cross-over phase.
Note: Percentages are with respect to the number of subjects in the Safety Population for the study type/treatment.
[1] All subjects who were randomized into a study and received at least one dose of study medication.
[2] Only subjects < 36 months are included.

Note: Despite four deaths in the IS studies, none were listed as the reason for discontinuation on the CRF termination page.

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/s/

Jerry Boehm
7/7/2008 01:05:53 PM
MEDICAL OFFICER

Sally Yasuda
7/8/2008 02:59:06 PM
BIOPHARMACEUTICS

Clinical Review (R. Farkas): Vigabatrin Ophthalmic Adverse Effects – NDA 22006 (Infantile Spasms); 20427 (Complex Partial Seizures). ***Please refer to the 'NDA 20-427: Complex Partial Seizures – January 7, 2009' section for this review***

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA /Serial Number:	22-006
Drug Name:	Vigabatrin (Sabril®)
Indication:	Infant Spasms
Applicant:	Ovation Pharmaceuticals
Date of Submission:	12/28/2007
Review Priority:	Priority
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Jingyu (Julia) Luan, Ph.D. (HFD-710)
Concurrent Reviewer:	Kun Jin, Ph.D. (HFD-710)
	Kooros Mahjoob, Ph.D. (HFD-710)
	H.M. James Hung, Ph.D. (HFD-710)
Medical Division:	Division of Neurology Drug Product (HFD-120)
Clinical Team:	Gerard Boehm, M.D. (HFD-120)
	Ronald Farkas, M.D. (HFD-120)
	Phillip Sheridan, M.D. (HFD-120)
	Norman Hershkowitz, M.D. (HFD-120)
Project Manager:	Tamy Kim, Pharm. D. (HFD-120)

Key Words: Infantile spasm, Responder rate, Chi-square test, ANCOVA, Interim analysis

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

For Study 1-A, based on the primary efficacy results, it appears that there is a positive signal of treatment effect of vigabatrin for subjects with new onset infantile spasm. However, it is very difficult to make sound statistical inference due to the concerns (explained in Section 1.3) with Statistical Analysis Plan and issues in sample size increases and interim analyses.

Study 71754-W-019 did not demonstrate an effect of vigabatrin on infantile spasms, based on the pre-specified primary endpoint, the average percent change in daily spasm frequency, assessed during a predefined two-hour window. When this efficacy variable was based on data collected over the 24-hour window, there appears to be a treatment difference in favor of vigabatrin.

1.2 Brief Overview of Clinical Studies

This submission includes two well-controlled efficacy studies, Study 1-A and Study 71754-W-019, hereafter referred to as Study 1A and Study W019, respectively (The open label study 097WFR03 is not included in this review).

Study 1A was a multicenter, randomized, single-blind study of 14 to 21 days duration comparing two doses (high dose and low dose) of vigabatrin with an open-label, flexible dosing, long-term follow-up in subjects younger than 2 years of age with new onset infantile spasms (IS). Investigators were aware of treatment assignments while caregivers and non-investigator electroencephalographers were blinded. Two hundred and twenty-seven (227) subjects were enrolled into the study from 9 sites in the United States.

Study 1A was comprised of two phases. During the initial controlled phase, subjects were randomized to receive either low-dose (18 to 36mg/kg/day) or high-dose (100 to 148mg/kg/day) vigabatrin in a single-blind manner for 14 to 21 days. Study drug was titrated over 7 days, followed by a constant dose for 7 days. If the subject became spasm-free on or before day 14, another 7 days of constant dose was administered. The second phase was an open-label, dose-ranging, long-term follow-up (up to 3 years).

Study W019 was a randomized, double-blind, placebo-controlled, parallel group study, with an open follow-up, to investigate the safety and efficacy of vigabatrin monotherapy in children (up to the age of 18 months) with infantile spasms. This study enrolled 40 subjects from seven European countries (UK, Canada, France, Netherlands, Finland, Hungary and Serbia).

Study W019 was designed with 3 phases. Phase 1 was a 2 to 3 day pretreatment period. Subjects successfully completing this baseline period were then randomized to placebo or vigabatrin. The second phase was a 5 day double-blind period, during which subjects initially received a dose of 50mg/kg/day vigabatrin or placebo. If the spasms continued, the patients were titrated to a maximum of 150mg/kg/day. At the end of the double-blind phase, subjects entered phase 3, a 6-month open evaluation period of vigabatrin treatment.

1.3 Statistical Issues and Findings

1.3.1 STUDY 1A

Study 1A was sponsored by the Vigabatrin Infantile Spasm (IS) Study Group (VISSG), an unincorporated association of physicians and medical researchers dedicated to the study of IS. The 1A clinical study was conducted under an investigator-sponsored IND (47,707) beginning in January 1996. There was no industry sponsor involved in the conduct of this study, although Aventis Pharmaceuticals did provide a grant to Dr. Roy Elterman in the amount of $144,500.00 on March 17, 2000 to cover certain costs. Aventis also provided vigabatrin clinical study supplies for study 1A at no cost to the 9 participating VISSG investigators. Ovation Pharmaceuticals acquired an exclusive license to the Study 1A data per an agreement with Dr. Roy Elterman in April, 2002. Subsequently, Ovation acquired the North American rights to vigabatrin from Aventis in March 2004. It was only after this latter acquisition that Ovation began data monitoring and verification at the VISSG study sites.

The primary efficacy endpoint was the proportion of subjects achieving spasm cessation for 7 consecutive days beginning within the first 14 days of therapy and confirmed by caregiver assessment and via CCTV EEG monitoring within 3 days of the seventh day of spasm freedom. It was analyzed by Chi-square test to compare the proportions of subjects in the high- and low-dose vigabatrin treatment groups who were free of spasms.

Totally, 227 subjects were enrolled into the study. The first subject enrolled on January 22, 1996 and the last subject completed the study on April 2, 2002. Three analyses were performed with the data collection cut-off date May 31, 1997, February 28, 1999 and April 02, 2002.

Specifically, for the final analysis, 221 subjects were analyzed for efficacy (114 received low-dose vigabatrin and 107 received high-dose vigabatrin). Primary efficacy analysis showed that 11% (25/221) of the subjects were spasm-free: 16% (17/107) of the subjects in the high-dose treatment group and 7% (8/114) of subjects in the low-dose treatment group. The difference between treatment groups was statistically significant (Chi-square test, p=0.0375).

Based on the primary efficacy results, it appears that there is a positive signal of treatment effect of vigabatrin for subjects with new onset infantile spasm. However, it is very difficult to make sound statistical inference due to concerns in Statistical Analysis Plan and issues in sample size increases and interim analyses.

Statistical Analysis Plan

In the Clinical Study Report, the sponsor states that, the final data analysis was in accordance with the Statistical Analysis Plan (SAP) included as Appendix 16.1.15. In the response to the Agency's request, the sponsor states that this SAP was signed-off in October 2004 and not submitted to IND 47, 707 as the IND had been placed on inactive status prior to the creation of the SAP; the sponsor also states that Dr. Roy Elterman verified for Ovation that Aventis did not

develop an SAP for Study 1A, but Drs. Elterman and Shields included statistical methods in both the first and second interim Clinical Study Report that were used in efficacy analyses. However, it is not clear to this reviewer what impact of the first and second interim analysis was on the development of this SAP (i.e., Appendix 16.1.15) and on the final analysis.

Issues in Sample Size Increases

According to the Clinical Study Report, Study 1A was initially planned as a compassionate use study to allow physicians to distribute study drug while a New Drug Application (NDA) for vigabatrin was under FDA review. According to the original efficacy assumptions, 37-40 subjects needed to be enrolled. The protocol allowed for a maximum of 60 subjects. However, the study was redesigned as a high/low-dose comparative trial and a minimum of 44 subjects were to be enrolled. Furthermore, the sponsor states that, due to a delay in the expected marketing approval, the protocol was amended to include up to 150 subjects and further amended to allow up to 250 subjects. There was no additional power analysis conducted to determine the final two sample size increases; the adjustment was made to allow physicians to continue to administer drug while awaiting FDA approval. From the Clinical Study Report, totally 227 subjects were enrolled to Study 1A. It seems that the sample size for Study 1A was never fixed, and when the study was initiated, there was no pre-specified plan regarding how many subjects were to be enrolled and under what circumstance the sample size was to be increased.

Issues in Interim Analyses

According to the Clinical Study Report, three analyses (two interim analyses and one final analysis) were performed on the collected data. The results of the second interim analysis were published in *Neurology* in 2001. There are three issues associated with interim analyses:

- Firstly, it seems that the two interim analyses were not pre-specified and the p-value for final analysis was not adjusted for the two interim analyses.
- Secondly, the results of the second analysis were published in *Neurology* in October, 2001 and the last subject completed the study in April, 2002. The impact of the publication of the results of this interim analysis on the trial conduct and final analysis is unknown.
- Thirdly, it is not clear whether the participating sites had conducted any type of analyses before the first interim analysis.

1.3.2 STUDY W019

For Study W019, the primary efficacy variable was the average percent change in daily spasm frequency, assessed during a predefined two-hour window, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final two days of the period.

This primary efficacy variable was analyzed for ITT population using ANCOVA with Treatment and Geographical location as factors and Baseline spasm count as covariate. Based on this primary efficacy variable, the results in the two treatment groups are similar, with eight patients

in each group (40% placebo group and 47% vigabatrin group) achieving a greater than 70% improvement (i.e. reduction in spasm frequency), and three patients in each treatment group (15% of placebo and 18% of vigabatrin patients) achieving 40 to 69% improvement during the 2-hour time window. This treatment difference was not statistically significant (p=0.562).

When this efficacy variable was based on data collected over the 24-hour window, there appears to be a treatment difference in favor of vigabatrin. The sponsor explains this is due to the fact that the spasms did not occur at the same intensity every day as expected by the choice of the two hour window; but this is a post hoc analysis.

2 INTRODUCTION

2.1 Overview

Infantile spasms (IS) constitute a rare and refractory type of childhood epilepsy. Subjects with IS frequently have neurological deficits. Mental retardation is present in 70 to 90% of subjects with IS, with the majority of these subjects having severe-to-profound retardation. Mortality rates for infants with IS are high; these rates have been estimated to be 5 to 30%, with 10 to 33% of these deaths occurring before age 3.

The most commonly used therapies for the treatment of IS are ACTH and prednisone. Although a substantive proportion of patients treated with these drugs respond initially, the risk of relapse is high. Other therapies that have been used in efforts to treat IS include sodium valproate, benzodiazepines, and some newer AEDs. However, the efficacy of these agents has not been established. Moreover, clinical experience suggests they are not very effective and can cause significant adverse effects.

Vigabatrin was developed for the treatment of epilepsy and is indicated, in many countries throughout the world, for the treatment of resistant partial epilepsies, with and without secondary generalization, and for the management of infantile spasms (IS). Vigabatrin use has been limited by the occurrence of ophthalmologic abnormalities, including a specific VGB-induced retinal injury [visual field defects (VFD)].

This NDA submission includes two well-controlled efficacy studies, Study 1A and Study W019.

Study 1A was a multicenter, randomized, single-blind study of 14 to 21 days duration comparing two doses (high dose and low dose) of vigabatrin with an open-label, flexible dosing, long-term follow-up in subjects younger than 2 years of age with new onset infantile spasms (IS). Investigators were aware of treatment assignments while caregivers and non-investigator electroencephalographers were blinded. Two hundred and twenty-seven (227) subjects were enrolled into the study from 9 sites in the United States.

Study 1A was comprised of two phases. During the initial controlled phase, subjects were randomized to receive either low-dose (18 to 36mg/kg/day) or high-dose (100 to 148mg/kg/day)

vigabatrin in a single-blind manner for 14 to 21 days. Study drug was titrated over 7 days, followed by a constant dose for 7 days. If the subject became spasm-free on or before day 14, another 7 days of constant dose was administered. The second phase was an open-label, dose-ranging, long-term follow-up (up to 3 years).

Study W019 was a randomized, double-blind, placebo-controlled, parallel group study, with an open follow-up, to investigate the safety and efficacy of vigabatrin monotherapy in children (up to the age of 18 months) with infantile spasms. This study enrolled 40 subjects from seven European countries (UK, Canada, France, Netherlands, Finland, Hungary and Serbia).

Study W019 was designed with 3 phases. Phase 1 was a 2 to 3 day pretreatment period. Subjects successfully completing this baseline period were then randomized to placebo or vigabatrin. The second phase was a 5 day double-blind period, during which subjects initially received a dose of 50mg/kg/day vigabatrin or placebo; if the spasms continued, the patients were titrated to a maximum of 150mg/kg/day. At the end of the double-blind phase, subjects entered phase 3, a 6-month open evaluation period of vigabatrin treatment.

2.2 Data Sources

The sponsor's original electronic submission was stored in the directory of \\Fdswa150\nonectd\N22006\N_000\2007-12-28 of the center's electronic document room.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 PROTOCOL 1A

3.1.1.1 Brief History of Study 1A

Study 1A was sponsored by the Vigabatrin Infantile Spasm (IS) Study Group (VISSG), an unincorporated association of physicians and medical researchers dedicated to the study of IS. The 1A clinical study was conducted under an investigator-sponsored IND (47,707) beginning in January 1996. There was no industry sponsor involved in the conduct of this study, although Aventis Pharmaceuticals did provide a grant to Dr. Roy Elterman in the amount of $144,500.00 on March 17, 2000 to cover certain costs. Aventis also provided vigabatrin clinical study supplies for study 1A at no cost to the 9 participating VISSG investigators. Ovation Pharmaceuticals acquired an exclusive license to the Study 1A data per an agreement with Dr. Roy Elterman in April, 2002. Subsequently, Ovation acquired the North American rights to vigabatrin from Aventis in March 2004. It was only after this latter acquisition that Ovation began data monitoring and verification at the VISSG study sites.

Reviewer Comments:
This brief history is an excerpt from Ovation's response. Since the final Clinical Study Report was provided by Ovation Pharmaceuticals, in this review document, the sponsor and the Clinical Study Report refer to "Ovation Pharmaceuticals" and the final Clinical Study Report by Ovations Pharmaceuticals, respectively.

3.1.1.2 Study Objectives

The objective of this study was to evaluate the safety and efficacy of vigabatrin in children less than 2 years of age with new onset infantile spasm.

3.1.1.3 Study Design

This was a multicenter, randomized, single-blind study of 14 to 21 days duration comparing two doses (high dose and low dose) of vigabatrin with an open-label, flexible dosing, long-term follow-up in subjects with new onset IS. Investigators were aware of treatment assignments while caregivers and non-investigator electroencephalographers were blinded. Two hundred and twenty-seven (227) subjects were enrolled into the study from 9 sites in the United States.

3.1.1.4 Efficacy Measures

The primary endpoint of this study was the proportion of subjects who were free of spasms for 7 consecutive days beginning within the first 14 days of vigabatrin therapy and confirmed by caregiver assessment and via CCTV EEG monitoring within 3 days of the seventh day of spasm freedom.

The secondary efficacy endpoints of the study were to assess spasm freedom without the use of CCTV EEG, based only on caregiver assessment of spasm frequency in response to direct questioning regarding spasm frequency or as recorded in the seizure diary. The endpoints were:

- the proportion of subjects who were free of spasms for 7 consecutive days and remained spasm free for the duration of the study;
- the time to spasm cessation for subjects who were free of spasms for 7 consecutive days and remained spasm free for the duration of the study;
- the proportion of subjects who were free of spasms for 7 consecutive days during the study;
- the time to spasm cessation for subjects who were free of spasms for 7 consecutive days during the study;
- the proportion of subjects classified by etiology who were free of spasms according to the primary efficacy criteria;
- the proportion of subjects classified by etiology who were free of spasms for 7 consecutive days and remained spasm free for the duration of the study;
- the time to spasm cessation by etiology for subjects who were free of spasms for 7 consecutive days and remained spasm free for the duration of the study;

- the proportion of subjects classified by etiology who were free of spasms for 7 consecutive days during the study;
- the time to spasm cessation by etiology for subjects who were free of spasms for 7 consecutive days during the study;
- the proportion of subjects who were free of spasms according to the primary criteria, adjusting for whether or not the subject was taking AEDs at baseline;
- the number of spasm clusters per subject over the course of the study period;
- physician global assessment;
- caregiver global assessment.

3.1.1.5 Statistical Analysis Plan

Reviewer's Comments:

In the Clinical Study Report, the sponsor states that, the final data analysis was in accordance with the Statistical Analysis Plan (SAP) included as Appendix 16.1.15. In the response to the Agency's request, the sponsor states that this SAP was signed-off in October 2004 and not submitted to IND 47, 707 as the IND had been placed on inactive status prior to the creation of the SAP; the sponsor also states that Dr. Roy Elterman verified for Ovation that Aventis did not develop an SAP for Study 1A, but Drs. Elterman and Shields included statistical methods in both the first and second interim Clinical Study Report that were used in efficacy analyses. Table 1 is an excerpt from sponsor's response comparing the determination of responder in primary efficacy analysis and method for primary efficacy analysis.

Table 1 Comparison of Statistical Methods for Study 1A Interim and Final Analyses

Topic	Study 1A Report	Method / Comments
Determination of responder in primary efficacy analysis	First (Elterman/Shields)	CRF check box for spasm free (yes/no) and date and outcome (fixed categories) of EEG.
	Second (Elterman/Shields)	Same as in first interim report.
	Final (Ovation)	Algorithm incorporating CRF check box for spasm free, counts of spasm clusters, dates of visits, and date and outcome (fixed categories) of EEG.
	Summary of differences	Ovation used an algorithm to determine more stringently whether the subject was a responder per the primary criteria.
Method for analysis of primary efficacy analysis	First (Elterman/Shields)	Fisher's exact test
	Second (Elterman/Shields)	Mantel Haenszel chi-square test
	Final (Ovation)	Pearson chi-square test
	Summary of differences	The Aventis analysis in the first interim report used Fisher's exact test to handle small cell counts in the analysis by etiology. It is surmised that for consistency the same test was also used for the primary efficacy analysis. It is not known why the analysis in the second Aventis report used the Mantel Haenszel chi-square; possibly larger sample sizes accommodated the asymptotic test. The Ovation analysis had a larger sample size and number of responders, so that the Pearson chi-square test provided a valid inferential method. There is very little difference between the Mantel-Haenszel and Pearson chi-square statistic.

Source: Sponsor's Response on June 18, 2008

The following analysis methods for primary and secondary endpoints as well as the selected changes in the planned analysis were excerpted from the Clinical Study Report and the available Statistical Analysis Plan (Appendix 16.1.15 of the Clinical Study Report).

Primary Efficacy Analysis

The primary endpoint of this study was the proportion of subjects who were free of spasms for 7 consecutive days beginning within the first 14 days of vigabatrin therapy and confirmed by caregiver assessment and via CCTV EEG monitoring within 3 days of the seventh day of spasm freedom. This primary endpoint was analyzed using a Chi-square test on modified ITT population.

Secondary Efficacy Analyses

Chi-square tests, logistic regression, Kaplan-Meier estimates, negative binomial regression, and repeated measures analysis of variance were used to analyze secondary endpoints.

Changes in the Planned Analysis (Selected)

In the approved statistical analysis plan for the assessment of the primary efficacy endpoint, subjects were considered responders if the subject became spasm free on or before day 21 after randomization. This was based on the criterion that subjects must be spasm free for 7 consecutive days beginning within the first 14 days of treatment (e.g., 14 days plus 7 days). However, the last day a subject may be spasm free and still be considered a responder was actually day 20 after randomization (e.g., day 14 is the first day of the 7 consecutive day period of spasm freedom). As a result, a subject should have been considered a responder only if he/she became spasm free on or before day 20 after randomization. The analysis was conducted according to these corrected criteria.

Following approval of the statistical analysis plan, it was decided that due to the number of missing dates of last spasm, for the primary and secondary efficacy analysis, when a subject was designated as spasm free and a date of last spasm was not provided, visit date minus 7 would be used as a proxy for date of last spasm (i.e. visit date would be considered the 7th day of spasm freedom). Additionally, for the primary, secondary and ad hoc analysis, if the response to the question "Is patient infantile spasms free (by criteria)?" was "no" or not answered and the number of clusters since last visit was equal to 0 then the subject would be considered spasm free by criteria.

<u>Reviewer's Comments:</u>
This reviewer asked the sponsor to provide a sensitivity analysis for the aforementioned method for the primary efficacy analysis. The sponsor's response states that a sensitivity analysis for the method described above (if the response to the question "Is patient spasms free by primary criteria?" was "no" or not answered and the number of clusters since last visit was equal to 0 then the subject would be considered "NOT spasm free") demonstrates no impact on the primary endpoint results for Study 1A. There were no additional subjects considered spasm free using the criteria of "Is patient infantile spasms free (by criteria)" with "no" or not answered and the number of clusters since last visit was equal to 0".

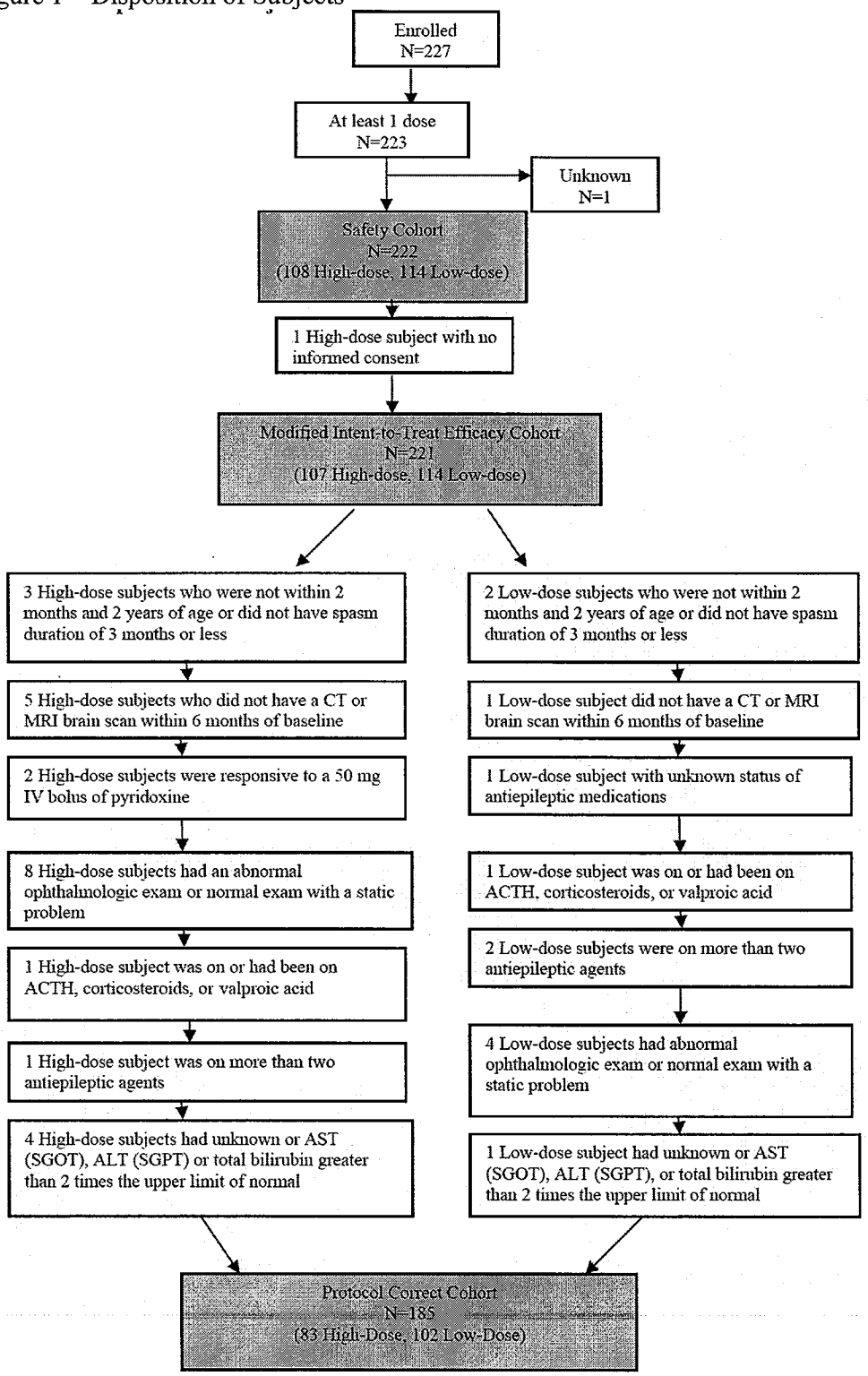
3.1.1.6 Patient Disposition and Demographic Characteristics

Patient Disposition

Two hundred and twenty-seven (227) subjects were randomized between January 22, 1996 and August 14, 2001. Figure 1 shows the disposition of these subjects. One of the 227 subjects was erroneously randomized and never officially enrolled. Of the 226 enrolled subjects, one subject became spasm free before the first visit and did not receive study drug, and two other subjects had no record of receiving vigabatrin. Of the 223 subjects that received at least one dose of study drug, the data for 1 subject did not include a treatment arm or enough information to determine a dose group, and thus the subject was removed from the analyses.

The safety cohort of subjects was made up of 222 subjects that were randomized and received at least 1 dose of vigabatrin (108 high-dose and 114 low-dose). Of these subjects, one high-dose subject did not have an informed consent. Therefore, 221 subjects met the criteria of the modified ITT cohort (107 high-dose and 114 low-dose) that was used for the efficacy analysis in this clinical study report.

Figure 1 Disposition of Subjects



Source: Figure 10-1 of sponsor's Clinical Study Report

Demographic Characteristics

Baseline characteristics for modified ITT population are summarized in Table 2.

Table 2 Baseline Characteristics

Characteristic	Statistic/ Category	High-dose (N=107)	Low-dose (N=114)	Total (N=221)
Age (yrs)[1]	N	102	112	214
	Mean±SD	0.6 ± 0.3	0.6 ± 0.3	0.6 ± 0.3
	Range	0.1 – 1.7	0.1 – 1.7	0.1 – 1.7
	Median	0.6	0.6	0.6
Gender	Male	45 (42.1)	63 (55.3)	108 (48.9)
	Female	61 (57.0)	50 (43.9)	111 (50.2)
	Missing	1 (0.9)	1 (0.9)	2 (0.9)
Race	African-American/Black	15 (14.0)	11 (9.7)	26 (11.8)
	Asian-American	3 (2.8)	0 (0)	3 (1.4)
	Caucasian/White	76 (71.0)	84 (73.7)	160 (72.4)
	Other	13 (12.2)	19 (16.7)	32 (14.5)
Weight (kg)[1]	N	106	112	218
	Mean±SD	7.9 ± 2.1	8.0 ± 2.0	8.0 ± 2.0
	Range	4.0 – 15.0	3.7 – 13.6	3.7 – 15.0
	Median	7.7	8.0	7.8
Etiology	Cryptogenic	27 (25.2)	30 (26.3)	57 (25.8)
	Symptomatic-Other	60 (56.1)	66 (57.9)	126 (57.0)
	Symptomatic-Tuberous Sclerosis	20 (18.7)	18 (15.8)	38 (17.2)

Source: Excerpt from Table 11.2a of sponsor's Clinical Study Report

The percentages of male subjects were 42% and 55% for high dose and low dose, respectively. With respect to age, race, weight and etiology, the treatment groups appeared generally similar.

3.1.1.7 Sponsor's Primary Efficacy Results

The primary efficacy analysis of this study compared the proportions of subjects in the high- and low-dose vigabatrin treatment groups who were free of spasms by both caregiver assessment and CCTV EEG confirmation within 3 days of the seventh day of spasm freedom. These subjects were considered to be primary responders to vigabatrin therapy. Based on these primary criteria, 11% (25/221) of the subjects were spasm free with CCTV EEG confirmation within 3 days, 16% (17/107) of the subjects in the high-dose treatment group and 7% (8/114) of subjects in the low-dose treatment group. The results are presented in Table 3.

Table 3 Treatment Comparison on Spasm Cessation via Primary Criteria

Treatment	Number (%) of Subjects with Spasm Cessation	Number (%) of Subjects with Spasm Non-Cessation	χ^2 Test Statistic	*P* Value
High-dose (N=107)	17 (15.9)	90 (84.1)		
Low-dose (N=114)	8 (7.0)	106 (93.0)	4.33	.0375
Total (N=221)	25 (11.3)	196 (88.7)		

Note: Primary criteria were based on caregiver assessment plus required CCTV EEG confirmation.

Source: Table 11.4a of sponsor's Clinical Study Report

3.1.1.8 Sponsor's Secondary Efficacy Results (Selected)

Spasm Cessation for 7 Consecutive Days and Remained Spasm Free During Study Period via Secondary Criteria

The first secondary efficacy analysis was the comparison of the proportions of subjects in the high- and low-dose vigabatrin treatment groups who were free of spasms for 7 consecutive days and remained spasm free for the duration of the study period based on caregiver assessment (secondary criteria).

In this analysis, 60% (132/221) of the subjects in the modified ITT cohort were spasm free, 68% (73/107) in the high-dose group and 52% (59/114) in the low-dose group. The results are summarized in Table 4.

Table 4 Treatment Comparison on Spasm Cessation for 7 Consecutive Days and Remained Spasm Free During Study Period via Secondary Criteria

Treatment	Number (%) of Subjects with Spasm Cessation N (%)	Number (%) of Subjects with Spasm Non-Cessation N (%)
High-dose (N=107)	73 (68.2)	34 (31.8)
Low-dose (N=114)	59 (51.8)	55 (48.3)
Total (N=221)	132 (59.7)	89 (40.3)

Source: Excerpt from Table 11.4b of sponsor's Clinical Study Report

Spasm Cessation for 7 Consecutive Days during Study Period via Secondary Criteria

The second secondary efficacy analyses was the comparison of the proportions of subjects in the high- and low-dose vigabatrin treatment groups who were spasm free for 7 consecutive days during the study period based on caregiver assessment, allowing for relapse.

In this analysis, 77% (171/221) of the subjects in the modified ITT efficacy cohort were spasm free, 78% (84/107) in the high-dose group and 76% (87/114) in the low-dose group. Table 5 summarizes the results.

Table 5 Treatment Comparison on Spasm Cessation for 7 Consecutive Days during Study Period via Secondary Criteria

Treatment	Number (%) of Subjects with Spasm Cessation	Number (%) of Subjects with Spasm Non-Cessation
High-dose (N=107)	84 (78.5)	23 (21.5)
Low-dose (N=114)	87 (76.3)	27 (23.7)
Total (N=221)	171 (77.4)	50 (22.6)

Source: Excerpt from Table 11.4c of sponsor's Clinical Study Report

3.1.2 PROTOCOL W019

3.1.2.1 Study Objectives

Primary Objective
To determine the safety and efficacy of vigabatrin, as compared to placebo, as the initial monotherapy in children with newly diagnosed and previously untreated infantile spasms.

Secondary Objective (Follow up - Open phase only)
To provide information on the duration of response to treatment by assessing both relapse rate and time to relapse.

3.1.2.2 Study Design

This was a randomized, double-blind, placebo-controlled, parallel group study, with an open follow-up, to investigate the safety and efficacy of vigabatrin monotherapy in children (up to the age of 18 months) with infantile spasms.

Study W019 was designed with 3 phases. Phase 1 was a 2 to 3 day pretreatment period. Subjects successfully completing this baseline period were then randomized to placebo or vigabatrin. The second phase was a 5 day double-blind period, during which subjects initially received a dose of 50mg/kg/day vigabatrin or placebo. If the spasms continued, the patients were titrated to a maximum of 150mg/kg/day. At the end of the double-blind phase, subjects entered phase 3, a 6-month open evaluation period of vigabatrin treatment.

3.1.2.3 Efficacy Measures

Spasm Count
A detailed history of the timing and number of spasms per day was obtained from the parents of each patient to ascertain the point during the day when the majority of spasms occurred for that patient. For each patient, a two-hour intensive monitoring period was then scheduled to coincide with the predicted peak in spasms. During this two-hour period, all spasms were recorded. Although the two-hour sampling time was different for each child, once a child was entered into the study, the sampling times for that individual remained constant throughout the baseline and the double-blind period. For the remainder of the 24-hour period, spasms were recorded as and when they were observed.

The primary efficacy variable was the percent change in the average frequency of spasms, assessed during a predefined two-hour window, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final two days of the period.

The secondary efficacy variables were:

- the average percent change in daily spasm frequency, assessed over the whole 24-hour period, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final two days of the period;

- the average percent change in daily spasm frequency, assessed during a predefined two-hour window, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final day of the period;

- the average percent change in daily spasm frequency, assessed over the whole 24-hour period, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final day of the period;

- the number of patients achieving cessation of spasms on the final day of the double-blind period, as assessed over the whole 24 hour period;

- the average percent change in frequency of clusters assessed during a predefined two-hour window, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final two days of the period;

- the average percent change in frequency of clusters, as assessed over whole 24 hour period, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final two days of the period;

- the average percent change in the duration of clusters from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final two days of the period;

- proportion of patients showing disappearance of hypsarrhythmia on final day of double-blind period;

- investigator's overall assessment of efficacy on final day of double-blind period;

- efficacy (i.e. total cessation, decrease or none/worse) in patients diagnosed as having symptomatic spasms compared with those diagnosed as having cryptogenic spasms on final day of double-blind period as assessed over whole 24-hour period.

3.1.2.4 Statistical Analysis Plan

The primary efficacy variable was the percent change in the average frequency of spasms, assessed during a predefined two-hour window, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final two days of the period. This primary efficacy endpoint (log transformed in analysis) was analyzed using

ANCOVA for ITT population with treatment and geographical location as factors and baseline spasm count as a covariate.

3.1.2.5 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

Forty (40) patients were screened, randomized and included in both the safety and ITT populations. Six patients were excluded from the 'protocol correct' analysis, which therefore included 34 patients (16 vigabatrin and 18 placebo patients). The primary population for determining efficacy was the ITT, the protocol correct analysis was used to confirm the ITT findings. No patients withdrew from the study during the double-blind phase.

Demographic and Baseline Characteristics

The demographic data are summarized in Table 6 and Table 7. The two treatment groups appeared generally similar with respect to demographic characteristics.

Table 6 Demographic Summary at Baseline I (ITT)

	Treatment					
	Placebo		VGB		Total	
	N	%	N	%	N	%
Gender						
male	11	55	8	40	19	48
female	9	45	12	60	21	53
Total	20	100	20	100	40	100
Race						
caucasian	17	85	18	90	35	86
black	1	5	0	0	1	3
mixed	2	10	1	5	3	8
other	0	0	1	5	1	3
Total	20	100	20	100	40	100
Patient Status						
out patient	6	30	7	35	13	33
normally hospitalized	14	70	13	65	27	68
normally institutionalized	0	0	0	0	0	0
Total	20	100	20	100	40	100

Source: Table 5a of sponsor's Clinical Study Report

Table 7 Demographic Summary at Baseline II (ITT)

	Treatment		
	Placebo	VGB	Total
Age at onset (months)			
n	20	20	40
missing	0	0	0
mean	6	7	6
median	6	6	6
sd	3	3	3
minimum	0	1	0
maximum	11	17	17
Age at study (months)			
n	20	20	40
missing	0	0	0
mean	8	8	8
median	8	7	8
sd	3	4	3
minimum	4	5	4
maximum	17	20	20
Height (cm)			
n	19	19	38
missing	1	1	2
mean	71	68	70
median	72	68	69
sd	8	6	7
maximum	58	57	58
minimum	91	81	91
Weight (kg)			
n	20	20	40
missing	0	0	0
mean	8	8	8
median	8	8	8
sd	2	1	2
minimum	4	5	4
maximum	13	10	13

Source: Table 5b of sponsor's Clinical Study Report

Pre-study clinical characteristics are summarized in Table 8. The two treatment groups appeared generally similar with respect to pre-study clinical characteristics, except epileptic history (three placebo patients (15%) had epileptic history compared to 9 patients (45%) in vigabatrin group.)

Table 8 Clinical Characteristics (ITT)

	Treatment					
	Placebo		VGB		Total	
	N	%	N	%	N	%
Family history of epilepsy/febrile convulsions						
not known	0		1		1	
no	15	75	16	84	31	79
yes	5	25	3	16	8	21
Total	20	100	20	100	40	100
Perinatal complications						
no	11	55	9	45	20	50
yes	9	45	11	55	20	50
Total	20	100	20	100	40	100
Epileptic history						
no	17	85	11	55	28	70
yes	3	15	9	45	12	30
Total	20	100	20	100	40	100
Development status normal						
no	18	90	17	85	35	88
yes	2	10	3	15	5	13
Total	20	100	20	100	40	100
Denver Test						
missing	3		1		4	
normal	2	12	1	5	3	8
suspect	15	88	14	74	29	81
untestable	0	0	4	21	4	11
Total	20	100	20	100	40	100

Source: Table 6 of sponsor's Clinical Study Report

3.1.2.6 Sponsor's Primary Efficacy Results

The primary efficacy variable was the percentage change in the average frequency of spasms as assessed from the two-hour intensive monitoring window, from baseline to the end of the double-blind period, where the end of the double-blind period was defined as the last two days of that treatment period. This primary efficacy variable (log-transformed) was analyzed using ANCOVA for ITT population. This analysis is summarized in Table 9.

The results in the two treatment groups are similar, with eight patients in each group (40% placebo group and 47% vigabatrin group) achieving a greater than 70% improvement (i.e. reduction in spasm frequency), and three patients in each treatment group (15% of placebo and 18% of vigabatrin patients) achieving 40 to 69% improvement during the 2-hour time window. However, in the placebo group eight patients (40%) had no improvement or worsened as compared to four patients (24%) in the vigabatrin group. This treatment difference was not statistically significant (p=0.562).

Table 9 Percentage Change in Average Frequency of Spasms – Double-blind Phase (over Final 2 Days) (ITT)

	% improvement	Treatment Placebo N	Placebo %	VGB N	VGB %	Total N	Total %	P-value*
2 hour								
	missing	0		3		3		
	>=70	8	40	8	47	16	43	
	40-69	3	15	3	18	6	16	
	1-39	1	5	2	12	3	8	
	<=0	8	40	4	24	12	32	
Total		20	100	20	100	40	100	
#	mean	59.5%		45.6%		$ 0.768		
	95% CI	(30%-117%)		(24%-88%)		(0.305-1.929)		0.562
24 hour								
	>=70	3	15	8	40	11	28	
	40-69	3	15	3	15	6	15	
	1-39	4	20	5	25	9	23	
	<=0	10	50	4	20	14	35	
Total		20	100	20	100	40	100	
#	mean	83.0%		31.1%		$ 0.374		
	95% CI	(43%-159%)		(17%-58%)		(0.155-0.902)		0.030

* Taken from final model from log analyses

The mean and 95% CI's for this primary variable are taken from the final log model over the complete distribution, estimated by $[(nspasm_{78} +1)/(nspasm_{123} +1)] * 100\%$

$ Relative risk with their corresponding CI's of VGB/Placebo from the final log model

Source: Table 13 of sponsor's Clinical Study Report

3.1.2.7 Sponsor's Secondary Efficacy Analyses (Selected)

24-hour Period - Baseline to Final Two Days (Double-blind Phase)

For the 24 hour monitoring window the differences between the treatment groups were greater than for the two-hour window. Eight vigabatrin patients (40%) compared to three placebo patients (15%) reported a greater than 70% improvement and 10 (50%) placebo patients as compared with four (20%) vigabatrin patients having either no improvement or a worsening. The results were presented in Table 9.

Cessation of Spasms (Double-Blind Phase)

The number of patients achieving complete cessation of spasms at the end of the double-blind phase is summarized in Table 10 and Table 11. When cessation of spasm was taken as no spasm at all on the final day of the double-blind period, seven (35%) vigabatrin patients compared to two (10%) placebo patients showed complete cessation of spasms on the final day.

Table 10 Number of Patients with Complete Cessation of Spasms (0 or 1 Spasms) on Final Day in 24-hour Window – Double-blind Phase (ITT)

Complete cessation*	Treatment					
	Placebo		VGB		Total	
	N	%	N	%	N	%
No	17	85	11	55	28	70
Yes	3	15	9	45	12	30
Total	20	100	20	100	40	100

* Includes 3 patients who had 1 isolated spasm as defined in the analysis plan

Source: Excerpt from Table 15a of sponsor's Clinical Study Report

Table 11 Number of Patients with Complete Cessation of Spasms (0 Spasms) on Final Day in 24-hour Window – Double-blind Phase (ITT)

Complete Cessation*	Treatment					
	Placebo		VGB		Total	
	N	%	N	%	N	%
No	18	90	13	65	31	78
Yes	2	10	7	35	9	23
Total	20	100	20	100	40	100

* Here defined as complete absence of spasms

Source: Excerpt from Table 15b of sponsor's Clinical Study Report

3.1.3 REVIEWER'S ANALYSIS/COMMENTS FOR STUDY 1A

This reviewer confirmed the efficacy results presented in this review for Study 1A.

Based on the primary efficacy results, it appears that there is a positive signal of treatment effect of vigabatrin for subjects with new onset infantile spasm. However, it is very difficult to make sound statistical inference due to the concerns with Statistical Analysis Plan and issues in sample size increases and interim analyses; details are elaborated below.

3.1.3.1 Concerns in Statistical Analysis Plan

In the Clinical Study Report, the sponsor states that, the final data analysis was in accordance with the Statistical Analysis Plan (SAP) included as Appendix 16.1.15. In the response to the Agency's request, the sponsor states that this SAP was signed-off in October 2004 and not

submitted to IND 47, 707 as the IND had been placed on inactive status prior to the creation of the SAP; the sponsor also states that Dr. Roy Elterman verified for Ovation that Aventis did not develop an SAP for Study 1A, but Drs. Elterman and Shields included statistical methods in both the first and second interim Clinical Study Report that were used in efficacy analyses. However, it is not clear to this reviewer what impact of the first and second interim analysis was on the development of this SAP (i.e., Appendix 16.1.15) and on the final analysis.

3.1.3.2 Issues in Sample Size Increases

According to the Clinical Study Report, Study 1A was initially planned as a compassionate use study to allow physicians to distribute study drug while a New Drug Application (NDA) for vigabatrin was under FDA review. According to the original efficacy assumptions, 37-40 subjects needed to be enrolled. The protocol allowed for a maximum of 60 subjects. However, the study was redesigned as a high/low-dose comparative trial and a minimum of 44 subjects were to be enrolled. Furthermore, the sponsor states that, due to a delay in the expected marketing approval, the protocol was amended to include up to 150 subjects and further amended to allow up to 250 subjects. There was no additional power analysis conducted to determine the final two increases in sample size; the adjustment was made to allow physicians to continue to administer drug while awaiting FDA approval. The dates for original protocol and subsequent amendments are listed below:

- Original protocol: 8/9/1995
- Amendment 1: 9/27/1995
- Amendment 2: 11/14/1995
- Amendment 3: 6/14/1996
- Amendment 4: 1/27/1997 (sample size was increased to 150 subjects)
- Amendment 5: 10/3/2000 (sample size was increased to 250 subjects)
- Amendment 5': 10/3/2000, version date is 1/26/2001

Based on the Clinical Study Report, totally 227 subjects were enrolled to Study 1A.

It seems that the sample size for Study 1A was never fixed, and when the study was initiated, there was no pre-specified plan regarding how many subjects were to be enrolled and under what circumstance the sample size was to be increased.

3.1.3.3 Issues in Interim Analyses

According to the Clinical Study Report, three analyses were performed on the collected data. The sponsor states that the first analysis was performed in response to the FDA's request for information on pediatric use of vigabatrin to be included in the proposed package insert. A second analysis, requested by Aventis Pharmaceuticals Inc, was performed to fulfill a request from the FDA. The results of this analysis were published in *Neurology* in 2001. The following table summarizes the results of the two interim analyses and final analysis by the sponsor, as well as the results for the first 40 and 44 subjects by this reviewer.

Table 12 Summary of Analyses for Study 1A

	Reviewer's Analysis		Sponsor's Analysis			
	First 40	First 44	1st Interim	2nd Interim (a)	2nd Interim (b)[2]	Final
Cut-off date	9/11/1996[1]	9/27/1996[1]	5/31/1997[4]	2/28/1999	2/28/1999	4/2/2002
No. of subjects randomized	-	-	89	179	179	227
No. of Subjects Included in Analysis	40 MITT	44 MITT	62 Efficacy Evaluable	142 Efficacy Evaluable	142 Efficacy Evaluable	221 (MITT)
Responder rate for low dose	0% (0/21)	0% (0/22)	15% (5/33)	11% (8/75)	5% (4/75)	7 % (8/114)
Responder rate for high dose	11% (2/19)	14% (3/22)	28% (8/29)	36% (24/67)	15% (10/67)	16% (17/107)
P-value[3]	0.2192	0.2326	0.349	P<0.001	P=0.0883	0.0375[5]

Source: Reviewer's Analysis and sponsor's Reports.

[1]: The 40th and 44th MITT subject were enrolled into the study on September 11, 1996 and September 27, 1996, respectively.

[2]: The number of responders were provided by the sponsor upon request (please see the paragraph below for details); this reviewer used Fisher's Exact test to generate the p-value.

[3]: P-values are nominal p-values;
Fisher's Exact test were used by this review to analyze the data for the first 40 and 44 subjects and the 2nd interim analysis (b), due to some small cell counts.
The sponsor used Fisher's Exact Test, Mantel Haenszel Chi-square test, and Pearson Chi-square test for the 1st interim analysis, the 2nd interim analysis (a) and the final analysis, respectively.

[4]: Interim analysis report indicates the cut-off date was June 30, 1997.

[5]: The p-value is 0.0544, based on Fisher's Exact Test.

The results for the second interim analysis (a) was excerpted from sponsor's 2nd interim analysis report dated 1 Feb 2000. However, since noticing that the number of responders for high dose group was decreased from 24 to 17 from the second interim analysis (a) to the final analysis, this reviewer raised this question to the sponsor and the sponsor states that the definition of a responder is the same but for the final analysis the responder definition was applied in a more conservative manner (please refer to Table 1 for details). This reviewer asked the sponsor to re-produce the results of the responder rate for the second interim analysis according to this "more conservative manner". The results are presented as 2nd Interim Analysis (b), in which the sponsor provided the number of responders by dose group and this reviewer used Fisher's Exact Test to generate the p-value.

There are three issues associated with interim analyses.

Firstly, it seems that the two interim analyses were not pre-specified and the p-value for the final analysis was not adjusted for the two interim analyses.

Secondly, the results of the second analysis were published in *Neurology* in October, 2001 and the last subject completed the study in April, 2002. The impact of the publication of the results of this interim analysis on the trial conduct and final analysis is unknown.

Thirdly, it is not clear whether or not any type of analysis was conducted for this study before the first interim analysis. By the time of Protocol Amendment 4 in which the sample size was increased from 44 to 150, 64 subjects had been enrolled into the study. This means, before Amendment 4, Study 1A had enrolled more subjects than the planned sample size of 44 subjects. However, it is not clear whether the sponsor conducted any type of analysis before Amendment 4 and first interim analysis. Below is sponsor's response to this reviewer's question "Before the first interim analysis, was there any type of analysis conducted on the data for Study 1A?"

> *Ovation conferred with Dr. Elterman and he confirmed that there was no compilation of results from the participating sites or analyses until issuance of the first interim analysis (i.e. first interim clinical study report).*

From this response, it is still not clear whether the participating sites had conducted any type of analyses before the first interim analysis.

3.1.4 REVIEWER'S ANALYSIS/COMMENTS FOR STUDY W019

This reviewer confirmed the efficacy results presented in this review for Study W019.

In Study W019, the primary efficacy variable was the percentage change in the average frequency of spasms as assessed from the two-hour intensive monitoring window, from baseline to the end of the double-blind period, where the end of the double-blind period was defined as the last two days of that treatment period. For this pre-specified primary endpoint, the difference between the vigabatrin group and placebo group was not statistically significant (p=0.562). When this efficacy variable was based on data collected over the 24-hour window, there appears to be a treatment difference in favor of vigabatrin. The sponsor explains this is due to the fact that the spasms did not occur at the same intensity every day as expected by the choice of the two hour window; but this is a post hoc analysis.

3.2 Evaluation of Safety

Please read Drs. Gerard Boehm's and Ronald Farkas' review for safety assessment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

4.1.1 STUDY 1A

Responder rate is summarized by subgroups and treatment group in Table 13.

Table 13 Responder Rate by Subgroups and Treatment Group

Subgroup	High-Dose Vagabatrin	Low-Dose Vagabatrin
Age <=0.6 yrs	17% (9/52)	14% (8/59)
Age>0.6 yrs	13% (7/52)	0% (0/55)
Male	16% (7/45)	3% (2/63)
Female	16% (10/61)	12% (6/50)
White	18% (14/76)	8% (7/84)
Black	7% (1/15)	9% (1/11)
Asian	33% (1/3)	0% (0/0)
Other	8% (1/13)	0% (0/19)

Source: Reviewer's Analysis

It appears that the point estimates of responder rate were in the same direction across the patient subgroups investigated.

4.1.2 STUDY W019

Study W019 did not demonstrate an effect of vigabatrin on infantile spasms, based on the pre-specified primary endpoint. Therefore, the subgroup analysis was omitted.

4.2 Other Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 STUDY 1A

Study 1A was sponsored by the Vigabatrin Infantile Spasm (IS) Study Group (VISSG), an unincorporated association of physicians and medical researchers dedicated to the study of IS. The 1A clinical study was conducted under an investigator-sponsored IND (47,707) beginning in January 1996. There was no industry sponsor involved in the conduct of this study, although Aventis Pharmaceuticals did provide a grant to Dr. Roy Elterman in the amount of $144,500.00 on March 17, 2000 to cover certain costs. Aventis also provided vigabatrin clinical study supplies for study 1A at no cost to the 9 participating VISSG investigators. Ovation Pharmaceuticals acquired an exclusive license to the Study 1A data per an agreement with Dr. Roy Elterman in April, 2002. Subsequently, Ovation acquired the North American rights to vigabatrin from Aventis in March 2004. It was only after this latter acquisition that Ovation began data monitoring and verification at the VISSG study sites.

The primary efficacy endpoint was the proportion of subjects achieving spasm cessation for 7 consecutive days beginning within the first 14 days of therapy and confirmed by caregiver assessment and via CCTV EEG monitoring within 3 days of the seventh day of spasm freedom. It was analyzed by Chi-square test to compare the proportions of subjects in the high- and low-dose vigabatrin treatment groups who were free of spasms.

Totally, 227 subjects were enrolled into the study. The first subject enrolled on January 22, 1996 and the last subject completed the study on April 2, 2002. Three analyses were performed with the data collection cut-off date May 31, 1997, February 28, 1999 and April 02, 2002.

Specifically, for the final analysis, 221 subjects were analyzed for efficacy (114 received low-dose vigabatrin and 107 received high-dose vigabatrin). Primary efficacy analysis showed that 11% (25/221) of the subjects were spasm-free: 16% (17/107) of the subjects in the high-dose treatment group and 7% (8/114) of subjects in the low-dose treatment group. The difference between treatment groups was statistically significant (Chi-square test, p=0.0375).

Based on the primary efficacy results, it appears that there is a positive signal of treatment effect of vigabatrin for subjects with new onset infantile spasm. However, it is very difficult to make sound statistical inference due to concerns in Statistical Analysis Plan and issues in sample size increases and interim analyses.

Statistical Analysis Plan

In the Clinical Study Report, the sponsor states that, the final data analysis was in accordance with the Statistical Analysis Plan (SAP) included as Appendix 16.1.15. In the response to the Agency's request, the sponsor states that this SAP was signed-off in October 2004 and not submitted to IND 47, 707 as the IND had been placed on inactive status prior to the creation of the SAP. The sponsor also states that Dr. Roy Elterman verified for Ovation that Aventis did not

develop an SAP for Study 1A, but Drs. Elterman and Shields included statistical methods in both the first and second interim Clinical Study Report that were used in efficacy analyses. However, it is not clear to this reviewer what impact of the first and second interim analysis was on the development of this SAP (i.e., Appendix 16.1.15) and on the final analysis.

Issues in Sample Size Increases

According to the Clinical Study Report, Study 1A was initially planned as a compassionate use study to allow physicians to distribute study drug while a New Drug Application (NDA) for vigabatrin was under FDA review. According to the original efficacy assumptions, 37-40 subjects needed to be enrolled. The protocol allowed for a maximum of 60 subjects. However, the study was redesigned as a high/low-dose comparative trial and a minimum of 44 subjects were to be enrolled. Furthermore, the sponsor states that, due to a delay in the expected marketing approval, the protocol was amended to include up to 150 subjects and further amended to allow up to 250 subjects. There was no additional power analysis conducted to determine the final two sample size increases; the adjustment was made to allow physicians to continue to administer drug while awaiting FDA approval. From the Clinical Study Report, totally 227 subjects were enrolled to Study 1A. It seems that the sample size for Study 1A was never fixed, and when the study was initiated, there was no pre-specified plan regarding how many subjects were to be enrolled and under what circumstance the sample size was to be increased.

Issues in Interim Analyses

According to the Clinical Study Report, three analyses (two interim analyses and one final analysis) were performed on the collected data. The results of the second interim analysis were published in *Neurology* in 2001. There are three issues associated with interim analyses:

- Firstly, it seems that the two interim analyses were not pre-specified and the p-value for final analysis was not adjusted for the two interim analyses.
- Secondly, the results of the second analysis were published in *Neurology* in October, 2001 and the last subject completed the study in April, 2002. The impact of the publication of the results of this interim analysis on the trial conduct and final analysis is unknown.
- Thirdly, it is not clear whether the participating sites had conducted any type of analyses before the first interim analysis.

5.1.2 STUDY W019

For Study W019, the primary efficacy variable was the average percent change in daily spasm frequency, assessed during a predefined two-hour window, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final two days of the period.

This primary efficacy variable was analyzed for ITT population using ANCOVA with Treatment and Geographical location as factors and Baseline spasm count as covariate. Based on this primary efficacy variable, the results in the two treatment groups are similar, with eight patients in each group (40% placebo group and 47% vigabatrin group) achieving a greater than 70%

improvement (i.e. reduction in spasm frequency), and three patients in each treatment group (15% of placebo and 18% of vigabatrin patients) achieving 40 to 69% improvement during the 2-hour time window. This treatment difference was not statistically significant (p=0.562).

When this efficacy variable was based on data collected over the 24-hour window, there appears to be a treatment difference in favor of vigabatrin. The sponsor explains this is due to the fact that the spasms did not occur at the same intensity every day as expected by the choice of the two hour window; but this is a post hoc analysis.

5.2 Conclusions and Recommendations

For Study 1-A, based on the primary efficacy results, it appears that there is a positive signal of treatment effect of vigabatrin for subjects with new onset infantile spasm. However, it is very difficult to make sound statistical inference due to the concerns (explained in Section 1.3) with Statistical Analysis Plan and issues in sample size increases and interim analyses.

Study 71754-W-019 did not demonstrate an effect of vigabatrin on infantile spasms, based on the pre-specified primary endpoint, the average percent change in daily spasm frequency, assessed during a predefined two-hour window. When this efficacy variable was based on data collected over the 24-hour window, there appears to be a treatment difference in favor of vigabatrin.

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-006
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	12/28/07
PRODUCT:	Sabril (vigabatrin) for Oral Solution
INTENDED CLINICAL POPULATION:	pediatric epilepsy (infantile spasms)
SPONSOR:	Ovation Pharmaceuticals
REVIEW DIVISION:	Division of Neurology Products (HFD-120)
PHARM/TOX REVIEWER:	Ed Fisher
PHARM/TOX SUPERVISOR:	Lois Freed
DIVISION DIRECTOR:	Russell Katz
PROJECT MANAGER:	Tamy Kim

I. TOXICOLOGY

1. Oral (Gavage) Repeated-Dose Toxicity Study of Vigabatrin in Rats (Report No. OV-1007, dated 6/7/06, conducted by Charles River, Horsham, PA, GLP)

a. Methods

Young rats (80/sex/dose main; whole litter design) were given 0 (water), 5, 15, or 50 mg/kg VGB by oral gavage (5 ml/kg) once daily from postnatal day (PND) 4 through PND 65. Subsets of approximately 20/sex/group were sacrificed on PND 67 or following a recovery period (on day 13 of presumed gestation in subset of females mated or PND 196 through 201 for males). TK blood samples were collected from 2-3/sex/group/timepoint after dosing on PNDs 17 and 65. The following parameters were evaluated for all rats: viability, clinical observations, body weight and body weight changes, feed consumption, and gross necropsy observations for the treatment and recovery periods. Subsets of rats (at least 10/sex/group) were evaluated for alterations in the eye (electroretinograms [5/sex/group] and ophthalmoscopic examination) on 3 occasions (after approximately 3 weeks, end of dosing, and end of recovery); other parameters (sexual maturation, and for motor activity, functional observation battery, acoustic startle habituation and prepulse inhibition, hematology, clinical chemistry, urinalysis, organ weights, and histopathology) were assessed either during dosing or at the end of the treatment period, and either during or at the end of the recovery period. During the recovery period, subsets of rats (at least 10/sex/group) were evaluated for estrus cycle, mating and fertility, sperm motility and count, and learning and memory (simple spatial discrimination water maze and a Morris water maze).

Strain. Crl:CD(SD)
Drug Lot #. 152972

Dose selection was based on a dose range-finding study in which oral doses of 30, 50, 100, 300, 500 and 1000 mg/kg/day were given to rats (SD) from PND 4 for 2 weeks. Severe and early toxic effects were seen at ≥300 mg/kg (all animals were euthanized within 5 days). Deaths, marked clinical signs (absence of milk in the stomach and decrease/absence of motor activity), and a marked decrease in body weight gain were seen at 100 mg/kg. Effects at 50 mg/kg/day were less severe and included transient absence of milk intake and/or decreased motor activity in some animals and reduced body weight gain. Changes at 30 mg/kg/day were limited to a minimal decrease in body weight gain. Scattered nuclei in the photoreceptor layer and an increased number of apoptotic bodies in the inner nuclear layer of the retina were observed at 50 or 100 mg/kg (see **Table II.2**). 30 mg/kg/day was considered to be close to a NOAEL.

b. Results

i. Mortality, clinical signs

A total of 3, 5, 2, and 7 rats in the C, LD, MD, and HD groups, respectively, died or were sacrificed prior to scheduled termination. Three (1 male, 2 females) of the seven HD deaths were considered treatment-related (T-R), based on clinical signs (spasms or tremors) and/or body weight losses; the other deaths were due to either dosing or anesthesia accidents. Whole body spasm occurred in a significantly increased number of male (28) and female (23) rats at the HD. No other T-R clinical signs were noted.

ii. Body weight

Significant reductions in BW gain were seen at the MD and HD in males and at the HD in females (**Table I.1.1**). BWs in the respective dose groups were 3, 10, and 27% below C in males and +3.0, -2, and 20% above/below C in females on

PND 65. Post-treatment BW gains continued to be reduced in males (8, 13, and 24%) but not females. Terminal body weights in the respective groups were 5, 11, and 27 below C in males and +2, -1, and -18% above/below C in females.

iii. Developmental Landmarks

The days on which preputial separation or vaginal patency were observed significantly increased at the HD (**Table I.1.2**). These delays in sexual maturation correlated with reduction in BW, although BW at maturation was significantly reduced only in males.

iv. Ophthalmologic and ERG Examinations

According to the consultant's report, there were no indications of T-R ocular damage in the ophthalmoscopic examinations. The ERG measurements (onset latency of the b-wave [1 Hz], baseline-to-peak amplitude of the b-wave [1, 10, 15 Hz], and peak-to-peak amplitude of the oscillatory responses [1 Hz)]) were generally comparable among the dosage groups in all testing sessions, and according to the report, there was no evidence that drug exposure was associated with altered ERG responses at the doses and time points evaluated.

v. Developmental Neurotoxicity Testing

In males, the average startle response during the habituation phase was attenuated somewhat (not statistically significant [NS]) at the HD on PNDs 59-63 and increased (NS) at all doses on PND 89-91 (**Tables I.1.3**). There was also an increased response to prepulse inhibition at the MD in the recovery period. There were no apparent changes in females at either evaluation time.

No clear effects on motor activity (number of movements and time spent in movement) were seen during the dosing period (PND 56 ±1 day) or during the recovery period (PND 86 ±1 day).

In the FOB, landing foot splay and forelimb and hindlimb grip strength (maximum and average values) were dose-dependently (D-D) decreased (statistically significant [SS] in MD and/or HD) in treated males and females during the dosing (PNDs 56, 57, 58 or 59) and post-dosing periods (PNDs 87, 88 or 89). BW on day of testing was decreased (SS) in MD and HD males and in HD females. (**Tables I.1.4-5**)

In a simple water (M) maze conducted during the recovery phase (beginning on PND 105), there was an increase in the number of HD females (3/18: 6707, 7107 and 7307) that failed to meet the criterion during the reversal learning session (**Table I.1.6**).

Although there was some tendency (NS) for increased latencies in treated groups in the Morris maze, particularly during the initial trials, there was no clear effect on learning or memory in this test (**Table I.1.7**). It should be noted that this was performed very late (PNDs 153-177) due to the test being added to the protocol after the study had started.

vi. Reproductive Performance (13th week of age, 1:1 non-sibling mating)

Estrous cyclicity was D-D reduced in treated females (**Table I.1.8**). The mating and fertility data are anomalous, and do not allow a valid assessment of drug

effects. Only 50-60% of C, LD, and MD rats mated, while 90% of HD animals mated; thus, while there is the suggestion of an effect on fertility, the D-R is non-monotonic (fertility index: 100.0, 45.4, 66.7, and 93.8% at C, LD< MD, and HD).

Reproductive outcome parameters at laparotomy were generally similar among groups; however, due to the poor pregnancy rate only 9, 6, 8, and 15 litters were available in the C, LD, MD, and HD groups, respectively.

There were no T-R differences in sperm parameters. Absolute testicular and epididymal weights were decreased in HD males, but relative weights were increased.

vii. Pathology

No T-R gross lesions were observed. Terminal body weights were decreased in MD and HD males and in HD females. Absolute brain weights were significantly reduced at the MD and HD in males and females (**Table I.1.9**), and epididymis and testis weights were decreased at the HD. However, relative brain (**Table I.1.10**) and testis weights were increased at the HD. Terminal body weights remained significantly reduced after the recovery period at the HD. The brain weight reductions also persisted into the recovery period (SS in HD males and females after 19 weeks).

Microscopic Findings:

Of the 20/sex/group necropsied on PND 67, 1/2 were perfusion-fixed and the brains and retinas of all of these animals from all groups were microscopically examined by the study neuropathologist. The other 1/2 had tissues immersion-fixed and a general histopathology examination involving all tissues from the C and HD groups was performed by the study pathologist. Another subset was necropsied during PND 196-210 after an approximately 19-week recovery period and 10/sex/group were perfusion-fixed for neuropathology examination by the same pathologist.

With the exception of the CNS, all tissues appeared normal on histological evaluation. For the immersion-fixed tissues, three sections of brain were examined from each C and HD rat. The report noted that "vacuolations in white matter and/or gray matter of minimal or mild severity involving one or more brain regions of posterior thalamus, hypothalamus, hippocampus and/or brainstem (midbrain and hindbrain) were evident in 8/9 males and 7/9 females administered 50 mg/kg/day of Vigabatrin from Group 4 and terminated on PND 67."

All perfusion-fixed HD male and female brains examined by the neuropathologist had increased levels (over background) of vacuolation within the neuropil of selected brain regions on PND 67 (**Tables I.1.11-12**). The following is verbatim from the neuropathologist's (Robert Garman) report:

> "The most commonly affected brain regions included the following (listed in the approximate order of frequency affected): central midbrain (tegmentum), substantia nigra, dorsal subiculum, medulla oblongata, hippocampal CA1 region, thalamus, deep cerebellar nuclei and basal forebrain (particularly the medial forebrain bundle). In most of these regions, vacuolation was graded as minimal to mild. Although some white matter tracts had increased numbers of vacuoles (*viz.* the medial longitudinal fasciculus and medial forebrain bundle), most foci of vacuolation were present in subcortical grey matter or mixed grey and

white matter regions. The specific cellular/subcellular locations of the vacuoles could not be determined at the light microscopic level. Although vacuolation in brain sections often represents a nonspecific finding (relative to pathogenesis) and may sometimes be the result of artifact, the consistent inter-animal pattern of vacuolation in the high dose group rats and the absence of this degree of vacuolation within the other treatment groups in this study indicates that the vacuolation represents a treatment-related effect... Within the substantia nigra (which was not present on section for all rats), vacuolation always involved the most lateral portion of the pars compacta. Within the midbrain, the most consistently vacuolated region was within the medial longitudinal fasciculus and the adjacent neuropil present just inferior to the midline raphe nuclei. In the cerebella, vacuolation was typically restricted to the deep cerebellar nuclei. [Note that only a minority of the rats had the deep cerebellar nuclei represented within the sections.] Although the CA1 sector of the hippocampus was occasionally characterized by minimal to mild vacuolation, it was the dorsal subicular region (immediately medial to the CA1 pyramidal layer of the hippocampus) that was most consistently vacuolated."

Two MD males also had single foci of minimal neuropil vacuolation ("in the dorsal subicular region of one rat and in the deep cerebellar nuclear region of the other"). Although one HD female rat had a unilateral focus of gliosis within the hippocampus, this was considered by the neuropathologist to represent a background lesion. Dr. Garman also considered several instances of Fluoro-Jade B staining to represent background degenerative processes even though these were also only seen in MD and HD animals. Other microscopic findings within the nervous system other than for the eye were considered to be incidental; this conclusion seems questionable in some cases.

With the exception of a minimal finding in 1 C female, retinal dysplasia (minimal to mild, "characterized by the formation of rosettes within the outer nuclear layer of the retina that typically protruded inwards into overlying inner nuclear layer") was detected only in MD and HD males and females.

Although frequencies of both neuropil vacuolation and retinal dysplasia were decreased in the post-recovery period rats, minimal to mild vacuolation ("highly restrictive in location") was present in 2 HD males and 1 HD female. In all three rats, the foci of vacuolation were restricted to the deep cerebellar nuclei and/or pons. One focus of vacuolation within the deep cerebellar nucleus of the HD female had two small-sized foci of mineralization. There was no evidence of gliosis (based on GFAP staining) in any of the foci of vacuolation. The Fluoro-Jade B-stained sections from recovery rats were considered to indicate only background degenerative processes not related to treatment. One HD male and 5 females (2 each in LD and MD groups and 1 HD) had retinal dysplasia (all minimal in degree).

viii. Plasma drug levels

TK data are summarized in **Table I.1.13** below.

c. Conclusions

Administration of VGB to young rats from PND 4 through PND 65 at doses of 0, 5, 15, or 50 mg/kg increased mortality (HD), decreased BW gain (MD, HD), produced clinical signs of neurotoxicity (spasms or tremors at HD), delayed sexual maturation (HD), altered

estrus cyclicity (all doses), decreased absolute brain weights (D-D), and produced neurobehavioral (altered FOB performance, deficits in maze learning) and neurohistopathological (brain vacuolation and retinal dysplasia) changes (MD, HD) in treated animals.

Table I.1.1 Body Weight Gain in Juvenile Rats

Males

DOSAGE GROUP DOSAGE (MG/KG/DAY) a		I 0	II 5	III 15	IV 50
DOSAGE PERIOD:					
RATS TESTED	N	80	80	80	80
INCLUDED IN ANALYSES	N	75b	80	80	80
BODY WEIGHT CHANGE (G)					
ALL SUBSETS:					
DAYS 4 - 11	MEAN±S.D.	+13.0 ± 2.6	+11.9 ± 2.9*	+12.1 ± 3.0	+8.7 ± 2.3**
DAYS 11 - 17	MEAN±S.D.	+14.1 ± 2.7	+14.3 ± 2.7 [79]b	+13.2 ± 3.3	+11.3 ± 3.2**
SUBSETS 2, 3 AND 4:					
DAYS 17 - 24	MEAN±S.D.	+26.6 ± 4.1 [59]b	+27.5 ± 4.1 [58]b	+24.7 ± 4.4** [60]	+19.5 ± 4.0** [59]b
DAYS 24 - 29	MEAN±S.D.	+30.1 ± 4.6 [59]b	+31.2 ± 4.0 [58]b	+28.8 ± 3.8 [60]	+21.4 ± 4.0** [57]b
SUBSETS 2 AND 3:					
DAYS 29 - 36	MEAN±S.D.	+56.0 ± 8.2 [40]	+55.8 ± 7.2 [40]	+51.0 ± 7.0** [40]	+40.3 ± 6.7** [40]
DAYS 36 - 42	MEAN±S.D.	+58.4 ± 5.9 [40]	+56.2 ± 5.2 [40]	+54.4 ± 6.4** [40]	+42.8 ± 6.0** [40]
DAYS 42 - 49	MEAN±S.D.	+65.7 ± 8.2 [40]	+62.6 ± 7.6 [40]	+58.7 ± 5.7** [40]	+47.9 ± 6.8** [40]
DAYS 49 - 56	MEAN±S.D.	+64.9 ± 10.0 [40]	+61.9 ± 8.2 [40]	+58.3 ± 7.6** [40]	+47.1 ± 9.7** [39]b
DAYS 56 - 63	MEAN±S.D.	+51.5 ± 9.4 [40]	+48.3 ± 9.1 [40]	+44.6 ± 7.7** [40]	+39.4 ± 9.2** [39]b
DAYS 63 - 65	MEAN±S.D.	+16.7 ± 5.8 [40]	+15.0 ± 3.8 [40]	+12.6 ± 5.6** [40]	+9.7 ± 4.8** [39]b
DAYS 4 - 65	MEAN±S.D.	+398.0 ± 38.4 [40]	+383.8 ± 38.1 [40]	+357.5 ± 32.9** [40]	+286.2 ± 32.5** [39]b
RECOVERY PERIOD:					
RATS TESTED	N	80	80	80	80
INCLUDED IN ANALYSES	N	20	20	20	20
BODY WEIGHT CHANGE (G)					
SUBSET 3:					
DAYS 67 - 70	MEAN±S.D.	+17.3 ± 5.3	+19.5 ± 5.5	+17.6 ± 3.2	+15.2 ± 4.9
DAYS 70 - 77	MEAN±S.D.	+41.7 ± 10.1	+42.0 ± 9.0	+37.8 ± 8.6	+31.4 ± 8.7**
DAYS 77 - 84	MEAN±S.D.	+32.4 ± 8.3	+29.8 ± 6.7	+31.6 ± 8.6	+28.2 ± 5.6
DAYS 84 - 91	MEAN±S.D.	+29.7 ± 8.8	+24.8 ± 13.2	+25.7 ± 7.4	+22.8 ± 8.1
DAYS 91 - 98	MEAN±S.D.	+22.8 ± 11.4	+23.3 ± 10.6	+17.9 ± 9.3	+19.6 ± 7.8
DAYS 67 - 98	MEAN±S.D.	+144.0 ± 27.0	+139.4 ± 24.1	+130.6 ± 16.8	+117.2 ± 20.2**
DAYS 98 -125	MEAN±S.D.	+82.5 ± 19.0	+73.1 ± 15.9	+62.9 ± 35.6	+61.2 ± 14.0**
DAYS 125 -152	MEAN±S.D.	+52.2 ± 13.1	+46.2 ± 15.7	+46.5 ± 15.0	+36.2 ± 12.3**
DAYS 152 -181	MEAN±S.D.	+19.3 ± 20.9	+17.7 ± 16.0	+22.2 ± 13.0	+15.9 ± 12.8
DAYS 181 -195	MEAN±S.D.	+12.5 ± 14.6	+10.2 ± 11.2	+6.9 ± 12.3	+7.1 ± 9.0
DAYS 67 -195	MEAN±S.D.	+310.4 ± 75.6	+286.6 ± 65.2	+270.0 ± 54.4*	+237.6 ± 36.6**
DAYS 4 -195	MEAN±S.D.	+723.7 ± 108.7	+688.2 ± 95.7	+664.0 ± 72.9**	+527.4 ± 59.5**

NOTE TERMINATIONS: SUBSET 1 - POSTNATAL DAY 17 OR 18; SUBSET 2 - POSTNATAL DAY 67; SUBSET 3 - POSTNATAL DAYS 195 - 201; SUBSET 4 - POSTNATAL DAY 29

DAYS = POSTNATAL DAYS

a. Dosage occurred on postnatal days 4 through 65.

* Significantly different from the control group value ($p<0.05$).

** Significantly different from the control group value ($p<0.01$).

Females

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0	II 5	III 15	IV 50
DOSAGE PERIOD:					
RATS TESTED	N	80	80	80	80
INCLUDED IN ANALYSES	N	80	79b	80	80
BODY WEIGHT CHANGE (G)					
ALL SUBSETS:					
DAYS 4 - 11	MEAN±S.D.	+12.7 ± 2.4	+11.6 ± 2.8*	+11.5 ± 3.2**	+8.8 ± 2.3**
DAYS 11 - 17	MEAN±S.D.	+13.4 ± 2.5	+13.5 ± 2.7	+12.2 ± 3.0	+11.5 ± 3.0**
SUBSETS 2, 3 AND 4:					
DAYS 17 - 24	MEAN±S.D.	+24.8 ± 3.0 [60]	+25.2 ± 4.0 [58]b	+22.4 ± 3.2** [59]b	+13.1 ± 4.7** [60]
DAYS 24 - 29	MEAN±S.D.	+26.5 ± 3.6 [60]	+27.0 ± 3.9 [58]b	+25.7 ± 2.8 [58]b	+20.4 ± 3.5** [59]b
SUBSETS 2 AND 3:					
DAYS 29 - 36	MEAN±S.D.	+41.6 ± 5.3 [40]	+43.5 ± 4.6 [40]	+40.5 ± 4.8 [40]	+31.8 ± 4.4** [40]
DAYS 36 - 42	MEAN±S.D.	+31.8 ± 4.2 [40]	+32.3 ± 4.3 [40]	+32.7 ± 4.8 [40]	+30.8 ± 5.1 [40]
DAYS 42 - 49	MEAN±S.D.	+27.7 ± 5.6 [40]	+29.2 ± 6.0 [40]	+26.2 ± 5.5 [40]	+23.7 ± 5.9** [40]
DAYS 49 - 56	MEAN±S.D.	+27.8 ± 6.3 [40]	+28.0 ± 4.8 [40]	+26.5 ± 7.3 [40]	+20.7 ± 5.8** [40]
DAYS 56 - 63	MEAN±S.D.	+19.2 ± 7.4 [40]	+20.0 ± 6.3 [40]	+20.2 ± 6.6 [40]	+18.4 ± 6.7 [39]b
DAYS 63 - 65	MEAN±S.D.	+6.3 ± 5.8 [40]	+6.8 ± 6.0 [40]	+7.2 ± 5.4 [40]	+5.0 ± 5.1 [39]b
DAYS 4 - 65	MEAN±S.D.	+231.4± 20.0 [40]	+237.3± 21.0 [40]	+226.2± 21.3 [40]	+183.8± 20.6** [39]b
RECOVERY PERIOD:					
RATS TESTED	N	20	20	20	19
BODY WEIGHT CHANGE (G)					
SUBSET 3:					
DAYS 67 - 70	MEAN±S.D.	+9.1 ± 4.5	+8.1 ± 6.2	+12.5 ± 8.8	+6.3 ± 4.2
DAYS 70 - 77	MEAN±S.D.	+16.0 ± 6.7	+14.2 ± 9.4	+12.8 ± 6.8	+11.8 ± 5.5
DAYS 77 - 84	MEAN±S.D.	+11.6 ± 6.1	+10.3 ± 7.6	+12.2 ± 8.3	+10.8 ± 6.3
DAYS 84 - 91	MEAN±S.D.	+8.0 ± 6.4	+8.4 ± 7.2	+8.2 ± 7.3	+9.8 ± 5.2
DAYS 91 - 98	MEAN±S.D.	+11.5 ± 12.8	+7.6 ± 7.0 [19]b	+6.8 ± 6.0	+10.4 ± 6.5 [18]b
DAYS 67 - 98	MEAN±S.D.	+56.2 ± 15.9	+49.2 ± 10.4 [19]b	+52.5 ± 15.3	+49.4 ± 11.0 [18]b
DAYS 98 -125	MEAN±S.D.	+23.4 ± 10.2 [19]b	+27.0 ± 11.8 [19]b	+23.1 ± 11.8	+16.8 ± 8.7 [18]b
DAYS 125 -153	MEAN±S.D.	+19.5 ± 7.4 [19]b	+19.7 ± 17.6 [19]b	+21.4 ± 12.5	+15.9 ± 8.4 [18]b
DAYS 153 -170	MEAN±S.D.	+7.5 ± 9.7 [19]b	+10.0 ± 9.2 [19]b	+10.6 ± 14.4	+7.5 ± 7.0 [18]b
DAYS 67 -170	MEAN±S.D.	+106.0 ± 26.9 [19]b	+105.9 ± 26.3 [19]b	+107.7 ± 33.0	+89.6 ± 18.2 [18]b
DAYS 4 -170	MEAN±S.D.	+343.2 ± 43.2 [19]b	+349.7 ± 38.5 [19]b	+338.7 ± 46.1	+277.8 ± 35.1** [18]b

NOTE TERMINATIONS: SUBSET 1 - POSTNATAL DAY 17 OR 18; SUBSET 2 - POSTNATAL DAY 67; SUBSET 3 - DAY 12 OF PRESUMED GESTATION; SUBSET 4 - POSTNATAL DAY 29
DAYS = POSTNATAL DAYS [ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on postnatal days 4 through 65.
b. Excludes values for rats that were found dead or sacrificed due to moribund condition.
** Significantly different from the control group value ($p<0.01$).

Table I.1.2 Morphological Landmarks in Juvenile Rats

DOSAGE GROUP DOSAGE (MG/KG/DAY) a		I 0	II 5	III 15	IV 50
SUBSET 2					
MALE RATS	N	20	20	20	19b
PREPUTIAL SEPARATION c	MEAN±S.D.	46.0 ± 2.8	45.4 ± 3.2	46.4 ± 2.8	48.1 ± 2.5*
BODY WEIGHT AT MATURATION (G)	MEAN±S.D.	243.8 ± 23.8	234.8 ± 27.6	226.0 ± 24.4	195.8 ± 21.3**

a. Dosage occurred on postnatal days 4 through 65.
b. Excludes rat 7704, which was found dead on postnatal day 54.
c. Average day postnatal that the prepuce was observed to be separated.
* Significantly different from the control group value ($p \leq 0.05$).
** Significantly different from the control group value ($p \leq 0.01$).

DOSAGE GROUP DOSAGE (MG/KG/DAY) a		I 0	II 5	III 15	IV 50
SUBSET 2					
FEMALE RATS	N	20	20	20	20
VAGINAL PATENCY b	MEAN±S.D.	34.0 ± 2.1	33.6 ± 1.7	34.0 ± 2.0	36.4 ± 2.3**
BODY WEIGHT AT MATURATION (G)	MEAN±S.D.	113.8 ± 14.9	114.2 ± 10.2	109.7 ± 13.3	105.8 ± 9.2

a. Dosage occurred on postnatal days 4 through 65.
b. Average day postnatal that the vagina was observed to be patent.
** Significantly different from the control group value ($p \leq 0.01$).

Table I.1.3 Acoustic startle response in males during the dosing and post-dosing periods

DOSAGE GROUP DOSAGE (MG/KG/DAY) a		I 0	II 5	III 15	IV 50
SUBSET 2					
POSTNATAL DAY 59,60,62 OR 63					
NUMBER OF RATS		20	20	20	19
ACOUSTIC STARTLE HABITUATION					
INCLUDED IN ANALYSES b		17	17	19	17
BLOCK 1	MEAN ± S.D.	101.76 ± 43.46	102.18 ± 52.27	111.62 ± 44.29	88.47 ± 39.01
BLOCK 2	MEAN ± S.D.	80.04 ± 50.40	83.86 ± 46.82	83.66 ± 42.51	71.91 ± 41.99
BLOCK 3	MEAN ± S.D.	68.20 ± 36.18	72.14 ± 34.50	87.69 ± 49.48	69.08 ± 46.19
BLOCK 4	MEAN ± S.D.	68.19 ± 35.46	67.29 ± 44.81	88.44 ± 46.78	59.49 ± 40.96
BLOCK 5	MEAN ± S.D.	70.83 ± 30.09	59.39 ± 27.58	71.95 ± 36.98	57.55 ± 32.45
AVERAGE	MEAN ± S.D.	77.82 ± 34.07	77.17 ± 35.07	88.67 ± 29.82	69.30 ± 36.40
PREPULSE INHIBITION c					
INCLUDED IN ANALYSES d		15	14	16	14
CONTROL	MEAN ± S.D.	4443 ± 1104	4448 ± 880	4610 ± 525	4076 ± 538
PREPULSE (70dB)	MEAN ± S.D.	3381 ± 715	3337 ± 485	3473 ± 624	3360 ± 316
PREPULSE (90dB)	MEAN ± S.D.	2176 ± 748	2214 ± 768	1917 ± 740	2564 ± 562

BLOCK = AVERAGE OF 10 TRIAL SESSIONS MINUS THE BODY WEIGHT
CONTROL = AVERAGE OF RESPONSES IN 10 TRIAL SESSIONS MINUS THE BODY WEIGHT.
PREPULSE = AVERAGE OF RESPONSES IN THE 70dB OR 90dB PREPULSE CONDITION MINUS THE BODY WEIGHT.

a. Dosage occurred on postnatal days 4 through 65.
b. Excludes rats with extremely low responses or whose responses to the stimulus were apparently affected by a mechanical mal
c. Normalized (standardized) response values.
d. Excludes rats with extremely low responses to the stimulus or whose responses were apparently affected by a mechanical or malfunction.

DOSAGE GROUP		I	II	III	IV
DOSAGE (MG/KG/DAY) a		0	5	15	50
SUBSET 2					
POSTNATAL DAY 89, 90 OR 91					
NUMBER OF RATS		20	20	20	20
ACOUSTIC STARTLE HABITUATION					
INCLUDED IN ANALYSES b		15	17	18	18
BLOCK 1	MEAN ± S.D.	113.71 ± 56.96	132.00 ± 49.43	222.45 ± 136.28	145.82 ± 65.61
BLOCK 2	MEAN ± S.D.	108.64 ± 56.41	106.06 ± 60.53	209.94 ± 170.59	116.93 ± 52.40
BLOCK 3	MEAN ± S.D.	88.28 ± 58.62	85.98 ± 53.18	178.17 ± 137.79	88.30 ± 39.21
BLOCK 4	MEAN ± S.D.	79.00 ± 43.69	74.31 ± 47.30	156.59 ± 108.45	73.36 ± 33.10
BLOCK 5	MEAN ± S.D.	83.71 ± 59.75	70.00 ± 46.71	157.53 ± 105.70	69.64 ± 31.43
AVERAGE	MEAN ± S.D.	95.69 ± 48.51	92.67 ± 48.73	184.94 ± 120.24**	97.81 ± 40.40
PREPULSE INHIBITION c					
INCLUDED IN ANALYSES b		15	17	18	18
CONTROL	MEAN ± S.D.	4036 ± 639	4928 ± 761	4811 ± 954*	4244 ± 554
PREPULSE (70dB)	MEAN ± S.D.	3828 ± 553	3542 ± 565	3546 ± 856	3434 ± 709
PREPULSE (90dB)	MEAN ± S.D.	2125 ± 675	2130 ± 516	1693 ± 382*	2327 ± 552

BLOCK = AVERAGE OF 10 TRIAL SESSIONS MINUS THE BODY WEIGHT

CONTROL = AVERAGE OF RESPONSES IN 10 TRIAL SESSIONS MINUS THE BODY WEIGHT.

PREPULSE = AVERAGE OF RESPONSES IN THE 70dB OR 90dB PREPULSE CONDITION MINUS THE BODY WEIGHT.

a. Dosage occurred on postnatal days 4 through 63.

b. Excludes rats with extremely low responses to the stimulus, rats that escaped from the holding cage during the testing or any squads that included such a rat or rats that were apparently affected by an acoustical malfunction.

c. Normalized (standardized) response values.

* Significantly different from the control group value ($p \leq 0.05$).

** Significantly different from the control group value ($p \leq 0.01$).

Table I.1.4 Functional Observational Battery scores in males during the dosing and post-dosing periods

DOSAGE GROUP		I	II	III	IV
DOSAGE (MG/KG/DAY) a		0	5	15	50
SUBSET 2					
POSTNATAL DAY 56, 57, 58 OR 59					
MALE RATS	N	20	20	20	19b
AIR RIGHTING RESPONSE					
(1) All feet land on ground	N	20	20	20	18
(2) Lands on side	N	0	0	0	1
(3) Lands on back	N	0	0	0	0
	MEAN SCORE	1.0	1.0	1.0	1.0
PUPIL RESPONSE TO LIGHT	N	20	20	20	19
FORELIMB GRIP TEST					
Maximum (G)	MEAN±S.D.	358.0 ± 108.0	339.8 ± 112.1	322.2 ± 144.2	292.9 ± 84.3
Average (G)	MEAN±S.D.	322.6 ± 100.0	290.4 ± 98.6	276.9 ± 125.6	240.5 ± 69.9
HINDLIMB GRIP TEST					
Maximum (G)	MEAN±S.D.	417.8 ± 118.1	402.5 ± 91.6	396.5 ± 94.8	330.0 ± 100.6*
Average (G)	MEAN±S.D.	374.8 ± 103.7	371.0 ± 77.5	355.5 ± 70.1	293.7 ± 72.6**
LANDING FOOT SPLAY					
Average (CM)	MEAN±S.D.	7.4 ± 1.1	7.2 ± 1.3	6.5 ± 1.2*	6.0 ± 1.0**
BODY TEMPERATURE (°C)	MEAN±S.D.	37.7 ± 0.6	37.7 ± 0.4	37.7 ± 0.6	37.5 ± 0.5
BODY WEIGHT (G)	MEAN±S.D.	348.7 ± 40.6	333.1 ± 35.2	318.6 ± 30.4**	258.0 ± 36.5**

n: = Category number for descriptive test item.

(n) = Score assigned to graded test items; mean score was calculated by multiplying each score by the number of rats with that score and then dividing the sum of the products by the total number of rats

a. Dosage occurred on postnatal days 4 through 63.

b. Excludes rat 7704, which was found dead on postnatal day 54.

* Significantly different from the control group value ($p \leq 0.05$).

** Significantly different from the control group value ($p \leq 0.01$).

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0	II 5	III 15	IV 50
SUBSET 2					
POSTNATAL DAY 22 ± 1					
MALE RATS	N	20	20	20	20
AIR RIGHTING RESPONSE					
(1) All feet land on ground	N	19	20	19	20
(2) Lands on side	N	1	0	1	0
(3) Lands on back	N	0	0	0	0
	MEAN SCORE	1.0	1.0	1.0	1.0
PUPIL RESPONSE TO LIGHT	N	20	20	20	20
FORELIMB GRIP TEST					
Maximum (G)	MEAN±S.D.	637.5 ± 230.0	568.5 ± 212.0	559.2 ± 226.6	344.0 ± 135.2**
Average (G)	MEAN±S.D.	550.0 ± 179.7	508.8 ± 188.5	502.4 ± 208.0	309.8 ± 120.9**
HINDLIMB GRIP TEST					
Maximum (G)	MEAN±S.D.	476.8 ± 128.4	436.8 ± 116.2	460.5 ± 79.0*	289.5 ± 72.5**
Average (G)	MEAN±S.D.	418.9 ± 102.7	384.2 ± 93.2	369.0 ± 77.4*	288.6 ± 63.2**
LANDING FOOT SPLAY					
Average (CM)	MEAN±S.D.	7.18 ± 1.31	6.86 ± 1.31	6.11 ± 1.52*	5.02 ± 1.00**
BODY TEMPERATURE (°C)	MEAN±S.D.	37.4 ± 0.5	37.5 ± 0.5	37.2 ± 0.8	37.5 ± 0.7
BODY WEIGHT (G)	MEAN±S.D.	536.2 ± 56.9	507.0 ± 70.3	488.8 ± 46.1*	389.4 ± 43.8**

n: = Category number for descriptive test item.
(n) = Score assigned to graded test items; mean score was calculated by multiplying each score by the number of rats with that score and then dividing the sum of the products by the total number of rats
a. Dosage occurred on postnatal days 4 through 65.
* Significantly different from the control group value ($p \leq 0.05$).
** Significantly different from the control group value ($p \leq 0.01$).

Table I.1.5 Functional Observational Battery scores in females during the dosing and post-dosing periods

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0	II 5	III 15	IV 50
SUBSET 2					
POSTNATAL DAY 56, 57, 58 OR 59					
FEMALE RATS	N	20	20	20	19b
AIR RIGHTING RESPONSE					
(1) All feet land on ground	N	20	19	20	19
(2) Lands on side	N	0	1	0	0
(3) Lands on back	N	0	0	0	0
	MEAN SCORE	1.0	1.0	1.0	1.0
PUPIL RESPONSE TO LIGHT	N	20	19c	20	19
FORELIMB GRIP TEST					
Maximum (G)	MEAN±S.D.	288.0 ± 88.2	282.0 ± 94.5	256.5 ± 88.2	200.8 ± 67.2**
Average (G)	MEAN±S.D.	247.0 ± 72.6	241.2 ± 86.2	222.9 ± 85.0	176.4 ± 54.8**
HINDLIMB GRIP TEST					
Maximum (G)	MEAN±S.D.	370.8 ± 75.5	339.5 ± 114.7	334.5 ± 83.6	259.2 ± 49.2**
Average (G)	MEAN±S.D.	331.5 ± 62.4	302.4 ± 94.5	300.2 ± 71.9	239.6 ± 50.4**
LANDING FOOT SPLAY					
Average (CM)	MEAN±S.D.	6.4 ± 0.8	6.4 ± 1.0	6.1 ± 0.9	5.0 ± 0.8**
BODY TEMPERATURE (°C)	MEAN±S.D.	38.4 ± 0.5	38.4 ± 0.5	38.2 ± 0.5	38.5 ± 0.6
BODY WEIGHT (G)	MEAN±S.D.	216.8 ± 18.5	222.5 ± 22.0	210.1 ± 15.7	174.4 ± 18.5**

n: = Category number for descriptive test item.
(n) = Score assigned to graded test items; mean score was calculated by multiplying each score by the number of rats with that score and then dividing the sum of the products by the total number of rats
a. Dosage occurred on postnatal days 4 through 65.
b. Excludes rat 7709, which was not tested for functional observation battery.
c. Excludes rat 2306, which was not tested due to corneal opacity.
** Significantly different from the control group value ($p \leq 0.01$).

DOSAGE GROUP		I	II	III	IV
DOSAGE (MG/KG/DAY)a		0	5	15	50
SUBSET 3					
POSTNATAL DAY 88 ± 1					
FEMALE RATS	N	20	20	20	19b
AIR RIGHTING RESPONSE					
(1) All feet land on ground	N	20	20	20	18
(2) Lands on side	N	0	0	0	1
(3) Lands on back	N	0	0	0	0
	MEAN SCORE	1.0	1.0	1.0	1.0
PUPIL RESPONSE TO LIGHT	N	20	20	20	19
FORELIMB GRIP TEST					
Maximum (G)	MEAN±S.D.	375.2 ± 125.0	388.5 ± 100.2	380.5 ± 111.2	266.6 ± 92.1**
Average (G)	MEAN±S.D.	329.5 ± 110.5	351.1 ± 95.5	320.4 ± 93.0	228.7 ± 71.4**
HINDLIMB GRIP TEST					
Maximum (G)	MEAN±S.D.	295.5 ± 86.1	266.5 ± 67.0	241.8 ± 75.4*	202.9 ± 65.5**
Average (G)	MEAN±S.D.	262.0 ± 63.3	242.9 ± 68.6	217.1 ± 69.2*	180.4 ± 54.2**
LANDING FOOT SPLAY					
Average (CM)	MEAN±S.D.	5.47 ± 1.11	5.61 ± 1.17	5.16 ± 0.95	4.19 ± 0.86**
BODY TEMPERATURE (°C)	MEAN±S.D.	37.9 ± 0.4	38.0 ± 0.4	37.9 ± 0.6	38.1 ± 0.5
BODY WEIGHT (G)	MEAN±S.D.	290.1 ± 30.0	296.4 ± 21.2	284.4 ± 26.5	226.6 ± 31.1**

n: = Category number for descriptive test item.
(n) = Score assigned to graded test items; mean score was calculated by multiplying each score by the number of rats with that score and then dividing the sum of the products by the total number of rats
a. Dosage occurred on postnatal days 4 through 65.
b. Excludes rat 7207, which was found dead on postnatal day 59.
* Significantly different from the control group value ($p \leq 0.05$).
** Significantly different from the control group value ($p \leq 0.01$).

Table I.1.6 M-maze performance in female rats during the post-dosing period (PND 105)

DOSAGE GROUP		I	II	III	IV
DOSAGE (MG/KG/DAY)a		0	5	15	50
SUBSET 3					
SESSION 1b	N	19c	19c	20	18c
TRIALS TO CRITERION	MEAN±S.D.	7.9 ± 2.2	7.9 ± 1.8	8.0 ± 2.1	7.6 ± 1.5
ERRORS PER TRIAL	MEAN±S.D.	0.30 ± 0.14	0.24 ± 0.12	0.35 ± 0.23	0.42 ± 0.30
LATENCY TRIAL 2d	MEAN±S.D.	14.9 ± 10.2	13.9 ± 9.5	11.5 ± 3.8	13.9 ± 7.9
FAILED TO LEARN e	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
SESSION 2b	N	19c	19c	20	18c
TRIALS TO CRITERION	MEAN±S.D.	6.9 ± 2.4	6.9 ± 3.1	7.2 ± 2.5	6.7 ± 2.6
ERRORS PER TRIAL	MEAN±S.D.	0.17 ± 0.23	0.16 ± 0.20	0.16 ± 0.16	0.10 ± 0.15
LATENCY TRIAL 1d	MEAN±S.D.	12.5 ± 10.5	11.1 ± 8.0	12.6 ± 11.8	11.1 ± 9.3
REVERSAL SESSION	N	19c	19c	20	18c
TRIALS TO CRITERION	MEAN±S.D.	9.2 ± 2.5	8.8 ± 2.3	8.3 ± 2.7	9.9 ± 3.0
ERRORS PER TRIAL	MEAN±S.D.	0.63 ± 0.33	0.72 ± 0.44	0.62 ± 0.35	0.62 ± 0.35
LATENCY TRIAL 1d	MEAN±S.D.	27.6 ± 19.6	25.4 ± 10.9	27.8 ± 14.3	23.9 ± 15.5
FAILED TO LEARN	N(%)	0(0.0)	0(0.0)	0(0.0)	3(16.7)**

a. Dosage occurred on postnatal days 4 through 65.
b. Sessions 1 (Learning Phase) and 2 (Retention Phase) of testing were separated by a one-week interval; Reversal Session occurred immediately after the rat had met the criterion for the initial phase of the second test session.
c. Excludes values for rats that were found dead or unscheduled sacrificed.
d. The latency was recorded in seconds.
e. Number of rats that did not meet the criterion in Session 1 (Learning Phase); Session 2 (Retention Phase) values for these rats were excluded from summarization and statistical analyses.
** Significantly different from the control group value ($p \leq 0.01$).

Table I.1.7 Morris Maze performance in juvenile rats

Males

DOSAGE GROUP		I	II	III	IV
DOSAGE (MG/KG/DAY)a		0	5	15	50
SUBSET 2					
POSTNATAL DAYS 153 THROUGH 177b					
RATS TESTED	N	10	10	10	10
SESSION 1					
AVERAGE TRIALS 1-3	MEAN ± S.D.	36.7 ± 10.2	43.0 ± 12.4	39.0 ± 10.6	45.0 ± 10.6
AVERAGE TRIALS 4-6	MEAN ± S.D.	24.2 ± 17.3	23.8 ± 9.1	23.5 ± 13.3	24.4 ± 11.0
AVERAGE TRIALS 7-11	MEAN ± S.D.	17.8 ± 9.6	15.4 ± 7.2	17.2 ± 16.2	15.7 ± 9.1
PROBE TRIAL (%)c	MEAN ± S.D.	45.7 ± 15.9	48.0 ± 13.9	47.0 ± 21.7	51.7 ± 19.4
SESSION 2					
AVERAGE TRIALS 1-3	MEAN ± S.D.	16.0 ± 10.2	14.5 ± 8.1	17.3 ± 13.9	18.5 ± 11.1
AVERAGE TRIALS 4-6	MEAN ± S.D.	7.6 ± 2.9	6.8 ± 2.3	9.5 ± 6.3	11.8 ± 7.6
AVERAGE TRIALS 7-11	MEAN ± S.D.	6.9 ± 4.8	8.4 ± 6.6	8.1 ± 2.6	10.3 ± 4.7
PROBE TRIAL (%)c	MEAN ± S.D.	55.3 ± 23.2	45.0 ± 11.1	48.3 ± 14.7	60.3 ± 18.4
SESSION 3					
AVERAGE TRIALS 1-3	MEAN ± S.D.	13.1 ± 12.8	15.2 ± 13.2	14.4 ± 8.5	10.0 ± 5.2
AVERAGE TRIALS 4-6	MEAN ± S.D.	6.7 ± 5.5	8.4 ± 6.2	9.2 ± 4.1	7.8 ± 3.7
AVERAGE TRIALS 7-11	MEAN ± S.D.	5.7 ± 2.2	7.9 ± 3.8	7.8 ± 2.6	6.8 ± 3.8
PROBE TRIAL (%)c	MEAN ± S.D.	47.7 ± 17.2	48.7 ± 15.1	55.3 ± 10.6	35.7 ± 21.4

AVERAGE TRIALS = AVERAGE TIME (SECONDS) TO REACH THE PLATFORM FOR ALL RATS IN A GROUP FOR THE SPECIFIED TRIALS

a. Dosage occurred on postnatal days 4 through 85.
b. Age of the rats ranged from postnatal day 153 through 177; testing occurred over a three day period for each rat.
c. Probe trial was recorded in seconds and reported as a percentage of time the rat spent in the goal quadrant.

Females

DOSAGE GROUP		I	II	III	IV
DOSAGE (MG/KG/DAY)a		0	5	15	50
SUBSET 2					
POSTNATAL DAYS 153 THROUGH 177b					
RATS TESTED	N	10	10	10	10
SESSION 1					
AVERAGE TRIALS 1-3	MEAN ± S.D.	29.9 ± 13.2	42.0 ± 11.2	40.8 ± 18.7	34.3 ± 10.5
AVERAGE TRIALS 4-6	MEAN ± S.D.	19.0 ± 11.4	20.3 ± 12.6	21.8 ± 11.6	30.2 ± 13.4
AVERAGE TRIALS 7-11	MEAN ± S.D.	13.8 ± 7.5	12.4 ± 8.4	18.2 ± 9.0	30.1 ± 12.6
PROBE TRIAL (%)c	MEAN ± S.D.	50.0 ± 11.6	48.7 ± 13.1	51.0 ± 9.4	54.7 ± 21.2
SESSION 2					
AVERAGE TRIALS 1-3	MEAN ± S.D.	17.0 ± 8.6	13.9 ± 9.0	24.0 ± 10.0	21.6 ± 11.5
AVERAGE TRIALS 4-6	MEAN ± S.D.	12.0 ± 9.0	10.9 ± 8.4	9.4 ± 3.8	12.4 ± 4.5
AVERAGE TRIALS 7-11	MEAN ± S.D.	9.8 ± 6.0	8.5 ± 5.0	9.8 ± 5.8	10.1 ± 6.3
PROBE TRIAL (%)c	MEAN ± S.D.	44.3 ± 14.1	44.2 ± 14.0	51.3 ± 13.8	45.0 ± 13.1
SESSION 3					
AVERAGE TRIALS 1-3	MEAN ± S.D.	13.2 ± 9.9 [9]d	13.2 ± 11.3	8.8 ± 5.0	16.4 ± 11.5 [9]d
AVERAGE TRIALS 4-6	MEAN ± S.D.	7.7 ± 2.2 [9]d	5.7 ± 3.7	7.3 ± 3.7	8.7 ± 3.0 [9]d
AVERAGE TRIALS 7-11	MEAN ± S.D.	8.8 ± 4.5 [9]d	5.4 ± 1.9	11.0 ± 8.2	8.5 ± 3.2 [9]d
PROBE TRIAL (%)c	MEAN ± S.D.	57.4 ± 13.5 [9]d	51.3 ± 11.8	58.8 ± 15.3	38.5 ± 21.6 [9]d

AVERAGE TRIALS = AVERAGE TIME (SECONDS) TO REACH THE PLATFORM FOR ALL RATS IN A GROUP FOR THE SPECIFIED TRIALS

[ ] = NUMBER OF VALUES AVERAGED

a. Dosage occurred on postnatal days 4 through 85.
b. Age of the rats ranged from postnatal day 153 through 177; testing occurred over a three day period for each rat.
c. Probe trial was recorded in seconds and reported as a percentage of time the rat spent in the goal quadrant.
d. Excludes values for rats that had an error during testing in session 3.

Table I.1.8 Reproductive performance in juvenile rats.

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0	II 5	III 15	IV 50
RATS IN COHABITATION	N	20	19b	20	18b
DAYS IN COHABITATION c,d	MEAN±S.D.	5.0 ± 2.4	4.5 ± 2.4	4.7 ± 2.3	3.0 ± 1.5
RATS THAT MATED d	N(%)	10(50.0)	11(57.9)	12(60.0)	16(88.9)
FERTILITY INDEX e,f	N/N (%)	10/ 10 (100.0)	5/ 11** (45.4)	8/ 12* (66.7)	15/ 16 (93.8)
RATS WITH CONFIRMED MATING DATES	N	10	11	12	16
MATED WITH FEMALE g DAYS 1-7	N(%)	10(100.0)	11(100.0)	12(100.0)	16(100.0)
RATS PREGNANT/RATS IN COHABITATION f	N/N (%)	10/ 20 (50.0)	5/ 19 (26.3)	8/ 20 (40.0)	15/ 18** (83.3)

a. Dosage occurred on postnatal days 4 through 65.
b. Excludes values for rats that were not assigned to cohabitation because there were no available female rats.
c. Restricted to rats with a confirmed mating date and rats that did not mate.
d. Includes only one mating for each male rat.
e. Number of pregnancies/number of rats that mated.
f. Includes only one pregnancy for each rat that impregnated more than one female rat.
g. Restricted to rats with a confirmed mating date.
** Significantly different from the control group value (p<0.01).

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0	II 5	III 15	IV 50
ESTROUS CYCLING OBSERVATIONS					
RATS EVALUATED	N	20	20	20	19b
PRECOHABITATION ESTROUS CYCLING					
ESTROUS STAGES/ 72 DAYS	MEAN±S.D.	15.6 ± 2.4 [19]b	15.3 ± 3.0 [19]b	14.7 ± 2.6	14.5 ± 3.2 [18]b
RATS WITH 6 OR MORE CONSECUTIVE DAYS OF DIESTRUS	N	4	7	6	7
RATS WITH 6 OR MORE CONSECUTIVE DAYS OF ESTRUS	N	0	2	1	1

[ ] = NUMBER OF VALUES AVERAGED
a. Dosage occurred on postnatal days 4 through 65.
b. Excludes values for rats that were found dead or sacrificed due to moribund condition.

Table I.1.9 Mean brain weight and brain/bw ratios in juvenile rats at the end of treatment

	Absolute (gm)		Brain/BW Ratio (%)	
	Male	Female	Male	Female
Control	2.18	2.05	0.563	0.925
5 mg/kg	2.09	2.04	0.589	0.925
15 mg/kg	2.02**	1.95*	0.600	0.910
50 mg/kg	1.94**	1.79**	0.636	1.026*

* p≤0.05
** p≤0.01

Table I.1.10 Mean brain weight and brain/bw ratios in juvenile rats at the end of the recovery period

	Absolute (gm)		Brain/BW Ratio (%)	
	Male	Female	Male	Female
Control	2.43	2.16	0.349	0.591
5 mg/kg	2.40	2.13	0.348	0.582
15 mg/kg	2.37	2.06	0.371	0.575
50 mg/kg	2.23**	1.96**	0.439**	0.683**

* p≤0.05
**p≤0.01

Table I.1.11

SUMMARY OF MICROSCOPIC DIAGNOSES – PND 67 MALE RATS

	GROUP:	1	2	3	4
Number of animals included		10	10	10	10
Piriform Cortex					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	9
No. With Microscopic Diagnoses		0	0	0	1
NEUROPIL VACUOLATION		0	0	0	1
	mild	-	-	-	1
NEURON DEGENERATION (FLUORO-JADE)		0	0	0	1
	minimal	-	-	-	1
Frontal Cortex					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Cingulate Cortex					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Septal Nuclei					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	9
No. With Microscopic Diagnoses		0	0	0	1
NEUROPIL VACUOLATION		0	0	0	1
	minimal	-	-	-	1
Anterior Commissure					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Parietal Cortex					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Caudate Nucleus/Putamen					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Globus Pallidus					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Basal Forebrain					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	6
No. With Microscopic Diagnoses		0	0	0	4
NEUROPIL VACUOLATION		0	0	0	4a
	minimal	-	-	-	3
	mild	-	-	-	1
Corpus Callosum					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
External Capsule					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Internal Capsule					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Amygdala					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Retrosplenial Cortex					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10

Subiculum					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	9	5
No. With Microscopic Diagnoses		0	0	1	5
NEUROPIL VACUOLATION		0	0	1	5a
	minimal	-	-	1	1
	mild	-	-	-	4
Hippocampus, CA1					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	8
No. With Microscopic Diagnoses		0	0	0	2
NEUROPIL VACUOLATION		0	0	0	2
	mild	-	-	-	2
Hippocampus, CA2					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Hippocampus, CA3					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Hippocampus, CA4					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Dentate Gyrus					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Thalamus					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	6
No. With Microscopic Diagnoses		0	0	0	4
NEUROPIL VACUOLATION		0	0	0	4a
	minimal	-	-	-	3
	mild	-	-	-	1
Hypothalamus					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	8
No. With Microscopic Diagnoses		0	0	0	2
NEUROPIL VACUOLATION		0	0	0	2
	minimal	-	-	-	1
	mild	-	-	-	1
Temporal Cortex					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Occipital Cortex					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Fornix					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Mamillary Bodies					
Number of Tissues Examined		0	0	0	1
No. With Microscopic Diagnoses		-	-	-	1
NEUROPIL VACUOLATION		-	-	-	1
	mild	-	-	-	1

Midbrain					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	0
No. With Microscopic Diagnoses		0	0	0	10
NEUROPIL VACUOLATION		0	0	0	10b
	minimal	-	-	-	5
	mild	-	-	-	5
Entorhinal Cortex					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Substantia Nigra, Comp					
Number of Tissues Examined		0	0	0	5
No. With Microscopic Diagnoses		-	-	-	5
NEUROPIL VACUOLATION		-	-	-	5
	minimal	-	-	-	1
	mild	-	-	-	4
Substantia Nigra, Retic					
Number of Tissues Examined		0	0	0	2
No. With Microscopic Diagnoses		-	-	-	2
NEUROPIL VACUOLATION		-	-	-	2
	minimal	-	-	-	1
	mild	-	-	-	1
Cerebral Peduncle					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Cerebellar Cortex					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Cerebellar nuclei					
Number of Tissues Examined		0	0	1	3
No. With Microscopic Diagnoses		-	-	1	3
NEUROPIL VACUOLATION		-	-	1	3
	minimal	-	-	1	1
	mild	-	-	-	1
	moderate	-	-	-	1
Cerebellar White Matter					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Pons					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	9
No. With Microscopic Diagnoses		0	0	0	1
NEUROPIL VACUOLATION		0	0	0	1
	mild	-	-	-	1
Trapezoid Body					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Vestibular Nucleus					
Number of Tissues Examined		0	0	0	1
No. With Microscopic Diagnoses		-	-	-	1
NEUROPIL VACUOLATION		-	-	-	1
	mild	-	-	-	1

Reticular Formation					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Medulla Oblongata					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	5
No. With Microscopic Diagnoses		0	0	0	5
NEUROPIL VACUOLATION		0	0	0	5a
	minimal	-	-	-	3
	mild	-	-	-	2
Pyramids					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Trigeminal Tract					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	10
Spinal Cord, Cervical					
Number of Tissues Examined		10	0	0	10
Microscopically Normal		10	-	-	9
No. With Microscopic Diagnoses		0	-	-	1
AXON DEGENERATION		0	-	-	1
	minimal	-	-	-	1
Spinal Cord, Lumbar					
Number of Tissues Examined		10	0	0	10
Microscopically Normal		6	-	-	10
No. With Microscopic Diagnoses		4	-	-	0
AXON DEGENERATION		4	-	-	0a
	minimal	4	-	-	-
Spinal Nerve Roots					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		9	10	9	8
No. With Microscopic Diagnoses		1	0	1	2
NERVE FIBER DEGENERATION		1	0	1	2
	minimal	1	-	-	1
	mild	-	-	1	1
Dorsal Root Ganglia					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	9
No. With Microscopic Diagnoses		0	0	0	1
GANGLION CELL PALLOR & VACUOLATION		0	0	0	1
	mild	-	-	-	1
Gasserian Ganglia					
Number of Tissues Examined		10	0	0	10
Microscopically Normal		10	-	-	9
No. With Microscopic Diagnoses		0	-	-	1
GANGLION CELL PALLOR & VACUOLATION		0	-	-	1
	mild	-	-	-	1
Sciatic Nerve					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		9	10	9	7
No. With Microscopic Diagnoses		1	0	1	3
NERVE FIBER DEGENERATION		1	0	1	3
	minimal	1	-	1	3

Tibial Nerve					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		10	10	10	9
No. With Microscopic Diagnoses		0	0	0	1
NERVE FIBER DEGENERATION		0	0	0	1
	minimal	-	-	-	1
Brain, NOS					
Number of Tissues Examined		0	0	1	0
No. With Microscopic Diagnoses		-	-	1	-
HYDROCEPHALUS		-	-	1	-
	minimal	-	-	1	-
Eye					
Number of Tissues Examined		10	10	10	10
Microscopically Normal		9	10	7	7
No. With Microscopic Diagnoses		1	0	3	3
RETINAL DYSPLASIA		0	0	3	2
	minimal	-	-	2	1
	mild	-	-	1	1
CORNEAL OSSIFICATION		1	0	0	1
	mild	-	-	-	1
	moderate	1	-	-	-
Skeletal Muscle					
Number of Tissues Examined		10	0	0	10
Microscopically Normal		10	-	-	10

Group Legend: 1 is 0 mg/kg/day, 2 is 5 mg/kg/day, 3 is 15 mg/kg/day, 4 is 50 mg/kg/day

Statistics performed using Fisher's exact (1-tail)

a = Significantly different from GROUP 1 at P<=0.05

b = Significantly different from GROUP 1 at P<=0.01

Table I.1.12

SUMMARY OF MICROSCOPIC DIAGNOSES - PND 67 FEMALE RATS

	GROUP:	1	2	3	4
Number of animals included		10	10	10	11
Piriform Cortex					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Frontal Cortex					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Cingulate Cortex					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Septal Nuclei					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Anterior Commissure					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Parietal Cortex					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	10
No. With Microscopic Diagnoses		0	0	0	1
NEUROPIL VACUOLATION		0	0	0	1
	minimal	-	-	-	1
Caudate Nucleus/Putamen					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Globus Pallidus					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Basal Forebrain					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	8
No. With Microscopic Diagnoses		0	0	0	3
NEUROPIL VACUOLATION		0	0	0	3
	minimal	-	-	-	1
	mild	-	-	-	2
Corpus Callosum					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
External Capsule					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Internal Capsule					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Amygdala					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Retrosplenial Cortex					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Subiculum					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	3
No. With Microscopic Diagnoses		0	0	0	8
NEUROPIL VACUOLATION		0	0	0	7b
	minimal	-	-	-	2
	mild	-	-	-	5

NEURON DEGENERATION (FLUORO-JADE)		0	0	0	1
	minimal	-	-	-	1
Hippocampus, CA1					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	3
No. With Microscopic Diagnoses		0	0	0	8
NEUROPIL VACUOLATION		0	0	0	8b
	minimal	-	-	-	6
	mild	-	-	-	2
Hippocampus, CA2					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Hippocampus, CA3					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	10
No. With Microscopic Diagnoses		0	0	0	1
FOCAL GLIOSIS		0	0	0	1
	mild	-	-	-	1
Hippocampus, CA4					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Dentate Gyrus					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	9	11
No. With Microscopic Diagnoses		0	0	1	0
NEURON DEGENERATION (FLUORO-JADE)		0	0	1	0
	mild	-	-	1	-
Thalamus					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	6
No. With Microscopic Diagnoses		0	0	0	5
NEUROPIL VACUOLATION		0	0	0	5a
	minimal	-	-	-	3
	mild	-	-	-	2
Hypothalamus					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Temporal Cortex					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	9	11
No. With Microscopic Diagnoses		0	0	1	0
NEURON DEGENERATION (FLUORO-JADE)		0	0	1	0
	minimal	-	-	1	-
Occipital Cortex					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Fornix					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Mamillary Bodies					
Number of Tissues Examined		0	0	0	3
No. With Microscopic Diagnoses		-	-	-	3
NEUROPIL VACUOLATION		-	-	-	3
	minimal	-	-	-	2
	mild	-	-	-	1

Midbrain					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	0
No. With Microscopic Diagnoses		0	0	0	11
NEUROPIL VACUOLATION		0	0	0	11b
	minimal	-	-	-	5
	mild	-	-	-	5
	moderate	-	-	-	1
Entorhinal Cortex					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Substantia Nigra, Comp					
Number of Tissues Examined		0	0	0	7
No. With Microscopic Diagnoses		-	-	-	7
NEUROPIL VACUOLATION		-	-	-	7
	minimal	-	-	-	6
	mild	-	-	-	1
Substantia Nigra, Retic					
Number of Tissues Examined		0	0	0	6
No. With Microscopic Diagnoses		-	-	-	6
NEUROPIL VACUOLATION		-	-	-	6
	minimal	-	-	-	5
	mild	-	-	-	1
Cerebral Peduncle					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Cerebellar Cortex					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Cerebellar nuclei					
Number of Tissues Examined		0	0	0	5
No. With Microscopic Diagnoses		-	-	-	5
NEUROPIL VACUOLATION		-	-	-	5
	minimal	-	-	-	2
	mild	-	-	-	3
Cerebellar White Matter					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	9	10	11
No. With Microscopic Diagnoses		0	1	0	0
CYSTIC FOCUS		0	1	0	0
	mild	-	1	-	-
Pons					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	9
No. With Microscopic Diagnoses		0	0	0	2
NEUROPIL VACUOLATION		0	0	0	2
	minimal	-	-	-	2
Trapezoid Body					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11

Reticular Formation					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Medulla Oblongata					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	5
No. With Microscopic Diagnoses		0	0	0	6
NEUROPIL VACUOLATION		0	0	0	6b
	minimal	-	-	-	4
	mild	-	-	-	2
Pyramids					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Trigeminal Tract					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Spinal Cord, Cervical					
Number of Tissues Examined		10	0	0	11
Microscopically Normal		10	-	-	10
No. With Microscopic Diagnoses		0	-	-	1
AXON DEGENERATION		0	-	-	1
	minimal	-	-	-	1
Spinal Cord, Lumbar					
Number of Tissues Examined		10	0	0	11
Microscopically Normal		10	-	-	11
Spinal Nerve Roots					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		9	9	10	11
No. With Microscopic Diagnoses		1	1	0	0
Spinal Nerve Roots (continued)					
NERVE FIBER DEGENERATION		1	1	0	0
	minimal	1	1	-	-
Dorsal Root Ganglia					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	10	11
Gasserian Ganglia					
Number of Tissues Examined		10	0	0	11
Microscopically Normal		10	-	-	11
Sciatic Nerve					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	9	11
No. With Microscopic Diagnoses		0	0	1	0
NERVE FIBER DEGENERATION		0	0	1	0
	minimal	-	-	1	-
Tibial Nerve					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		10	10	9	11
No. With Microscopic Diagnoses		0	0	1	0
NERVE FIBER DEGENERATION		0	0	1	0
	minimal	-	-	1	-
Brain, NOS					
Number of Tissues Examined		0	0	1	0
No. With Microscopic Diagnoses		-	-	1	-
HYDROCEPHALUS		-	-	1	-
	minimal	-	-	1	-

Eye					
Number of Tissues Examined		10	10	10	11
Microscopically Normal		9	9	9	7
No. With Microscopic Diagnoses		1	1	1	4
RETINAL DYSPLASIA		1	0	1	4
	minimal	1	-	-	3
	mild	-	-	1	1
CORNEAL MINERALIZATION		0	1	0	0
	minimal	-	1	-	-
CORNEAL VASCULARIZATION		0	1	0	0
	mild	-	1	-	-
Skeletal Muscle					
Number of Tissues Examined		10	0	0	11
Microscopically Normal		10	-	-	11

Group Legend: 1 is 0 mg/kg/day, 2 is 5 mg/kg/day, 3 is 15 mg/kg/day, 4 is 50 mg/kg/day

Statistics performed using Fisher's exact (1-tail)

a = Significantly different from GROUP 1 at P<=0.05

b = Significantly different from GROUP 1 at P<=0.01

Table I.1.13. Summary of pharmacokinetic data in juvenile rats (Study OV-1007)

Gender	Dose (mg/kg/day)	Cmax µg/mL PND 17	Cmax µg/mL PND 65	$AUC_{0-\infty}$ µg•h/mL PND 17	$AUC_{0-\infty}$ µg•h/mL PND 65
Males	5	2.88	2.95	8.18	6.45
	15	10.69	10.42	28.26	17.33
	50	35.20	27.17	125.25	89.78
Females	5	3.55	3.22	9.40	5.58
	15	8.27	7.44	25.04	13.61
	50	31.03	21.60	110.68	49.53

2. Pathology working group (PWG) review of potential treatment-related lesions in the brain of rats from an oral (gavage) repeated-dose toxicity study of vigabatrin (Ovation Pharmaceuticals, Inc.'s Study Number OV-1007) (EPL Project No. 794-001, dated 5/11/06, Conducted By Experimental Pathology Laboratories, Inc., Research Triangle Park, NC; GLP)

a. Methods

In Study No. OV-1007, microscopic examination of multiple brain sections from perfusion fixed rats fixed showed that all HD (50 mg/kg/day) group rats had neuropil vacuolation in various brain regions at the PND 67 necropsy. Two MD (15 mg/kg/day) rats were also considered to have neuropil vacuolation, although the neuropathologist considered the vacuolar changes limited and not conclusively T-R. The neuropil vacuolation was attenuated in VGB-dosed animals after the 19-week recovery period but was still present in 2 males and 1 female from the HD group.

A Pathology Working Group (PWG) was convened to have a panel of experts confirm the presence of neuropil vacuolation in the brains of rats in Study OV-1007 and to provide expert advice on questions pertinent to the observed morphologic changes and their pathogenesis. The PWG (Henry Wall, Marc Del Bigio, Robert Garman, Georg Krinke, Reid Patterson, Karen Regan, and Stephen Collins) reviewed all H&E stained brain sections from all perfusion-fixed rats that were diagnosed by the study neuropathologist to have microscopic neuropil vacuolation in one or more brain regions and from all control rats that were killed at the end of the dosing period.

b. Results

Overall, the PWG panel agreed with the original study neuropathologist's characterization of the presence or absence of neuropil vacuolation in the different brain regions of the 62 animals examined (**Appendix A**). The exceptions were said to reflect "minor differences in diagnoses for alterations that were usually graded as minimal by the study neuropathologist or graded as minimal by the PWG." It should be noted, however, that the number of recovery animals with neuropil vacuolation present was increased in the PWG evaluation (from 2 males and 1 female to 2 males and 3 females). The differences did not influence the original interpretation of treatment-related effects and no changes in original diagnoses were considered warranted.

Based on the results of their peer review of slides and data available in published and unpublished reports, the Panel provided the following responses to specific questions regarding the morphologic characterization of vacuolation in the brain of rats and the relevance to humans (verbatim):

1. Is there general agreement that the primary neurohistologic change is multifocal vacuolation in the central midbrain (tegmentum), lateral portion of the pars compacta of the substantia nigra, dorsal subiculum, deep cerebellar nuclei, posterior thalamus, basal forebrain (particularly the medial forebrain bundle) and pons/medulla?

Yes, the PWG confirmed these changes as reported by the Study Neuropathologist. The PWG also noted recovery in rats receiving 50 mg/kg/day as demonstrated by the absence of neuropil vacuolation in all but two rats held untreated after PND 67 and necropsied on PND 196-210. (Note: there were actually 5 recovery rats with vacuolation).

2. Does the histologic presentation of these vacuoles provide sufficient information to determine the affected cell(s) in the neuropil?

• No, the specific characterization of the nature of the vacuoles or specific cells affected cannot be determined. It was noted that the vacuoles were in neuroanatomic areas where GABA is known to be a predominant neurotransmitter.
• However, the H&E-stained slides do allow the observer to exclude the involvement of some structures, namely neuron cell bodies, blood vessels, and astrocytic end processes around blood vessels as suggested by light microscopy.
• There is no light microscopic evidence of cell degeneration, cell loss, or gliosis. However, morphometric or stereologic procedures would need to be performed to quantify cell loss.
• Some of the possibilities for the potential location of the vacuoles included preterminal or perisynaptic vesicles, and terminals of GABAergic axons, as in some areas the vacuoles appear close to nerve cell bodies. The possibility that vacuoles are associated with multiple targets (e.g., axons or dendrites, microglia) could not be excluded. The effect was not considered to be an anti-glucose effect.

3. Are there methods available with these tissues to determine or confirm the cells that are vacuolated?

Morphologic methods to explore this possibility using existing paraffin-embedded tissues may include the use of additional special stains:
• Neurofilament staining might help to localize the effect and characterize the structure of the vacuoles. The neurofilament stain may also be useful for comparing the diameters of axons in controls to the diameters of axons in VGB-treated rats.
• Staining for GABAergic neurons (e.g. with parvalbumin) may help determine if the vacuoles are associated with terminals of these neurons.
• Lectin staining (e.g., Griffonia simplicifolia) will demonstrate blood vessels and microglial proliferation. If the vacuoles are not associated with microglia, it would suggest that the vacuolation is more likely to be indicative of a fluid distribution problem rather than a more destructive process.
• Amyloid precursor protein (APP) was considered to be more specific than Fluro Jade® for staining degenerating neurons. Chromagranin A immunostaining was considered to be a useful alternate marker for damaged axons.
• Sections stained with the selected stains should be evaluated using at least five controls and five animals at 50 mg/kg with vacuolated brain areas.
• Luxol Fast Blue/Periodic Acid-Schiff (LFB/PAS) was considered advantageous for evaluating axons and myelin together. The PAS-stained axon could help to distinguish effects in axons from those that may be limited to myelin.
• Review of the available LFB-stained sections may help to determine if the flocculent material observed in some vacuoles contain lipoproteins that may have become a cellular inclusion.

4. Are the vacuolar changes in the white matter identical to those in the gray matter or different?

As viewed by light microscopy within this study, vacuolar changes in the gray matter and white matter are morphologically similar. They vary in size and sometimes contain granular or flocculent material, and borders of the vacuoles are indiscrete.

5. Are the white-matter changes consistent with or different from what is termed intramyelinic edema as was described in older rats given VGB?

• The white matter findings by light microscopy are not characteristic of intramyelinic edema.
• Some differences that may be observed in older rats as compared to younger rats could be attributable to differences in bioavailability due to different routes of dosing, differences in dose, differences in length of exposure, age at start of exposure or at the

time of neurohistopathologic examination, and differences in the GABA system (e.g., the GABA excitatory/inhibitory switch).
• A better understanding of the morphology and pathogenesis of white matter lesions may clarify differences in lesion appearance.

6. If these changes are different from intramyelinic edema, are there hypotheses to explain why these rats failed to develop the lesion (seen in rats of equivalent age and treatment duration to these rats) toward the end of the study?

If the drug is present during the early stage of myelination, then the myelin may be more resistant to the development of IME as seen in rats exposed much later after myelination has commenced (i.e., adaptation may play a roll). There may have been differences in other pertinent factors, such as, design, dose level, and duration of dosing.

7. Do you concur that there is little evidence to indicate gliosis, increased neuronal apoptosis or hypocellularity that would support loss of neuropil?

The PWG concluded that there is no evidence via light microscopy of H&E-stained sections to indicate gliosis, increased neuronal apoptosis or hypocellularity that would support loss of neuropil. Morphometric analysis may be necessary to quantify any potential indication of a morphologic effect on these structures.

8. Do these microscopic changes indicate or suggest probable pathogenetic mechanisms?

The morphologic information obtained via this study is insufficient to elucidate the pathogenesis of the vacuolar change.

9. Do you concur that the few rats with similar but more focal lesions in the mid-dose group are not conclusively related to VGB treatment?

The PWG concluded that the brains of animals in the mid-dose group did not differ from the controls and were, therefore not affected by treatment with VGB.

10. Do you concur that the recovery brains indicated some reduction in the incidence and severity of the vacuolar changes and no evidence for other neuronal pathology.

Yes, the PWG noted the absence of vacuoles in the brain of most VGB-treated rats following a recovery period after dosing was discontinued. Three rats in the recovery 50mg/kg/day group had focal vacuolar changes in the brain.

11. Would these lesions likely lead to the "spasms" described in association with handling or with the reduced neuromuscular performance in these rats, or is the latter more likely to be due to the marked growth suppression by the high dose of VGB?

• Until the affected cell or possible biochemical and/or molecular changes are better understood, it is not possible to make a definitive statement concerning the relationship of the vacuolar lesions and the clinically described "spasms."
• The "spasms" mayor may not be related to the vacuolar change.
• The "spasms" could be related to earlier changes (physiological or pharmacological) that led to the vacuole formation.
• Marked growth suppression may have influenced the neuromuscular performance of these rats, as measured by landing foot splay and fore/hindleg grip strength.
(Note: long-term neuromotor impairment in FOB was also observed in MD females in the absence of significant growth deficit. Similar findings have been reported with triethyltin and hexachlorophene).

12. What studies would you suggest to better understand the pathogenesis and targeted cells within the neuropil that become vacuolated?

The Panel suggested further morphologic characterization via light microscopy using histochemistry, with transmission electron microscopy (EM) follow-up to determine the precise anatomic location of the vacuoles. The additional morphologic characterization should sample animals at multiple time points after exposure beginning on postnatal day 4 (PND 4). Sampling is suggested at PND 25, PND 46 and PND 67. Five animals per group (controls and 50 mg/kg groups) per time point dosed PND4-65, as in the current study, and using males only were suggested. If feasible, an additional five animals per group per time point should be designated for freezing of half of the brain for potential frozen section immunohistochemistry and immersion fixation the other half of the brain in formalin followed by storage in absolute alcohol (95%) for potential paraffin-embedded section immunohistochemistry. Areas for evaluation should include brain (sites where vacuolation was seen via light microscopy), optic nerve, and cervical spinal cord, and the light microscopy should incorporate evaluation of 1um-thick plastic sections, where practical. These additional morphologic evaluations are expected to provide some direction for subsequent investigations of the pathogenesis of neuropil vacuoles in the brains of VGB-treated juvenile rats.

c. Conclusions

The PWG Panel concluded:

- *The location of the vacuolar changes in the brain include the central midbrain (tegmentum), pars compacta of the substantia nigra, dorsal subiculum, pons/medulla, hippocampal CA1 region, thalamus, deep cerebellar nuclei, and basal forebrain.*
- *Vacuolar effects may be attributable to biochemical perturbations in GABAergic neurons or nerve terminals.*
- *The microscopic evaluation of paraffin-embedded brain suggests areas that are not vacuolated (e.g., neuron cell bodies, blood vessels, and astrocytic end processes around blood vessels).*
- *Vacuolar changes in white matter and gray matter are morphologically similar via light microscopy, and have a morphologic appearance that is not characteristic of intramyelinic edema.*
- *There is no morphologic evidence of gliosis, neuronal apoptosis or hypocellularity in the H&E stained material.*
- *The vacuolar changes are dose-related, occurring only at 50 mg/kg, and are reversible in most animals after a 19-week recovery period.*
- *Light microscopic observations alone are insufficient to explain the pathogenesis of vacuoles observed in the brains of rats treated with VGB.*
- *Specific light and electronic microscopic methods may be applied to better characterize the vacuolar changes and gain direction for investigation of the pathogenesis of the brain vacuoles.*
- *Based on available human clinical, imaging and pathology literature, there is no evidence that the vacuolar changes in rats are relevant in humans receiving vigabatrin.*

The scientific basis for the last statement is unclear, but it was presumably made without knowledge of the recent MRI data from children taking vigabatrin.

APPENDIX A
PWG Consensus Diagnoses for Individual Animals

Chemical Name: Vigabatrin
Oral (Gavage) Repeated-Dose Toxicity Study of Vigabatrin in Rats
Study No.: OV-1007

Animal No.	Necropsy Day	No. of Slides	Study Pathologist's Diagnoses	PWG Consensus Diagnoses
Group 0 mg/kg/day – Male Rats				
202	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
302	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
502	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
1102	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
1202	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
1502	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
1702	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
1802	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
1902	PND 67	2	No Neuropil Vacuolation Present	Cerebrum Neuropil Vacuolation, Present
2002	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
Group 15 mg/kg/day – Male Rats				
4202	PND 67	2	Cerebellum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present	No Neuropil Vacuolation Present
5702	PND 67	2	Cerebrum Neuropil Vacuolation, Present	Cerebrum Neuropil Vacuolation, Present
Group 50 mg/kg/day – Male Rats				
6402	PND 67	2	Cerebrum Neuropil Vacuolation, Present Cerebellum No Neuropil Vacuolation Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons No Neuropil Vacuolation Present	Cerebrum Neuropil Vacuolation, Present Cerebellum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present
6502	PND 67	2	Mid-Brain Neuropil Vacuolation, Present	Mid-Brain Neuropil Vacuolation, Present Cerebrum Neuropil Vacuolation, Present
6602	PND 67	2	Cerebellum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present	Cerebellum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present
6702	PND 67	2	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present	Cerebrum Neuropil Vacuolation, Present
6902	PND 67	2	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present
7302	PND 67	2	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present
7502	PND 67	2	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present
7602	PND 67	2	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present	Cerebrum Neuropil Vacuolation, Present Cerebellum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present
7702	PND 67	2	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present	Cerebrum Neuropil Vacuolation, Present Cerebellum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present
8002	PND 67	2	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present
Group 50 mg/kg/day Post-Recovery Period – Male Rats				
6203	PND 196-210	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
6303	PND 196-210	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
6603	PND 196-210	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
6703	PND 196-210	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
6903	PND 196-210	2	Cerebellum Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present	Cerebellum Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present

7303	PND 196-210	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
7503	PND 196-210	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
7703	PND 196-210	2	Medulla/Pons Neuropil Vacuolation, Present	Medulla/Pons No Neuropil Vacuolation Present
7804	PND 196-210	2	No Neuropil Vacuolation Present	Medulla/Pons Neuropil Vacuolation, Present
7903	PND 196-210	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
Group 0 mg/kg/day – Female Rats				
106	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
306	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
406	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
606	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
706	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
806	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
906	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
1006	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
1606	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
1706	PND 67	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
Group 50 mg/kg/day – Female Rats				
6106	PND 67	2	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present	Cerebrum Neuropil Vacuolation, Present Cerebellum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present
6206	PND 67	2	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present
6506	PND 67	2	Cerebrum Neuropil Vacuolation, Present Cerebellum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present	Cerebellum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present
6606	PND 67	2	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons No Neuropil Vacuolation Present	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present
6906	PND 67	2	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons No Neuropil Vacuolation Present	Cerebrum Neuropil Vacuolation, Present Cerebellum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present
7006	PND 67	2	Cerebrum Neuropil Vacuolation, Present Cerebellum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present	Cerebrum Neuropil Vacuolation, Present Cerebellum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present
7206	PND 67	2	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present
7306	PND 67	2	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons No Neuropil Vacuolation Present	Cerebrum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present
7606	PND 67	2	Cerebrum Neuropil Vacuolation, Present Cerebellum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present	Cerebrum Neuropil Vacuolation, Present Cerebellum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present
7708	PND 67	2	Cerebrum Neuropil Vacuolation, Present Cerebellum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present	Cerebrum Neuropil Vacuolation, Present Cerebellum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present
8006	PND 67	2	Cerebrum Neuropil Vacuolation, Present Cerebellum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present	Cerebrum Neuropil Vacuolation, Present Cerebellum Neuropil Vacuolation, Present Mid-Brain Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present
Group 50 mg/kg/day Post-Recovery Period – Female Rats				
6107	PND 196-210	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
6607	PND 196-210	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
6807	PND 196-210	2	No Neuropil vacuolation Present	Cerebrum Neuropil Vacuolation, Present
6907	PND 196-210	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
7007	PND 196-210	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
7107	PND 196-210	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present
7307	PND 196-210	2	Cerebellum Neuropil Vacuolation, Present Medulla/Pons Neuropil Vacuolation, Present	Cerebellum Neuropil Vacuolation, Present
7507	PND 196-210	2	No Neuropil Vacuolation Present	Cerebellum Neuropil Vacuolation, Present
7707	PND 196-210	2	No Neuropil Vacuolation Present	No Neuropil Vacuolation Present

3. Nine-Week Oral (Gavage) Repeat-Dose Toxicity Study of Vigabatrin in Neonatal Rats (Study No. No. OVNC-9004, report dated 7/25/06, conducted by Charles River, Horsham, PA, GLP)

a. Methods

Forty male rat pups were assigned to 8 dose groups (Groups I through VIII, **Table I.3.1**), 5/group, to receive VGB (50 mg/kg, 5 mL/kg) or vehicle (water) by oral gavage once daily on postnatal days (PNDs) 4 through 25 (Groups I and V), 4 - 46 (Groups II and VI), 4 - 65 (Groups III and VII), and 12 - 26 (Groups IV and VIII). Pups were examined for viability, clinical observations, and body weights. All surviving rats were sacrificed on the last day of dose administration. Rats were administered a combination of heparin and sodium pentobarbital and perfused *in situ* with paraformaldehyde plus gluteraldehyde. Immediately after perfusion, the calvaria were removed, and the entire brain was weighed and dissected along the mid-saggital plane. The right half was placed in chilled neutral buffered 10% formalin, while the left half was immersed in chilled perfusate solution. All samples were shipped to the College of Veterinary Medicine, Virginia Tech, for histological evaluation. Initially, multiple levels of the brains stained with H&E were examined (1-caudate nucleus, thalamus; 2-midbrain; 3-cerebellum, medulla). This led to study of selected blocks of epoxy resin embedded brain for light microscopic study. Based upon the latter, thin sections were selected for electron microscopic examination of the cerebellar nuclei and adjacent white matter.

Strain. Crl:CD(SD)
Drug Lot #. 160207

The single daily dose of 50 mg/kg was selected on the basis of the previous study (OV-1007) in which this dose produced brain lesions evident by light microscopic examination.

Table I.3.1

Dosage Group	Dosage[a] (mg/kg/day)	Concentration (mg/mL)	Dosage Volume (mL/kg)	Days of Dosage	Number of Male Pups/Rats	Assigned Pup/Rat Numbers
I	50	10	5	PNDs 4 to 25	5	101 - 105
II	50	10	5	PNDs 4 to 46	5	201 - 205
III	50	10	5	PNDs 4 to 65	5	301 - 305
IV	50	10	5	PNDs 12 to 26	5	901 - 905
V	0 (Vehicle)	0	5	PNDs 4 to 25	5	401 - 405
VI	0 (Vehicle)[b]	0[b]	5	PNDs 4 to 46	5	501 - 505
VII	0 (Vehicle)	0	5	PNDs 4 to 65	5	601 - 605
VIII	0 (Vehicle)	0	5	PNDs 12 to 26	5	1001 - 1005

b. Results

i. Mortality, clinical signs

A total of 3 rats were found dead (1/5 in each of Groups II, III and IV on PNDs 46, 30, and 25). These deaths were considered treatment-related (T-R), based on clinical signs (tremors or convulsions) in 2 (Grps II and III) and the reduced body weight gains observed in all treated groups.

Clinical signs observed in Groups II and III included decreased motor activity, impaired righting reflex, ptosis, tremors, and chromorhinorrhea. Additionally, a clonic convulsion was observed in the Group II rat that was found dead on PND 46 and 2 rats in Group III were hyperreactive to touch. These observations often occurred as the rat was handled for observation as noted in the previously

conducted study. No clinical signs were noted in the rats in Groups I and IV, indicating that duration of dosing is important in the development of these signs.

ii. Body weight

Body weight gains were reduced in all treatment groups compared to C (55, 13, 18, and 29% in Groups I-IV over the respective treatment periods). On the day of sacrifice, mean body weights were 52 (Group I), 88 (Group II), 83 (Group III), and 85% (Group IV) of the respective control values.

iii. Necropsy observations

No gross lesions related to treatment were observed.

iv. Brain weights

Brain weights were reduced (SS in Grps I and II) in all treated groups compared to the respective controls, but the ratios of brain to terminal body weights were increased (also SS in Grps I and II).

v. Histopathology

According to the histopathology report, based on examination of the H&E stained sections, neuropil vacuoles were particularly prominent in Group I rats where there was said to be "marked involvement of the cerebellar white matter, including the folial and subcortical regions. The latter extended into the cerebellar nuclei. In addition, lesions were prominent in the medulla, in particular involving regions such as the dorsomedial trigeminal, spinal trigeminal tract and reticular nuclei." According to the report, "lesser involvement was seen in midbrain regions, including the substantia nigra." In Group II, lesions were seen in the cerebellum and medulla, but the white matter vacuolization was said to be diminished; and vacuoles were also noted in the midbrain, involving the substantia nigra and other nuclei, thalamus and region of the basal forebrain. In Group III, in addition to the medullary and cerebellar lesions, there was said to be involvement of more rostral regions such as the midbrain, thalamus and basal forebrain. Group IV showed vacuoles with a similar appearance and distribution, but which were said to be somewhat less extensive than those in rats with treatment beginning on PND 4.

Because of prominent involvement of the cerebellum and medulla found in the examination of H&E stained sections, these were the regions of focus in studies using 1 micron thick sections stained with toluidine blue and safranin, although in some cases more rostral levels of the brain were also examined (see **Table I.3.2**, below). The cerebellar sections included the nuclei and surrounding white matter, and the medullary sections included several levels of that part of the brain. In the cerebellum of Group I rats, there was demyelination and markedly diminished residual myelination of fibers. Vacuoles were said to be related to this myelinopathy. Thinly myelinated cerebellar white matter fibers were also seen in Group II rats. According to the report "vacuoles were found in the neuropil of nuclei and in myelinated fiber regions of the cerebellum, the medullary nuclei, in particular the trigeminal and reticular regions noted above, and midbrain (where examined) in Groups I, II, III and IV. They varied in shape and contain sparse stainable material. The latter often presented as wisps of fine membranous material, sometimes in contact with margin of the vacuole. In addition, more densely stained small bodies were seen, which occasionally were noted to

protrude from myelin sheaths on the margin of the vacuole. The vacuoles often were in contact with myelin sheaths, glia and neurons." The association of vacuoles with myelin was said to be particularly prominent in the regions examined. Some vacuoles were observed to have "a complete or partial thin myelin-like limiting membrane." Direct microscopic counts of cerebellum (nuclei and adjacent white matter) and medullary nuclear regions in rats of Groups III and VII indicated that a large proportion of the vacuoles had direct contact with myelin sheaths (**Table I.3.3**).

Table I.3.2 Blocks sectioned at 1 micron and stained with toluidine blue and safranin

	Treatment			Rat Number	Block Number (replicates)	Tissue Identification
	Group	Duration	Total Days			
TEST ARTICLE	Group I	PND 4-25	22	102	4E (3)	cerebellum
					5E (2)	medulla oblongata
				103	4E (3)	cerebellum
					5E (2)	medulla oblongata
				104	4E (3)	cerebellum
				105	5E (2)	medulla oblongata
	Group II	PND 4-46	43	202	2E (3)	dorsal hippocampus
					3E (3)	midbrain
					5E (3)	medulla oblongata
				204	1E (3)	basal forebrain
					3E (3)	midbrain
					4E (3)	cerebellum
					5E (2)	medulla oblongata
				205	2E (3)	dorsal hippocampus
					3E (3)	midbrain
					5E (3)	medulla oblongata
	Group III	PND 4-65	62	301	3E (3)	midbrain
					4E (3)	cerebellum
					5E (1)	medulla oblongata
				302	4E (1)	cerebellum
					5E (1)	medulla oblongata
				304	4E (3)	cerebellum
					5E (1)	medulla oblongata
				305	4E (3)	cerebellum
					5E (3)	medulla oblongata
	Group IV	PND 12-26	15	903	4E (3)	cerebellum
				904	5E (3)	medulla oblongata

VEHICLE	Group V	PND 4-25	22	401	4E (3)	cerebellum
					5E (2)	medulla oblongata
				402	4E (3)	cerebellum
				403	5E (2)	medulla oblongata
				404	4E (2)	cerebellum
	Group VI	PND 4-46	43	502	2E (3)	dorsal hippocampus
					3E (3)	midbrain
					5E (3)	medulla oblongata
				503	1E (3)	basal forebrain
					3E (3)	midbrain
					4E (3)	cerebellum
					5E (3)	medulla oblongata
				505	2E (3)	dorsal hippocampus
					3E (3)	midbrain
					5E (3)	medulla oblongata
	Group VII	PND 4-65	62	601	3E (3)	midbrain
					4E (1)	cerebellum
					5E (3)	medulla oblongata
				602	4E (2)	cerebellum
					5E (1)	medulla oblongata
				603	4E (3)	cerebellum
					5E (1)	medulla oblongata
				604	4E (5)	cerebellum
					5E (1)	medulla oblongata
				605	4E (1)	cerebellum
					5E (1)	medulla oblongata
	Group VIII	PND 12-26	15	1003	4E (3)	cerebellum
				1005	5E (3)	medulla oblongata

Table I.3.3

MICROSCOPIC COUNTS OF MYELIN-RELATED VACUOLES AFTER PND 4-64 EXPOSURE

	Cerebellum (slide 4E)		Medulla (slide 5E)	
	Myelin (+)	*Myelin (-)*	*Myelin (+)*	*Myelin (-)*
Group III* (test compound)	26	2	40	6
Group VII* (vehicle)	0	0	1	0

Myelin (+) - vacuole contacts adjacent myelin sheath
Myelin (-) - vacuole does not contact adjacent myelin sheath

*Direct counts of vacuoles in 4 microscopic fields from animals in these groups – see

Based on the examination of the toluidine blue and safranin stained sections, transmission electron microscopy was focused on sections of the cerebellum in the region of the (roof) nuclei and adjacent white matter, and regions of the medullary nucleus of the spinal tract of cranial nerve V and reticular nuclear regions (**Table I.3.4**). Relative to controls, there were said to be many non-myelinated or thinly myelinated fibers in Group I brains, particularly in cerebellar white matter. The report stated that, "Splits were noted in myelin sheaths, which appeared to expand along the intraperiod line in a fashion consistent with intramyelinic edema, giving rise to a vacuole bordered by a compressed lamellae of the sheath. Another form of vacuole was seen adjacent to demyelinated fibers, where the wall was made up of laminae of myelin debris. A striking feature at this stage was the presence of swollen glial cells adjacent to thinly or non-myelinated fibers. The nature of these glial cells was often difficult to discern, but some clearly were astrocytes."

Observations in Group II were consistent with retardation of myelination, although the active demyelination seen in Group I was not observed. Oligodendrocytes were prominent in the white matter in Group II, consistent with active myelination, and vacuoles were said to sometimes be associated with such cells. Most vacuoles in Groups II and III were said to be associated with myelin sheaths, and varied in ultrastructural appearance. According to the report, "Some were small, irregular and clearly related to splits of myelin sheaths. Others were expanded, with a more regular outline, contained granular and membranous material and had a thin membranous limiting membrane. At times lamellae were recognized in these membranous borders, consistent with attenuated myelin."

The report further stated that "medullary vacuoles derived from myelin splits, consistent with those described above, were present in a test article dosed animal from the same period (Group III). These demonstrated a series of evolutionary events as progressively larger vacuoles were examined. There was attenuation and multifocal interruption of the myelin limiting membrane. The membranous content of the vacuoles progressively increased, with protrusions from the altered limiting membrane being a source for them. These appeared to give rise to the frequently observed large vacuoles with prominent membranous material, but without a limiting membrane. Some of these membranes appeared to arise from adjacent compressed neuropil. However, significant degeneration of adjacent fibers was absent."

Table I.3.4 Blocks thin sectioned for ultrastructural examination by transmission electron microscopy

	TREATMENT			Rat Number	Block Number	Tissue ID
	Group	Duration	Total Days			
Test article	Group I	PND 4-25	22	103	4E	cerebellum
					5E	medulla oblongata
				104	4E	cerebellum
				105*	5E	medulla oblongata
	Group II	PND 4-46	43	204	4E	cerebellum
				205	5E	medulla oblongata
	Group III	PND 4-65	62	304	4E	cerebellum
				305	5E	medulla oblongata
	Group IV	PND 12-26	15	904	5E**	medulla oblongata
Vehicle	Group V	PND 4-25	22	402	4E	cerebellum
				403	5E	medulla oblongata
	Group VI	PND 4-46	43	503	4E	cerebellum
					5E	medulla oblongata
	Group VII	PND 4-65	62	601	5E	medulla oblongata
				603	4E	cerebellum

* Fixation was suboptimal as determined by electron microscopy, and limited observations were made from this grid.
** Sample could not be observed due to malfunction of TEM; see Procedural Outline Deviations for details.

c. Conclusions

Administration of vigabatrin (50 mg/kg) to male rats during the neonatal/juvenile period of development (PNDs 4-25, 4-46, 4-65, or 12-26) resulted in increased mortality, clinical signs (including convulsions), decreased BW and brain weights, and brain vacuolation and demyelination/hypomyelination. Ultrastructural examination of vacuoles focused on 2 brain regions (cerebellum and medulla) in a small number of treated rats (1-2/grp). At least some of these vacuoles appeared to originate as splits in the myelin sheaths along

the intraperiod line, and there was progressive expansion of the vacuoles with continuing exposure to vigabatrin by a process thought to be consistent with intramyelinic edema described in the adult rat and dog following chronic administration of vigabatrin (Gibson et al. Toxicol Pathol 18: 225-238, 1990). According to the histopathology report,

> "... the expansion of the vacuoles led to attenuation of myelin segments that formed their wall, although lamellae consistent with compressed intraperiod and major dense lines could be determined well into the process. These myelin derived vacuoles had fine granular contents, sometimes associated with membranous material. The latter were derived from the attenuating myelin limiting membrane, or from focal protrusions of adjacent myelin sheaths. Transitional stages between these clearly myelin-derived vacuoles and the larger ones noted below were seen. These had markedly thinned, focally interrupted myelin remnants forming the limiting membrane, and increase in intravacuolar membranous material. With progression, as seen with the longest exposure to the test compound (Group III - PND 4-65 dosing), the vacuoles increased in size, contained prominent membranous material, and often demonstrated loss of a definitive lining membrane. There was compression of adjacent neuropil by the expanding vacuoles, without significant associated neuronal injury. The ultrastructurally determined origin of vacuoles from split myelin sheaths is supported by light microscopic evidence of an association of vacuoles and myelin sheaths in the cerebellum and medulla in animals from Group III (PND 4-65 dosing with test compound)."

A prominent effect on myelination (demyelination, hypomyelination) was also noted in this study. This has been reported previously by Qiao et al. (Epilepsia 41:655-665, 2000) who examined the effect of vigabatrin during periods of active myelination in Wistar rats (25 mg/kg sc during PND 12-20 period, 40 mg/kg during PND 21-26). In animals sacrificed on PND 26 there was microvacuolation, oligodendroglial cell death, axonal swelling, and pallor of myelin staining in white matter of the brain.

II. SUMMARY AND EVALUATION

Juvenile rat studies of vigabatrin (VGB) were conducted, with oral (gavage) administration beginning on postnatal day (PND) 4 and extending for up to 8.5 weeks, in order to characterize the toxicity of VGB in young, developing animals and compare any effects to those seen in adults. These studies employed standard toxicological endpoints as well as specific assessments of neurotoxicity and retinal toxicity.

The data indicate increased sensitivity of juvenile rats to the systemic, retinal, and neurotoxic effects of VGB. Lethality occurred in young rats at a dose of 100 mg/kg given for 2 weeks, but was not seen in adults at <1,000 mg/kg after 2 weeks or <300 mg/kg after 3 and 12 months. Systemic toxicity, as manifested by decreased activity, food consumption, and body weight gain, was only seen at ≥200 mg/kg in adult rats, but was seen in young rats at doses as low as 30 mg/kg. Convulsions were reported in young rats after 23 days at doses as low as 30 mg/kg (**Table II.1**, from dose range-finding study), but were not reported in adult rats until they had received 200 mg/kg for at least 3 months or 100 mg/kg for at least 1 year. Young rats given 50 or 100 mg/kg for 2 weeks had retinal lesions characteristic in distribution and morphology to those described in adult rats given 300 mg/kg po for 13 weeks or 250 mg/kg ip for 45 days (**Table II.2,** dose range-finding study). Young rats were also more sensitive to the development of vacuolar changes in the brain following VGB administration. It is not clear whether these studies identified a unique neurotoxic effect in young animals or only an enhanced susceptibility to and different location of the characteristic brain lesion seen in adult animals. This is particularly relevant in light of the recent reports of brain MRI abnormalities associated with VGB exposure in patients treated for infantile spasms (IS).

Adult rats have been shown to consistently develop intramyelinic edema (IME) in the white matter (cerebellum, reticular formation, optic tracts) within 3 months of oral dosing with 300 mg/kg/day VGB, within 6 months with 100 mg/kg/day, and within 12 months with 30 mg/kg/day. This edema appears on light microscopy as vacuoles in the white matter and by electron microscopy has been shown to represent splitting of the myelin sheath at the intraperiod line, the membrane formed from fusion of the surface membranes of encircling oligodendrocyte cytoplasm. There seemed to be a plateau effect in rats, with lesions not becoming more severe or more advanced with continued dosing and not progressing to segmental demyelination, as noted with other agents (triethyltin, hexachlorophene, isoniazid) causing intramyelinic edema. While the vacuolar changes subsided with withdrawal of VGB treatment, rats continued to have swollen axons and mineralized bodies in the cerebellum, indicative of increased myelin turnover, axonal damage, and astrocytic gliosis. Rats also developed convulsions after 3 months at 200 mg/kg/day or 1 year at 100 mg/kg/day. The relationship of convulsions to intramyelinic edema is unclear.

In Study # OV-1007, in which neonatal/juvenile rats were treated with daily doses of 5, 15 or 50 mg/kg/day VGB from PND 4 through 65, light microscopic evaluation of perfusion fixed brain tissues revealed vacuolar changes within the neuropil of various brain regions in rats treated with 50 mg/kg/day (**Tables I.1.11-12** above). Most affected was the gray matter in the central midbrain (tegmentum), substantia nigra, dorsal subiculum, medulla oblongata, hippocampal CA1 region, thalamus, deep cerebellar nuclei, and basal forebrain (listed in the approximate order of frequency of effect). While vacuoles were found in some white matter tracks, such as the medial longitudinal fasciculus and the medial forebrain bundle, most vacuoles were in or near the gray matter. The specific cell type containing these vacuoles could not be verified by light microscopy. Although there was no clear evidence of cell degeneration, cell loss, or gliosis in this study, morphometric or stereologic procedures would have been necessary to quantify cell loss. The vacuolar changes were temporally associated with spasms in high-dose rats. In addition, long-term neuromotor impairment (decreased grip strength and hindlimb splay) was observed at both the mid- and high-dose (in the absence of body weight reduction in females), and an apparent learning deficit was seen at the high dose. Similar neurobehavioral findings have been reported in rodents treated with triethyltin or hexachlorophene. Although neuropil vacuolation was reduced in

rats necropsied after an approximately 19-week recovery period, it was still evident in several animals. Plasma exposures associated with a 50 mg/kg dose in juvenile rats are lower than those in infants and children given the same oral dose (**Tables I.1.13** and **II.3**). (Sponsor is proposing 150 mg/kg as MRHD.)

A pathology working group (PWG) assembled to review these neurolopathological findings (Study # 794001) agreed with the principal study neuropathologist on the regional location of the vacuolar changes in both gray and white matter of the brain of neonatal/juvenile rats given 50 mg/kg/day, the highest dose. Similar lesions were not confirmed at lower doses. While the panel could not determine by light microscopy which specific cells were vacuolated, they concluded that neuronal cell bodies, blood vessel endothelium, and perivascular astrocytic end processes were not affected; ultrastructural investigations would be necessary to confirm the cell type vulnerable to this vacuolation. Some of the suggested possibilities for the potential location of the vacuoles included preterminal or perisynaptic vesicles, and terminals of GABAergic axons, as in some areas the vacuoles appear close to nerve cell bodies. The possibility that vacuoles are associated with multiple targets (e.g., axons or dendrites, microglia) could not be excluded. These experts did not find morphologic evidence of neuronal cell death, hypocellularity, or reactive gliosis, but noted that the methods were not adequate to rule out cell loss. However, the panel stated that the morphologic appearance of the vacuoles was not characteristic of IME, which has been confined to white matter tracts in adult rats given VGB ("Vacuolar changes in white matter and gray matter are morphologically similar via light microscopy, and have a morphologic appearance that is not characteristic of intramyelinic edema").

Based on the recommendation of the expert panel, a neurohistopathology study was performed in juvenile rats using both light microscopy and ultrastructural examination to characterize the microvacuolation associated with VGB treatment. In this study (Study # OVNC-9004), VBG (50 mg/kg) or vehicle were administered by oral gavage to rats starting on PND 4 for varying periods up to 8.5 weeks. The single dose of 50 mg/kg was selected on the basis of the previous study in which it produced vacuolar lesions. Light microscopic examination of H&E stained sections confirmed the previous finding of neuropil vacuoles in the brains of treated rats. In rats dosed on PND 4-25 there was also marked involvement of the cerebellar white matter, which had not be reported in the previous study, with vacuoles extending into the cerebellar nuclei. In addition, lesions were prominent in the medulla in this group, with lesser involvement seen in midbrain regions. With longer dosing (PND 4-46 and PND 4-65), medullary and cerebellar lesions persisted, although the white matter vacuolation was diminished, and there was also involvement of more rostral regions such as the midbrain, thalamus and basal forebrain. When toluidine blue and safranin stained sections of cerebellum and medulla were examined by light microscope, hypomyelination, demyelination and gliopathy were noted, and vacuoles were thought to be related to this myelinopathy. Vacuoles were found in the neuropil of nuclei and in adjacent myelinated fiber regions of the cerebellum, the medullary nuclei, and midbrain (where examined) of treated rats. The vacuoles were said to often be found in contact with myelin sheaths, glia, and neurons. Direct microscopic counts of cerebellar and medullary nuclear regions showed that a large proportion of the vacuoles had demonstrable direct contact with myelin sheaths. Electron microscopic examination of sections of the cerebellum and medulla from rats in the PND 4-25 treatment group showed vacuoles that reportedly appeared to form from splits in the myelin sheath along the intraperiod line, consistent with descriptions of IME in adult rats and dogs. Examination of the other groups indicated a progressive expansion of vacuoles with continued exposure to VGB resulting in compression of the adjacent neuropil. The ultrastructurally determined origin of vacuoles from split myelin sheaths combined with the light microscopic evidence of an association of vacuoles and myelin sheaths in the cerebellum and medulla in animals treated from PND 4-65 (as in the previous study) led to the conclusion that the neuropil vacuoles observed in juvenile rats are consistent with IME pathology previously described in the white matter of adult animals. A prominent effect on myelination (demyelination, hypomyelination) was also noted in this study, however, which is clearly a unique effect seen with VGB administration during periods of active myelination.

The discrepancies between the neurohistopathology results and conclusions in the two juvenile rat studies have not been satisfactorily resolved. For example, it is not clear whether the vacuoles examined by EM were the only types present or if they occurred in addition to those described by the PWG as having a morphologic appearance not characteristic of IME; the ultrastructural study focused on only two affected brain areas, cerebellum and medulla, so the vacuoles examined may not have been representative of those in other areas. However, even if the pathogenesis is the same for neuropil vacuolation in juvenile rats and IME in adults, as concluded by the sponsor, the increased sensitivity of young animals and the different location of the vacuoles (ie, gray vs white matter) could be clinically significant. Discussion of the juvenile rat findings and suggestions for additional investigation are found in the memo from the FDA neuropathology expert consultant, Larry Schmued.

Table II.1 Incidence of tonic convulsions in juvenile rats treated with VGB

Gender	Dose per Period (mg/kg/day)[1]	Incidence (%)
Males	30-30	2/9 (22%)
	30-50	6/9 (67%)
	30-100	7/9 (78%)
Females	30-30	1/9 (11%)
	30-50	4/9 (44%)
	30-100	9/9 (100%)

[1] 30 mg/kg/day given to all rats for first 10 days, then 30, 50 or 100 mg/kg/day given on Study Days 11-28

Table II.2 Incidence of retinal changes in VGB-treated juvenile rats

Dose (mg/kg/day)	0		30		50		100	
Gender	M	F	M	F	M	F	M	F
N	8	8	6	6	6	6	5	6
Retinal changes	0	0	0	0	3	2	4	4

Table II.3 Plasma VGB exposures in pediatric subjects given 50 mg/kg oral dose

Treated Subjects	C_{max} (µg/mL)	AUC (µg•h/mL)
Human Infants (N=6)[1]		
Active S(+) VGB	13.90 ± 4.53	90.90 ± 27.90
Inactive R(-) VGB	21.00 ± 6.60	106.00 ± 28.50
Total VGB	34.90	196.90
Human Children (N=6)[1]		
Active S(+) VGB	23.80 ± 12.20	117.00 ± 26.00
Inactive R(-) VGB	41.30 ± 13.90	147.00 ± 34.00
Total VGB	65.10	264.00

III. RECOMMENDATIONS

Because the juvenile rat studies of vigabatrin indicate a risk for significant neurotoxicity at clinically relevant exposures, the application should not be approved from a pharmacology/toxicology standpoint.

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/s/

Edward Fisher
11/22/2008 11:36:19 AM
PHARMACOLOGIST

Lois Freed
11/22/2008 12:23:38 PM
PHARMACOLOGIST

Memo: Expert Opinion of VGB Neuropathology Reports. ***Please refer to the 'NDA 20-427: Complex Partial Seizures – January 7, 2009' section for this review.***

Review of Risk Management Proposal. ***Please refer to the 'NDA 20-427: Complex Partial Seizures – January 7, 2009' section for this review.***