CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-006

MEDICAL REVIEW(S)

MEMORANDUM

DATE: August 14, 2009

FROM: Russell Katz, M.D.
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Division of Neurology Products/HFD-120

TO: File, NDAs 20-427 & 22-006

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 as monotherapy for Infantile Spasms (IS) in children, respectively

NDAs 20-427 & 22-006, for the use of Sabril (vigabatrin) as adjunctive therapy for Complex Partial Seizures (CPS) in adults and as monotherapy for Infantile Spasms (IS) in children, respectively, have a long and complex regulatory history. NDA 22-006, for IS, was submitted by Ovation Pharmaceuticals on 12/28/07, but NDA 20-427, for CPS, was submitted initially in April, 1994. A response to the most recent action letter for that NDA, a Not Approvable letter that was issued on 10/26/98, was also submitted by Ovation Pharmaceuticals on 12/28/07.

These most recent submissions have been reviewed by Dr. Gerard Boehm of the division's safety group and Dr. Sally Yasuda, safety group team leader; 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, and Dr. Lois Freed, supervisory pharmacologist; 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; Dr. Sharon Watson, Division of Drug Marketing, Advertising, and Communications; Sharon Mills, Division of Risk Management; Dr. Judy Park and Linda M. Wisniewski, Division of Medication Errors and Technical Support (now DMEPA); the Interdisciplinary Review Team for QT Studies; Dr. John Duan, Office of Clinical Pharmacology; Dr. Monica Cooper, chemist; Dr. Katherine Bonson, Controlled Substance Staff; and Dr. Norman Hershkowitz, neurology team leader. In this memo, I will very briefly describe the regulatory history of these applications, as well as the effectiveness and safety data for both, and offer the division's recommendation for action on these applications.

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. We decided to discuss both NDAs at a meeting of the Peripheral and Central Nervous Systems Advisory Committee in January, 2009.

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	54%	69%
Placebo	41%	17%
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 be 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 initially 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 proposed to require that prescribers must receive education about

Sabril's risks, and that the product would be distributed through specialty pharmacies only when prescribers had attested to understanding the risks and the monitoring protocol. In addition, patients were to receive educational materials, and physicians and patients were to agree to re-assess the appropriateness of continued treatment with Sabril after 12 weeks on therapy. The sponsor believed that the proposed ophthalmological monitoring in both adults and pediatric patients was 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 had previously concluded that the safety data, particularly the visual toxicity, precluded approval), but have not previously considered the application for the 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.

Because of the complexity of the issues involved, we discussed these applications in a 2 day meeting of the Peripheral and Central Nervous Systems Advisory Committee on January 7 & 8, 2009, supplemented by experts in epilepsy, ophthalmology, pediatrics, and risk assessment.

Regarding NDA 20-427, for the use of Sabril in the treatment of patients with CPS, the committee voted unanimously (24-0) that the application should be approved for use in refractory patients. They clearly felt that its use should be reserved for those patients who had had an adequate trial of several AEDs, though they also felt that no additional effectiveness data should be required prior to approval (despite their conclusion that Sabril has not been shown to be more effective than other AEDs in a refractory population, and especially not compared to current AEDs). Regarding visual toxicity in this population, they concluded that continued treatment can result in clinically meaningful visual loss, that discontinuation of treatment has not been shown to prevent progression of the visual loss, that monitoring can detect visual loss before it is clinically meaningful (14 yes, 7 no, 3 abstain), and that it had not been adequately shown that Sabril does not cause central visual loss. They also concluded that Sabril should be available only under restricted conditions, with required visual testing performed periodically throughout treatment, and that continued access to the drug should be made contingent upon performance of visual testing (or

documentation that such testing was impossible in any given patient). The committee also concluded that there was no adequate data to address the relevance to adults of the intramyelinic edema seen in animals.

Regarding NDA 22-006, for the use of Sabril in patients with IS, the committee voted unanimously to recommend approval of the application (23-0). They also concluded that there is no evidence that Sabril treats or prevents other seizure types in these patients, although they agreed that Sabril causes cessation of spasms and can ameliorate the EEG in these patients. Regarding visual toxicity in this population, they concluded that there was no reliable way to adequately assess visual function in these very young patients, and that therefore visual toxicity may not be detected before it is severe and irreversible. In this regard, they recommended that parents/caregivers must be notified of this fact. The committee also recommended that, as for NDA 20-427, Sabril should be made available for IS only under restricted conditions, but did not mandate periodic ophthalmologic testing, because of its unreliability in this population. The committee also noted that there was inadequate data to address the relevance of the intramyelinic edema seen in animals to the MRI lesions seen in pediatric patients, although they did feel that the edema did not correlate with the MRI lesions. They also noted that there was inadequate data to address the relevance of the specific toxicity seen in juvenile animals to the MRI findings in this population.

Recommendations

NDA 20-427

The PCNS Advisory Committee has unanimously recommended that this NDA be approved under restricted conditions that include required periodic ophthalmologic monitoring. Dr. Hershkowitz, on the other hand, recommends that the application not be approved. He has concluded that the risks of visual toxicity do not outweigh the benefits seen. In particular, he notes that Sabril has not been shown to be superior to other available AEDs, and he notes that when these studies were performed, many of the current AEDs were not available, and so patients in these studies could not have been shown to have failed on any of the newer AEDs. Further, despite the sponsor's argument that the patients enrolled in these studies were particularly refractory (that is, had more serious epilepsy than the "typical" patient enrolled in regulatory studies), Dr. Hershkowitz believes that this is not the case.

I agree with Dr. Hershkowitz that there is no evidence that the patients enrolled in these studies had more refractory disease than those enrolled in other studies of new AEDs. Further, it is clearly true that most of the current AEDs were not approved at the time the Sabril studies were performed, so that clearly the patients enrolled in these studies could not have been shown to have failed on any of these drugs.

Despite these facts, I do believe that Sabril can be approved for patients who have failed (or cannot tolerate) a fair trial of other available AEDs.

First, refractory epilepsy is a serious, life-altering and life-threatening condition, and despite the availability of many newer AEDs, I believe that, if at all possible, additional therapies should be made available.

Although patients in these trials did not fail on the "newer" AEDs, they were "refractory" (by the usual definitions) to one or several of the standard AEDs available at the time (e.g., phenytoin, carbamazepine). Therefore, they were poorly controlled, and though the studies did not compare Sabril to another AED added to their background regimens (these studies never do), Sabril was shown to be clearly effective when added to these regimens (it should also be further noted that there is no good evidence that, in general, patients refractory to the older AEDs will be, or are, better controlled on the newer AEDs; indeed, there is a general view among epileptologists that the percentage of patients with epilepsy who were refractory to the older AEDs [widely considered to be on the order of 30%] is unchanged in the current era, despite the availability of many more AEDs).

Further, despite the occurrence of visual toxicity, it does not appear that there are many patients who have suffered significant visual loss. It must be admitted, to be sure, that we do not have the adequate follow-up of patients that we would like in this regard, but we are not aware of many patients who have significant disability related to Sabril-induced visual toxicity. Whether this is because the lesion had been detected early in some patients, or whether the lesion (in some patients) never progresses beyond a certain degree, even with continued treatment for some period of time, or whether patients can function reasonably well even with significant visual pathology, or other reasons, is not clear, but we do not have reports of significant visual impairment in many patients, even after years of treatment with Sabril. This is not to minimize the toxicity, but only to point out that patients have, generally, tolerated whatever pathology the drug has produced (here it should be noted that the drug has been available in many countries since the mid 1980's). In this regard, the REMS that has been discussed with the sponsor is fairly restrictive, and commits physicians to perform periodic ophthalmologic examinations (where possible) and be aware of the results before deciding to continue treatment. And although we do not have definitive evidence that the monitoring to be imposed under the REMS will definitely prevent toxicity (or detect it as early as we might like), we do believe that it is worthwhile, and is likely, at least in some patients, to detect any changes before they result in a clinically meaningful decrement in visual function.

For these reasons, then, I believe that Sabril can be approved for patients with refractory CPS, under the conditions imposed under the REMS and product

labeling (that is, with periodic monitoring and in patients who have failed a fair trial of available AEDs).

We will also require several post-marketing studies.

Under the Pediatric Research Equity Act (PREA) we will require a controlled trial in pediatric patients aged 10-16 years with CPS. We will waive the requirement for controlled trials in patients below the age of 10 years with CPS because visual toxicity is difficult to assess in these patients and other drugs are available to treat them.

As a Post-Marketing Requirement (PMR) under FDAAA, we will require the sponsor to analyze the visual data collected in the registry to be set up under the REMS (see below for a discussion of the elements of the REMS).

We will also require a study examining the effects of taurine on vigabatrin-induced retinal damage in rodents (see below for a further discussion of this issue).

Finally, we will ask the sponsor, as a Post-Marketing Commitment (PMC), to perform an in vitro study to evaluate Sabril's capacity to induce CYP1A2 and 3A4.

NDA 22-006

Regarding NDA 22-006, the committee voted unanimously to recommend approval. The clinical team agrees (in particular, despite the numerous flaws in the three clinical trials submitted, the committee and the review team concluded that there is substantial evidence of effectiveness in patients with IS, and I agree), but Dr. Fisher recommends that the application not be approved. Specifically, the sponsor most recently submitted the results of 4 and 9 week oral toxicology studies in the juvenile rat. Although the sponsor has concluded that these studies demonstrate the typical IME seen in adult animals (except that these lesions were seen in gray matter in addition to white matter), a Pathology Working Group constituted by the sponsor concluded that the lesions are "… not characteristic of intramyelinic edema.". Drs. Fisher and Schmued agree that there are lesions present in these studies that are different from IME. These lesions were seen at exposures to vigabatrin that are lower than those achieved in patients. In addition, seizures were noted in both studies.

Vigabatrin also caused retinal degeneration in the albino rat and mouse, but not in pigmented strains or species. There is also some evidence that vigabatrin-induced retinal toxicity can be prevented (or minimized) by taurine administration.

Dr. Freed agrees that the neurotoxicity seen in the juvenile rat studies differs from IME, but concludes that the application can be approved, with the company's commitment to perform additional studies after approval.

I agree.

As she (and the clinical team) notes, IS is a serious condition for which there are no approved treatments. Although there is no evidence that the control of the spasms that Sabril produces is associated with amelioration or prevention of the other deficits associated with IS (e.g., developmental abnormalities, occurrence of other seizure types), control of the spasms themselves produces a clear benefit in the lives of these children.

It is also true that there is general agreement among the experts we have consulted that there is no reliable method available to detect Sabril-induced visual toxicity at any early stage in these young patients. Nonetheless, the severity of the clinical condition being treated argues, in my view, for approval. Again, although we do not have the sort of prospective follow-up of these patients that we would like, we do not have reports of significant numbers of patients who were treated with Sabril as infants having important visual sequelae (here again it should be noted that Sabril has been used in this population for many years outside the US).

In addition, although we do not know the clinical consequences, if any, of the pathology seen in the juvenile animals, we are not aware of reports of significant decrements in functioning in these children after prolonged treatment with Sabril. Although it must be again acknowledged that we do not have adequate, prospective follow-up of these patients, we can take some (albeit admittedly minimal) comfort in the absence of reports of significant neurological "worsening" in these patients after such treatment.

As Dr. Freed notes, Dr. Schmued has recommended another toxicology study be performed in juvenile rats to better characterize the pathology, and Dr. Freed also recommends such a study in juvenile non-rodents. She also recommends that the sponsor be required to perform a study evaluating the effects of taurine on vigabatrin-induced retinal damage in the rodent. I agree that these three studies should be required as PMRs under FDAAA.

REMS

As noted above, the Advisory Committee has recommended that these applications be approved only with an adequate REMS in place. Also as noted above, the sponsor had submitted a preliminary REMS early in the current review cycle. This REMS has been reviewed by numerous Agency reviewers, including the OSE Vigabatrin REMS Review Team, and the sponsor's original proposal has been extensively revised.

The REMS is complex, and contains not only a Medication Guide and Communication Plan, but Elements to Assure Safe Use as well (as well as an implementation plan, and the required REMS assessments and a timetable for the submission of these assessments). I will point out several of the key aspects of the program.

Prescribers who wish to prescribe Sabril will be certified by the sponsor, meaning that, among other things, they will:

1) Document that they have read the PI and MedGuide,
2) Have experience treating patients with epilepsy,
3) Understand the risks,
4) Assess the effectiveness of Sabril within 4 weeks for IS and 12 weeks for CPS and will discontinue the drug if there is an insufficient response
5) Order and review appropriate visual assessments (to be performed by a practitioner with expertise in visual assessment) at baseline and every 3 months during treatment (although we acknowledge that formal visual testing is unreliable in patients with infantile spasms, the program still requires that some effort to assess visual function, however coarse, be attempted in these patients)
6) Educate patients
7) Report serious adverse events to the sponsor
8) Return to the sponsor ophthalmologic assessment forms every 3 months (with a grace period), documenting either the results of such testing or that such testing was not feasible.

Pharmacies will be certified by the sponsor and will ship Sabril only to those patients enrolled in the REMS and will be trained by the sponsor. In particular, the pharmacy will dispense Sabril only to those patients who the sponsor has documented have complied with the periodic ophthalmologic assessments.

Patients must agree to comply with the required assessments, read the MedGuide and understand the risks, and agree to be in a registry.

The REMS is comprehensive, and will ensure, to the extent possible, that appropriate visual monitoring is performed throughout treatment with Sabril.

We will also require the sponsor, as a PMR, to perform a study to assess the single and multiple dose kinetics in patients 1-5 months of age.

Finally, as a PMC, we will ask the sponsor to perform a controlled trial in patients with IS to characterize the minimum duration of therapy required to produce sustained remission of spasms.

For the reasons noted, then, I recommend that this application be approved,

under the constraints imposed by the REMS, with the described PMRs and PMCs, and under the conditions described in the package insert.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
08/14/2009

CLINICAL REVIEW

Application Type	NDA
Submission Number	022006
Submission Code	N 000
Letter Date	December 28, 2007
Stamp Date	December 31, 2007
PDUFA Goal Date	June 30, 2008
Reviewer Name	Philip H. Sheridan, M.D.
Review Completion Date	July 20, 2009
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

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approval of Sabril (vigabatrin) Oral Solution for Infantile Spasms with an appropriate Risk Evaluation and Mitigation Strategy (REMS).
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A REMS mandating a patient registry, drug distribution through specialty pharmacies, and an ongoing assessment of each patient's visual function is required to ensure that the benefits of the drug outweigh the risks. See 1.2.1 immediately below.

The Advisory Committee that met on January 8, 2009 endorsed the approval of Sabril for Infantile Spasms with an appropriate REMS.

The REMS is particularly important for this approval. 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.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The REMS will include:

- Visual function toxicity as a BOXED Warning in labeling
- MRI changes in infants as a Warning in labeling
- Mandatory enrollment of patients in a registry
- Drug distribution through specialty pharmacies
- Frequent monitoring of visual function in all patients
- A Med Guide

1.2.2 Required Phase 4 Commitments

1. An adequately controlled trial in infants treated with Sabril for Infantile Spasms to further characterize the minimum duration of therapy required for sustained submission of spasms. The protocol for the trial should be discussed with the Agency prior to being submitted as a special protocol assessment (SPA).

2. An open label clinical trial to assess the single and multiple dose (at steady state) pharmacokinetics in infants with infantile spasms that are 1-5 months of age at a clinically relevant dose.

3. A toxicology study in the juvenile rat examining the potential of vigabatrin exposure during development to produce neuronal damage. The study protocol should be submitted to the Division for comment prior to study initiation

4. A juvenile animal toxicity study of vigabatrin in a non-rodent species. The study protocol should be submitted to the Division for comment prior to study initiation

5. A study examining the effect of taurine on vigabatrin-induced retinal damage in rodent, as reported by Jammoul *et al*. (Jammoul A F *et al*. *Ann Neurol* 65:98-107, 2009), but administering vigabatrin by the oral route. An attempt should be made to induce retinal toxicity in pigmented animals by, for example, exposing them to high intensity light for an appropriate duration following induction of mydriasis (cf. Rapp LM, Williams TP *Vision Res* 20:1127-1131, 1980). If this is successful, the study should be conducted in both albino and pigmented animals. The final study protocol should be submitted to the Agency for comment prior to study initiation.

1.2.3 Other Phase 4 Requests

Not applicable.

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 s*ites 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 $\mathbf{p}<0.05$.

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

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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 (b) (4) 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 consec-utive 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 hydrocortisone for 4 weeks) Hydrocortisone 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 hydrocortisone in infants with TS (Bourneville's disease) and suffering from newly diagnosed and untreated IS	VGB 11/11 (No subjects crossed-over to receive hydrocortisone) Hydrocortisone 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) Hydrocortisone 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. 39 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 period (5-8 days)	0.063[b]
Placebo	2/20 (10)		
FR03			
VGB	11/11 (100)	End of first 4 weeks of study	0.001[c]
Hydrocortisone	4/11 (36)		

[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)

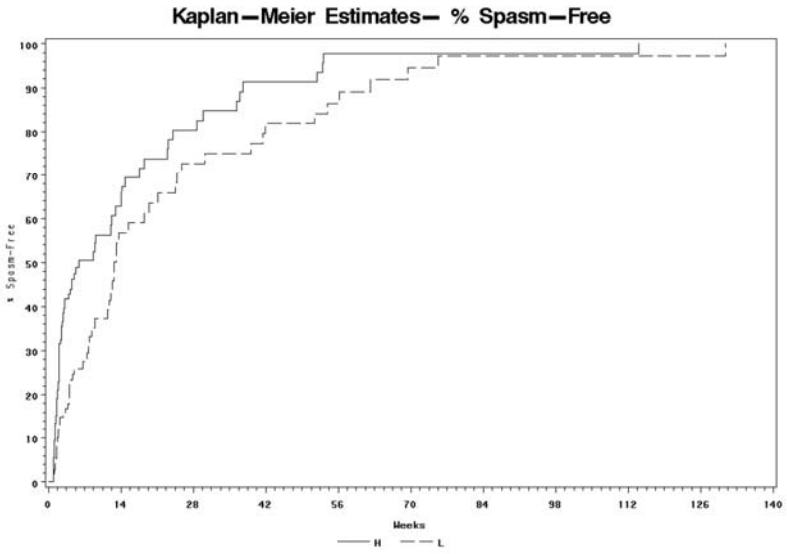
The results of secondary efficacy analyses of endpoints similar in 2 or more of the controlled studies are summarized in the following subsections.

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



Log Rank Test Statistic = 9.95, P-Value = 0.0016
High Dose Group: N= 107, Spasm-Free= 73, Median Time = 6
Low Dose Group: N= 114, Spasm-Free= 59, Median Time = 13

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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 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 plan 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.

Although, the usual standard for NDA approval is not met, the results of the pivotal studies are highly suggestive of efficacy. Given the inherent difficulties of further studying the efficacy and safety of vigabatrin therapy for IS and the lack of any currently approved treatment for IS, the Advisory Committee that met on January 8, 2009 endorsed the approval of vigabatrin for IS with an appropriate REMS. This reviewer agrees with this Advisory Committee recommendation as discussed in Section 9 of this review(Overall Assesssment).

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

The following paraphrases the final minutes concerning the recommendations made by the Advisory Committee on January 8, 2009:

- The committee unanimously voted that the sponsor provided sufficient evidence that vigabatrin is efficacious in the treatment of infantile spasms? (25 yea, 0 No, 0 Abstain)

- The committee agreed that the studies indicate that Sabril is efficacious in the cessation of spasms and there is substantial evidence that it can ameliorate the EEG. (No formal vote taken.)

- The majority of the committee did not feel that the studies indicate that Sabril prevents other seizure types later in life. (No formal vote taken.)

- The committee agreed that the sponsor should be required to adequately study (post-approval) whether chronic treatment with vigabatrin provides an additional benefit beyond a brief treatment course. Some committee members proposed that the sponsor should conduct a randomized

withdrawal study at some point post-approval. There was discussion regarding the design of a withdrawal study but the committee did not arrive at a consensus regarding the design of such a study. The Biostatisticians commented that data from a patient registry will not be adequate to study this question. (No formal vote taken.)

- The Ophthalmologists on the committee agreed that there is no method to practically and reliably predict or detect the lesion with the tests currently available. Additionally, it was agreed upon that ophthalmologic testing can not detect the visual defects any better than observations by the Pediatric Neurologists evaluating the patient. It was commented that visual defects can occur and can be severe and irreversible; thus, families need to be informed but also cautioned that visual testing may not prevent the occurrence of visual defects.(No formal vote was taken.)

- The committee agreed that Sabril should not be approved for use in any specific subset of patients, but rather be approved for all patients with infantile spasms. Patients who may have pre-existing visual conditions should be cautioned about the adverse effects but Sabril should not be contraindicated in any patient population. The committee also agreed that additional efficacy studies are not needed in any subset of patients. (No formal vote taken.)

- The committee agreed that Sabril (vigabatrin) should only be available under REMS and should be made available only under restricted conditions. The committee recommended that the REMS for the refractory complex partial seizure indication should be different than the REMS for the infantile spasms indication. (No formal vote taken.)

- Regarding the intramyelinic edema identified in animals, the committee noted that the intramyelinic edema seen in animals does not seem to correlate with MRI changes. The committee agreed that no data is available to answer this question. (No formal vote taken.)

- The committee separately considered the issue of neuropil vacuolation observed in young animals and agreed that that no data is available to determine if the phenomena are related to MRI findings in children and of clinical concern. (No formal vote taken.)

- The committee did not recommend that additional safety data should be obtained prior to approval of Sabril. (No formal vote taken.)

- The committee unanimously voted to approve Sabril for the indication of IS (23 yes, 0 No, 0 Abstain , 2 absent).

9 OVERALL ASSESSMENT

9.1 Conclusions

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 Advisory Committee that met on January 8, 2009 endorsed the approval of Sabril for Infantile Spasms with an appropriate Risk Evaluation and Mitigation Strategy (REMS).

9.2 Recommendation on Regulatory Action

Approval of Sabril (vigabatrin) Oral Solution for Infantile Spasms with an appropriate Risk Evaluation and Mitigation Strategy (REMS).

A REMS mandating a patient registry, drug distribution through specialty pharmacies, and an ongoing assessment of each patient's visual function is required to ensure that the benefits of the drug outweigh the risks. See Section 9.3.1 immediately below in this review.

The Advisory Committee that met on January 8, 2009 endorsed the approval of Sabril for Infantile Spasms with an appropriate REMS.

The REMS is particularly important for this approval. 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 further studying the efficacy and safety of vigabatrin therapy for IS and the lack of any currently approved treatment for IS, the Advisory Committee endorsed the approval of vigabatrin for IS with an appropriate REMS. This reviewer agrees with the Advisory Committee recommendation for approval.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The REMS will include:

- Visual function toxicity as a BOXED Warning in labeling
- MRI changes in infants as a Warning in labeling
- Mandatory enrollment of patients in a registry
- Drug distribution through specialty pharmacies
- Frequent monitoring of visual function in all patients
- A Med Guide

9.3.2 Required Phase 4 Commitments

1. An adequately controlled trial in infants treated with Sabril for Infantile Spasms to further characterize the minimum duration of therapy required for sustained submission of spasms. The protocol for the trial should be discussed with the Agency prior to being submitted as a special protocol assessment (SPA).

2. An open label clinical trial to assess the single and multiple dose (at steady state) pharmacokinetics in infants with infantile spasms that are 1-5 months of age at a clinically relevant dose.

3. A toxicology study in the juvenile rat examining the potential of vigabatrin exposure during development to produce neuronal damage. The study protocol should be submitted to the Division for comment prior to study initiation

4. A juvenile animal toxicity study of vigabatrin in a non-rodent species. The study protocol should be submitted to the Division for comment prior to study initiation

5. A study examining the effect of taurine on vigabatrin-induced retinal damage in rodent, as reported by Jammoul *et al*. (Jammoul A F *et al*. *Ann Neurol* 65:98-107, 2009), but administering vigabatrin by the oral route. An attempt should be made to induce retinal toxicity in pigmented animals by, for example, exposing them to high intensity light for an appropriate duration following induction of mydriasis (cf. Rapp LM, Williams TP *Vision Res* 20:1127-1131, 1980). If this is successful, the study should be conducted in both albino and pigmented animals. The final study protocol should be submitted to the Agency for comment prior to study initiation.

9.3.3 Other Phase 4 Requests

Not applicable

9.4 Labeling Review

Labeling under final review at this time.

9.5 Comments to Applicant

Not applicable.

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/s/

Philip Sheridan
7/22/2009 04:19:48 PM
MEDICAL OFFICER

Norman Hershkowitz
7/22/2009 04:46:43 PM
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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

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 boldby 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 progess 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 dependendent 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)	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 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	Uncontrolled CPS	Planned to be at least 52 weeks Actual approximately 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.

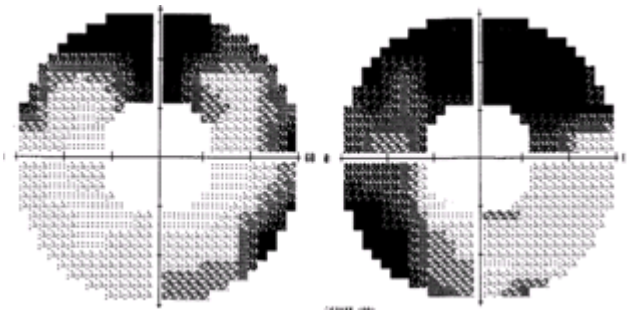
Additional findings

- 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."

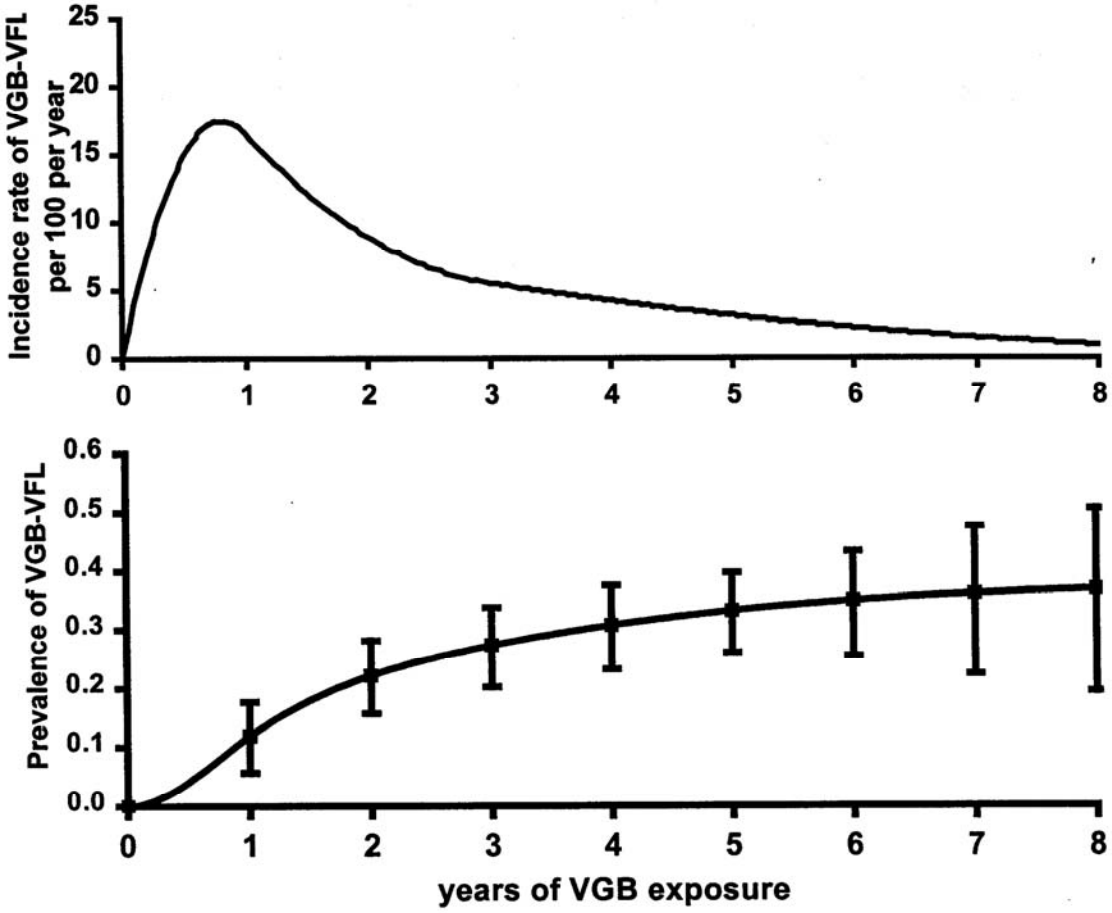
Since patients in this cohort were tested after treatment with VGB for varying lengths of time (Table 5), it was possible for the sponsor to estimate the time to onset (Figure 1) and cumulative dose (Figure 2) to onset of visual field defects using a statistical approach that estimated the most likely 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
0-0.5 kg	79
0.5-1 kg	46
1-2 kg	54
2-3 kg	58
3-4 kg	50
4-5 kg	42
5-6 kg	37
6-7 kg	18
7-8 kg	13
8-9 kg	7
9- kg	12
Total	**N=416**

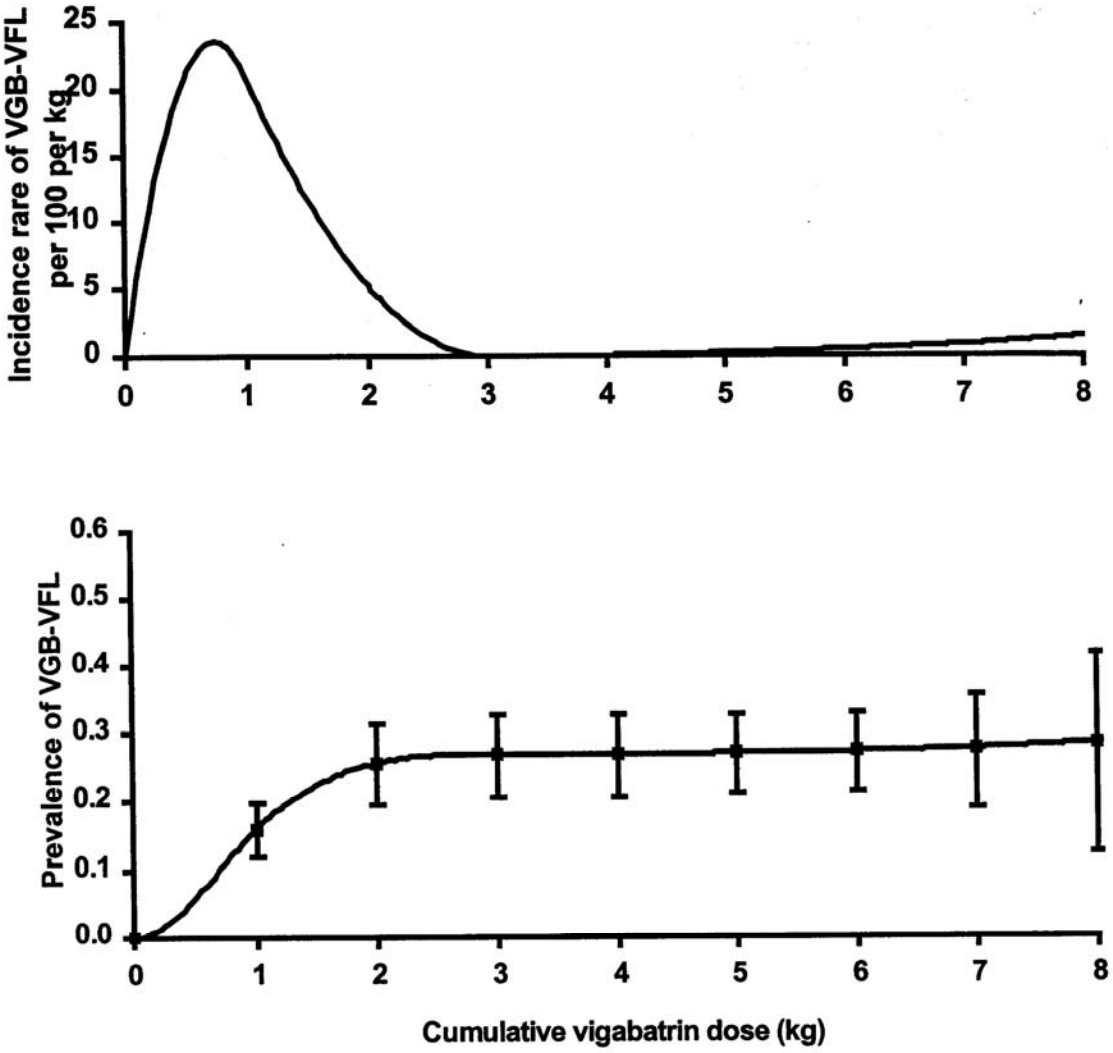
Duration of VGB therapy	Subjects
0-0.5 year	64
0.5-1 year	50
1-2 year	59
2-3 year	52
3-4 year	84
4-5 year	41
5-6 year	57
6-7 year	23
7-8 year	10
8-9 year	3
9- year	8
Total	**N=451**

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.

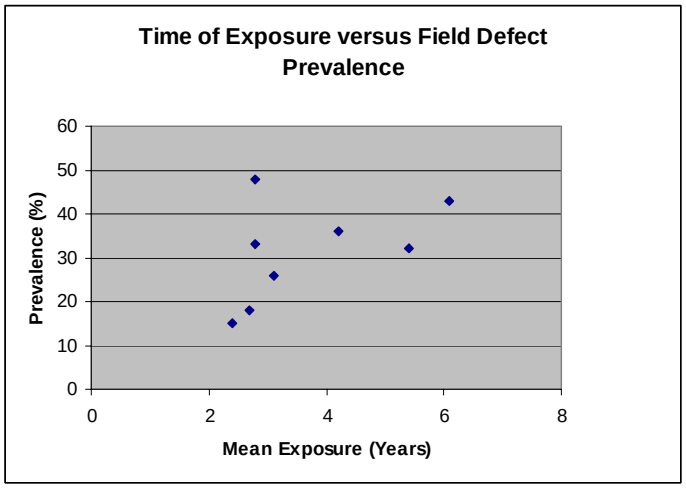
Type of epilepsy or ethnic origin was not reported to be a risk factor (Table 6).

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	Abnormal	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 14 (b) (6)).
- 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

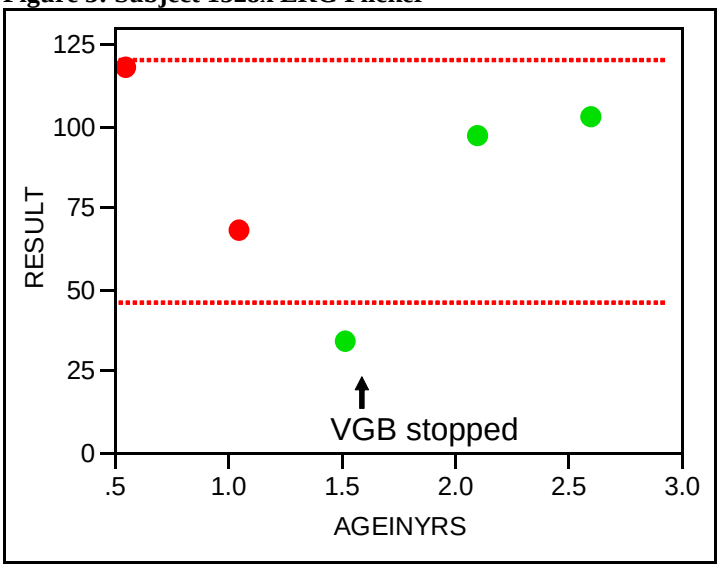


Figure 3: Upper and lower limit of normal are approximately represented by the red lines (normal age-related increase in values not shown). Red circles represent flicker result for left eye, and green for right eye. 'Result' is 30 Hz flicker result, in microvolts, versus patient age in years.

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

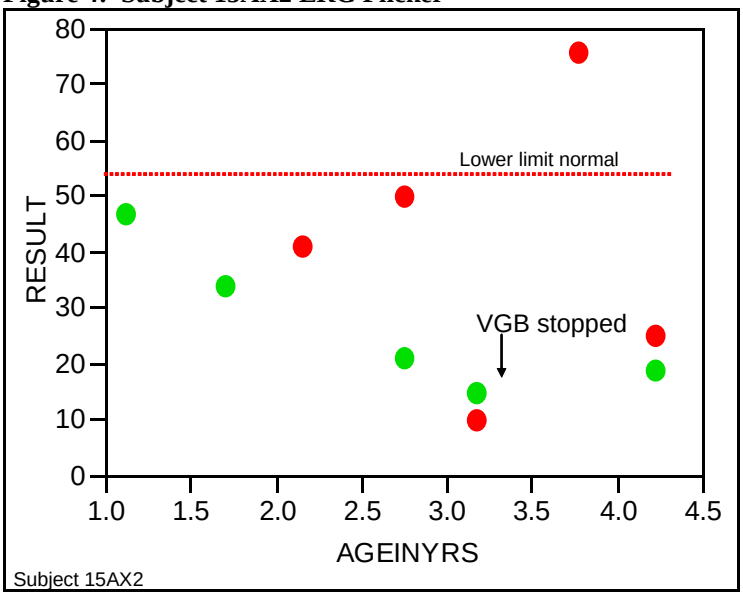


Figure 4: Lower limit of normal is approximately represented by the red line (normal age-related increase in value not shown). Red circles represent flicker result for left eye, and green for right eye. 'Result' is 30 Hz flicker result, in microvolts, versus patient age in years.

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

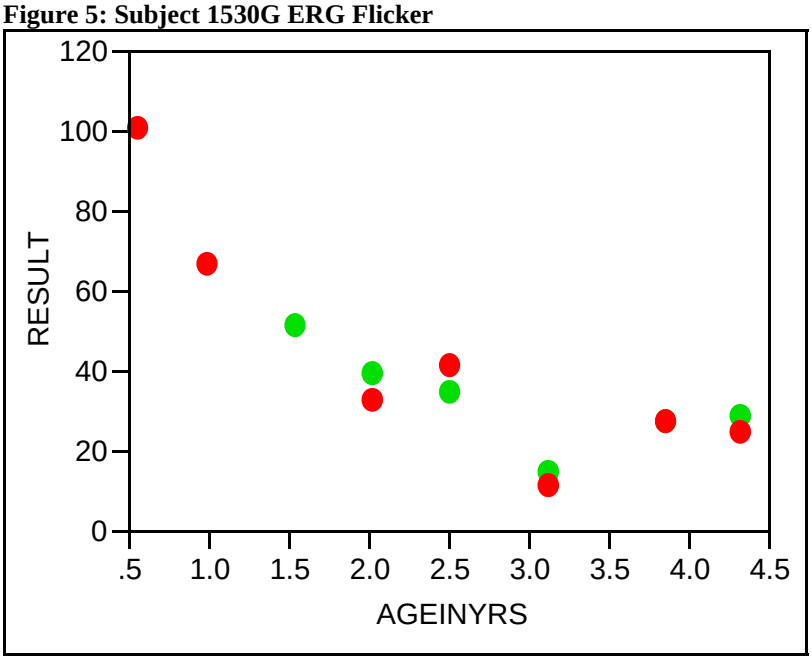


Figure 5: Red circles represent flicker result for left eye, and green for right eye. 'Result' is 30 Hz flicker result, in microvolts, versus patient age in years.

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 ERGmight 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.

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

[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.

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

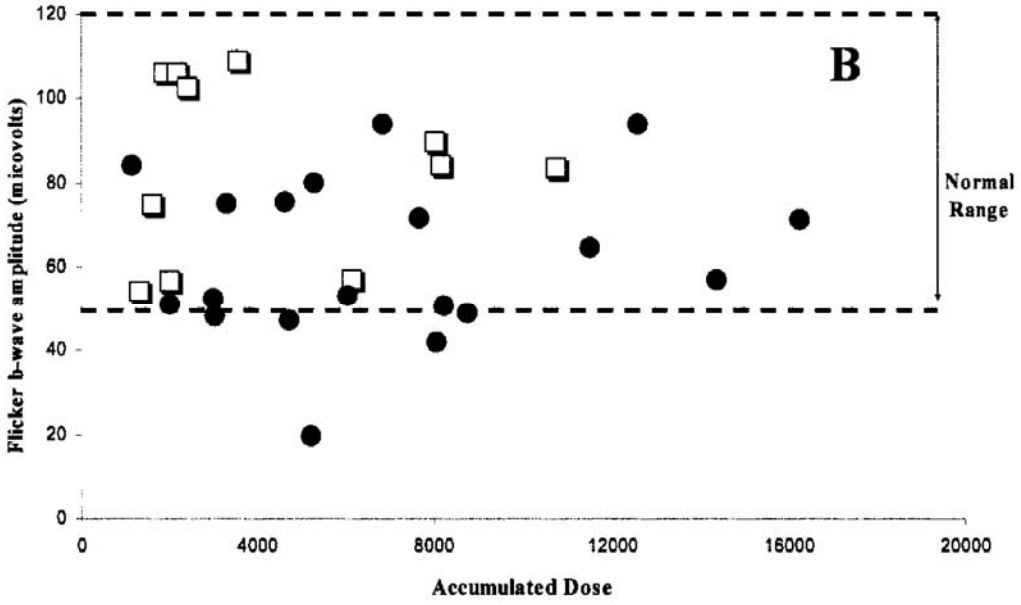


Figure 6: VGB patients with (solid circles) and without (open squares) bilateral visual field defects.

- *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

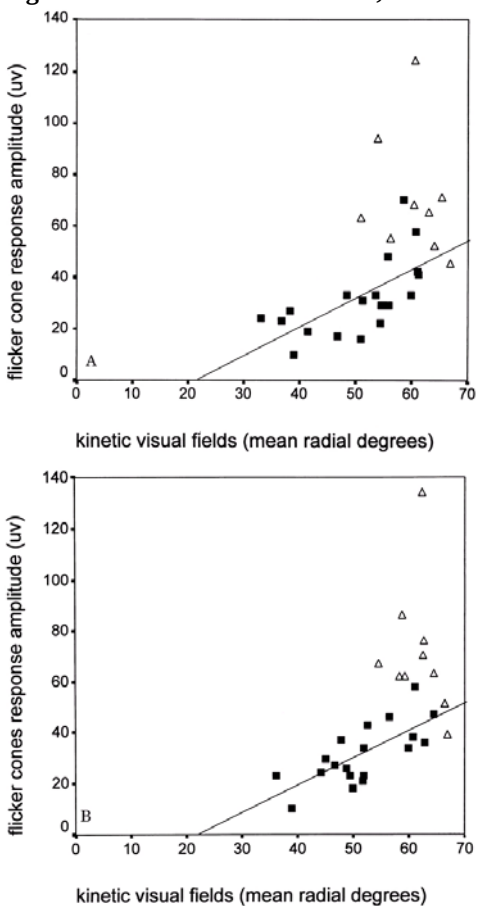


Figure 7: Filled squares are VGB patients, and triangles are controls. Right (top) and left (bottom) eyes shown separately.

- *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 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.

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[5] Miller NR et al., Visual dysfunction in patients receiving vigabatrin. Neurology 1999;53:2082
[6] Kinirons et al., Vigabatrin retinopathy in an Irish cohort: Lack of correlation with dose. Epilepsia 2006, 47:311-317.

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.

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.

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

[7] Malmgren K, Ben-Menachem E, Frisén L. Vigabatrin visual toxicity: Evolution and dose dependence. Epilepsia 2001;42:609-15

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

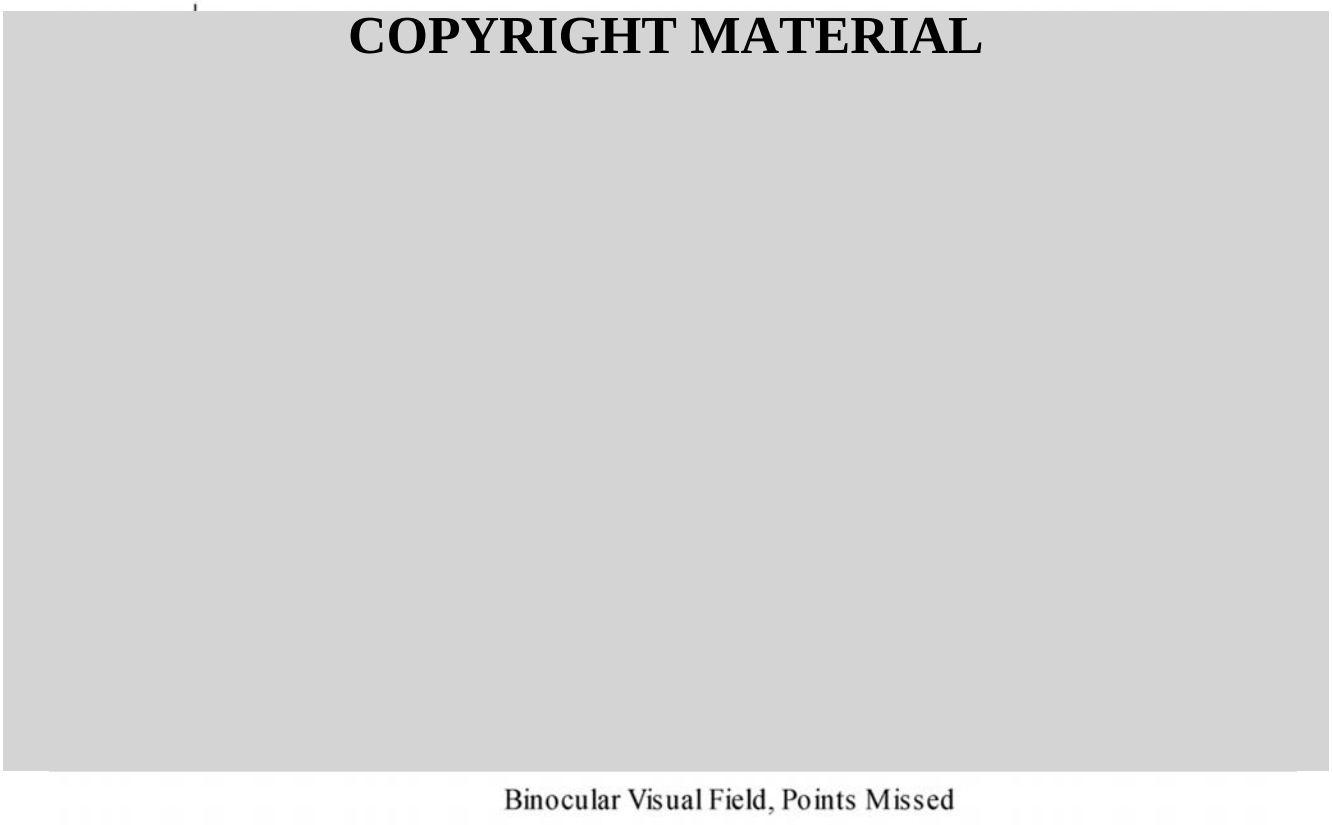


Figure 8: Scatter plot of overall Activities of Daily Vision Scale score by binocular visual field score, represented by 96 points to 60 degrees in the periphery. From Freeman et al., 2008

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 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].

[8] Freeman EE et al., Glaucoma and Quality of Life. Ophthalmology 2008;115:233-238.
[9] Buncic et al., Characteristic retinal atrophy with secondary 'inverse' optic atrophy identifies vigabatrin toxicity in children. Opthalmology 2004;111:1935-1942.

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.

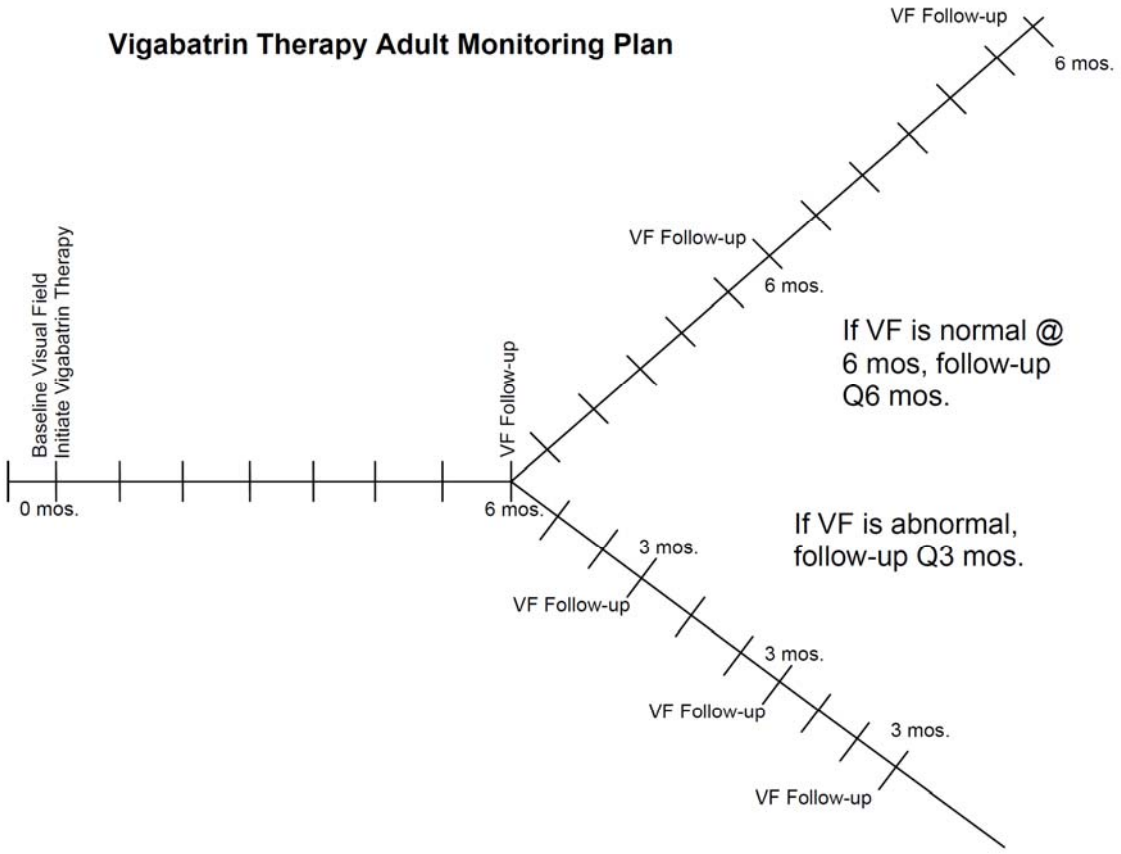
13. Ophthalmic Safety Monitoring Plan in Adults

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 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.

[10] Sorri et al., Ophthalmologic and neurologic findings in two children exposed to vigabatrin in utero. Epilepsy Res 2005;65:117-20.

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.

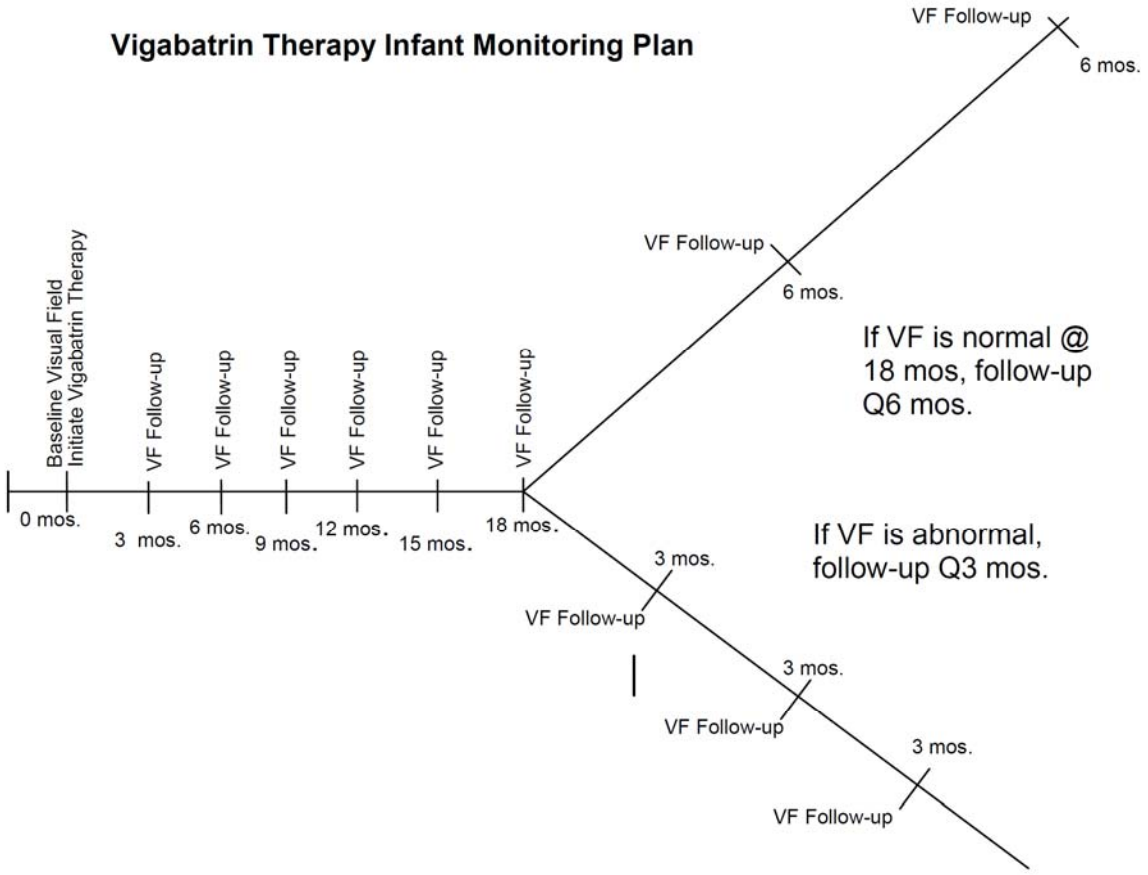
14. Ophthalmic Safety Monitoring Plan in Children

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 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

[11] Wild, JM. Detecting Vigabatrin Toxicity by Imaging of the Retinal Nerve Fiber layer. Invest. Ophth. Visual Sci 2006;47:917-924.

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.

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/s/

Ronald Farkas
7/18/2009 09:01:43 PM
MEDICAL OFFICER

Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

NDA: 22-006
Drug: Vigabatrin (SABRIL)
Route: Oral
Indication: Infantile Spasms
Sponsor: Ovation
Review Date: 3/17/09
Reviewer: Sally Usdin Yasuda, Safety Team Leader
Neurology Drug Products, HFD-120

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1 Background

Vigabatrin is an irreversible inhibitor of gamma-aminobutyric acid transaminase. The current submission is a new NDA for which the Sponsor is seeking approval for treatment of infantile spasms (IS). For infants 1 month to 2 years of age the proposed initial dose is 50 mg/kg/day given twice daily up to a maximum of 150 mg/kg/day.

The development program for vigabatrin had been put on hold in the 1980s due to findings of intramyelinic edema (IME). After resuming development, NDA 20-427 for vigabatrin was submitted to FDA in 1994 for treatment of complex partial seizures (CPS) in adults. The application was found Not Approvable in 1995 due to deficiencies in the presentation of safety data, according to the background provided by Dr. Jerry Boehm in his review of NDA 20-427. Vigabatrin received an approvable letter in 1997 after addressing identified deficiencies. However, the Sponsor subsequently withdrew the application prior to approval in the US, due to the finding of permanent visual field defects. Ovation filed the present submissions for NDA 20427 and for NDA 22-006 on 12/28/07. NDA 20-427 is currently under review.

Dr. Boehm has reviewed the safety data for NDA 22-006 except for visual field defects that are reviewed by Dr. Farkas and intramyelinic edema (IME)/MRI abnormalities that are reviewed by Dr. Phillip Sheridan separately. Several adverse events of concern in the CPS NDA, including liver injury, peripheral neuropathy, and edema will not be discussed in detail here (please refer to the reviews of NDA 20-427). This memorandum summarizes the primary concerns from the safety review, conducted by Dr. Boehm, of the Sabril NDA (22-006) for IS.

2 Summary of Findings from the Safety Review

2.1 Integrated Review of Safety

The current submission includes pooled safety data from 3 controlled IS studies and 1 uncontrolled IS study (n=325), as well as safety data from subjects < 3 y.o. from non-IS studies (n=21). It also includes data from a retrospective study of 250 IS patients, for which data were not integrated with the prospective studies. As Dr. Boehm reports, the

IS NDA submission therefore includes safety data from 346 subjects exposed to vigabatrin in combined controlled and uncontrolled trials; 172 subjects were exposed to vigabatrin for more than 6 months, 120 for more than 1 year, and 75 subjects did not have sufficient data to determine duration of exposure. These numbers fall short of the ICH guidelines, although in the entire development program (IS and CPS) the number exposed exceeds ICH guideline. The proposed dose range reflects the dose range used in the trials in the IS safety database. The duration of the controlled trials was 7 days of titration followed by a constant dose for 7-14 days for Study 1A, 5 days for Study W019, and 1-2 months in crossover study FR03. For the largest controlled trial, Study 1A (a randomized single blind study with open label follow-up, n=222, high dose vs low dose)[1], for the high dose group (mean 139 mg/kg/day, median 131 mg/kg/day, maximum 346.5 mg/kg/day) 75 subjects were exposed for at least 76 months and 58 subjects were exposed for at least 1 year. For the low dose group (mean 122 mg/kg/day, median 119 mg/kg/day, maximum 369.5 mg/kg/day) 86 subjects were exposed for at least 6 months and 67 were exposed for at least 1 year. The mean age of the study subjects was 1 year (range 0.1 to 12.5 years).

2.1.1 Deaths

According to Dr. Boehm's review there were 4 deaths in the integrated safety database for IS, and the mortality risk was 1.2% (4/346). Three deaths were from Study 1A. The deaths were due to sudden death, pneumonia (subject had been off vigabatrin for 3 weeks at the time of the adverse event), pulmonary hemorrhage (thought to be secondary to pulmonary angiomatosis), and cardiac arrest. There were 2 deaths in the retrospective study that occurred on vigabatrin treatment. One was a death in which a child with a condition similar to leucodystrophy, titrated to 200 mg/kg/day over 14 days without cessation of spasms, was found dead by parents, and had reportedly been getting progressively weaker. The second was reportedly due to bronchopneumonia.

2.1.2 Serious Adverse Events

Dr. Boehm has presented serious adverse events (SAEs) among vigabatrin subjects from the integrated data pool of IS study subjects (n=346), and reports that 23% experienced one or more SAEs. The most common SAEs were pneumonia (3.2%), status epilepticus (3.2%), pyrexia (1.7%), convulsion (1.5%), bronchospasm (1.2%), viral infection (1.2%), and gastroesophageal reflux disease (1.2%).

In postmarketing reports, there were 37 SAEs reported for children < 3 y.o. and 19 for children 3-12 y.o. For the < 3 y.o. 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. In the older age group, visual field defect (VFD) (n=6) was the only event reported more than twice, and 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.

[1] In the controlled, single-blind phase, subjects were randomized to receive either low-dose (18-36 mg/kg/day) or high dose (100-148 mg/kg/day).

Dr. Boehm also evaluated less frequent but potentially concerning SAEs. Of note, there were no SAEs of acute hepatic failure, acute renal failure, pancreatitis, aplastic anemia, rash, Stevens Johnson syndrome, toxic epidermal necrolysis, or hypersensitivity reported in the IS database. There were 3 SAEs of respiratory arrest, one of respiratory failure (in a patient with respiratory insufficiency secondary to tonsillar enlargement), and one of proteinuria/glomerulonephritis.

2.1.3 Dropouts and Other Significant Adverse Events

Sixty-two percent of the subjects in the safety population for IS discontinued a trial prematurely. The most common reason for discontinuation was other (22%); this included becoming seizure 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).The other most common reasons for discontinuation were lack of efficacy (19%), administrative reasons (10%), protocol violation (4%), and adverse event (3%). Twenty-two of 346 subjects in the safety database (6.4%) discontinued from a trial due to adverse events; among those there did not appear to be clusters of similar adverse events.

2.1.4 Common Adverse Events

In the IS controlled trials, adverse events occurring most commonly (>5%) included upper respiratory tract infection, otitis media, pyrexia, viral infection, irritability, somnolence, sedation, vomiting, constipation, pneumonia, diarrhea, insomnia, ear infection, rash, nasal congestion, decreased appetite, sinusitis, lethargy, bronchitis, and convulsion. In the retrospective study, 13.2% experienced adverse events, and the most common and that were reported more than once were somnolence, hyperkinesia, insomnia, hypotonia, nervousness. (Somnolence was also among the most common adverse events in the CPS controlled trials, and vigabatrin was associated with increased risk of several CNS AEs including somnolence, sedation, coordination abnormalities, and confusional state). The only available comparative data from controlled trials in the IS database come from FR03 (hydrocortisone n=12 vs vigabatrin n=18) and W019 (placebo n=20 vs vigabatrin n=20). In these data, the only AE that was greater in the vigabatrin group than in the comparator group was somnolence (20% for placebo, 40% for vigabatrin). As Dr. Boehm points out, the value of this analysis is limited by the small number of events and subjects. Comparison is made between treatment-related AEs in the low dose and high dose groups in the controlled portion of Study 1A. These data are limited by the short duration of exposure.

In the pooled safety database, 57% of subjects were Caucasian and 24% were of unknown race, 8% were black, and 11% were classified as other. This is not a sufficient data set to evaluate AE risk by race. In study 1A that allowed for a dose-comparison, there was not strong evidence of a dose-response for AEs within the first 14 days of treatment where this comparison could potentially be made. The safety population was nearly evenly divided in terms of sex. Without placebo comparator data, as Dr. Boehm observes, it is not possible to determine if observed differences in risk by sex are due to differences in background risk or drug sex interaction.

As outlined above, Dr. Boehm points out the analysis of drug-related AEs in this NDA does not allow for reliable assessment in the IS NDA, and that collection of adverse event data in this population is hampered by patient age and inability to verbalize complaints. Dr. Boehm suggests that comparative safety data from the adult database can be used, but recognizes that extrapolation from the CPS database to infants with IS may not be optimal. *I agree with his considerations, and recommend that the adult AE data be included in the labeling for the IS indication.*

2.1.5 Laboratory findings

Laboratory testing in the IS studies was not comprehensive. For Study 1A, lab values were not collected during the blinded phase of the trial, and are only available for the open label phase of the trial that allowed flexible dosing. Dr. Boehm has combined the data from both doses to which subjects were randomized, and I agree that this approach is appropriate.

There were several laboratory changes of concern, as presented by Dr. Boehm and these will be summarized below.

Hemoglobin/Hematocrit: At month 1, subjects in study 1A experienced a mean decline in hematocrit of -0.65% and hemoglobin of -0.33 g/dL. For platelets, study subjects consistently experienced mean decreases for all study months. Decreases from baseline were also observed in Study W019. For Study 1A, of the 145 subjects with normal hemoglobin at baseline, 12% had a low outlier result after 1 month of vigabatrin treatment. Of 147 subjects with normal hematocrit at baseline, 5.4% had a low result after 1 month of treatment. Of the 76 subjects with normal platelet counts at baseline, 2 developed low outliers at month 1. In the IS safety population, 2% had an anemia AE, and none of these were SAEs. (Decreases in hemoglobin and hematocrit were also observed in U.S. controlled epilepsy studies in the CPS NDA).

Dr. Boehm has recommended that any ongoing or planned vigabatrin clinical trials should incorporate monitoring of relevant hematologic parameters and that 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. *I agree with Dr. Boehm's recommendation.*

Liver Function Assessments: Dr. Boehm has noted a reduction of transaminases ALT (SGPT) and AST (SGOT) in Study 1A. At month 1, the mean change from baseline for AST was -10.2 U/L and for ALT was -17.7 U/L, with no marked additional declines during months 3-30. (The mean change in ALT is similar to that observed in the CPS database, and the mean change in AST is larger than that observed in the CPS database). For ALT, 6.8% of the 117 subjects with a normal result at baseline had a low outlier after 1 month. No subjects had a low outlier for AST. Study W019 similarly showed mean decreases from baseline in ALT and AST. The decrease in AST/ALT is likely due to an interaction directly with these transaminases. This inhibitory interaction has been demonstrated in vitro (measuring these enzyme activities in human serum in the presence

or absence of vigabatrin).[2] The relevance of this is that ALT/AST will not be reliable as early markers for liver disease or drug-induced hepatotoxicity.

A mean increase in alkaline phosphate (ALP) of 15.6 U/L was observed. At baseline 106 subjects had normal ALP, one had a low ALP, and 48 subjects had high ALP. Of the 106 subjects with normal ALP at baseline, 17 developed high outliers at 1 month. Eight subjects in the safety population (n=346) had an AE of blood ALP increased. In 1 case, this led to discontinuation from the trial. In that case baseline ALP was 245 and after 1 month on vigabatrin her ALP was 1498, with a repeat 6 days later of 1752. The subject did not have elevations of total bilirubin or transaminases, and calcium and phosphorous were normal. Vigabatrin was stopped, and repeat ALP was 384 approximately 2 weeks later.

2.1.6 Vital Signs and ECG

Heart Rate, Systolic and Diastolic Blood Pressure, and Respirations
Dr. Boehm does not find notable differences in vital signs mean changes from baseline in comparing the low and high dose groups at week 2 for study 1A. At the end of the double blind phase of Study W019, mean change from baseline for diastolic BP was similar for vigabatrin and placebo. For systolic BP, placebo subjects experienced a mean drop of 3.6 mm Hg and vigabatrin subjects experienced a mean increase of 2.3 mm Hg. There was a mean increase in heart rate of 4.9 bpm for placebo subjects and a decrease of 0.6 bpm for vigabatrin subjects. At the end of the open label phase, study subjects experienced mean increases in systolic and diastolic BP of 6.4 mm Mg and a mean decrease in heart rate of 4.6 bpm. Week 2 data for Study 1A showed a slightly higher outlier risk for systolic blood pressure for the high dose group compared to the low dose group.

Two subjects from the IS safety population discontinued for vital sign related AEs. One subject discontinued for infantile spasm and hypertension, but the hypertension was felt to be due to ACTH (the vigabatrin was discontinued on 29 Feb 1997 and the subject recovered from the hypertension on 29 May 1997). One subject discontinued for weight gain. This was a 4 y.o. child with an increase in weight of 0.9 kg (to 6.6 kg from baseline of 5.7 kg) in less than 1 month that led to discontinuation for approximately 1 month. Approximately 7 months after vigabatrin was restarted, the subject weighed 9.8 kg. Weight gain was observed in the CPS NDA, and as Dr. Boehm points out, long term consequences of vigabatrin-related weight gain in terms of cardiac and metabolic risk are not known. Collection of data that would allow for evaluation of this type of risk should be included in future studies of reasonable duration. (For a more detailed discussion of weight gain, please refer to the safety review of NDA 20-427).

None of the NDA IS studies recorded ECGs. A thorough QT study in adults (reviewed by the QT-IRT and summarized in my team leader memo for NDA 20-427) did not

[2] Richens A, McEwan JR, Deybach JC, Mumford JP. Evidence for both *in vivo* and *in vitro* interaction between vigabatrin and alanine transaminase. Br J Clin Pharmacol 1997; 43:163-168.

identify a risk for QT prolongation and there was not a signal for ECG-related changes in the CPS database in NDA 20-427.

2.1.7 Adverse Events of Special Interest

Dr. Ron Farkas reviewed *visual field changes* and Dr. Phillip Sheridan reviewed data related to *IME*. These were not evaluated by Dr. Boehm.

Edema was identified as an adverse event in the CPS database. In the IS database, 2/346 subjects had edema peripheral AEs and one subject had an edema AE. Dr. Boehm believes that assessment of edema risk in IS patients would be helpful. *I agree with his recommendation and suggest that this assessment should be included in future pediatric studies of any age.*

Peripheral neuropathy was an AE of concern in the CPS database in which vigabatrin subjects had increased risk for paresthesia and hyporeflexia. There were no reported AEs of hyporeflexia or parathesias for vigabatrin subjects in the IS studies. Information about peripheral neuropathy is included in the warnings section of the proposed label for the IS indication.

Liver injury risk was not well characterized in the CPS database. There were no reported AEs of liver failure or liver injury among vigabatrin treated subjects in the IS studies. Dr. Boehm recommends that the Sponsor should closely follow up any spontaneous reports of liver injury and should submit any serious livery injury cases as 15 day reports. *I agree with his recommendation.*

Growth
The Division asked Ovation to summarize data that would allow an assessment of growth in vigabatrin treated children. There were 4 studies in CPS and 3 in IS that recorded baseline and final height and weight. According to Dr. Boehm's review, the data suggest consistently greater mean increases in weight for pediatric CPS subjects exposed to vigabatrin compared to placebo (approximately 2x greater changes from baseline). Differences in height are based on small numbers and it is difficult to interpret those results. Dr. Boehm agreed with the Sponsor that the short duration for controlled phases of the IS studies precludes meaningful analysis of the data in that population. Please refer to additional discussions about weight gain in Section 2.1.6 above.

Dr. Boehm notes the lack of carefully measured height and weight data in children to allow assessment of growth and suggests that if approved for pediatric indications, Ovation should collect data that address the effect of vigabatrin on growth and development. *I agree with his recommendation.*

2.1.8 Other findings and considerations
Human Carcinogenicity: In the IS studies, 2 cancers were diagnosed. In study 1A, a 2 month old female was diagnosed with neuroblastoma 18 days after starting vigabatrin and a 13 month old female was diagnosed with angiosarcoma after 9 months of vigabatrin

treatment. In the vigabatrin development program there was also a 9 y.o. male that had an "excision of an occipital hole tumor" after 7 months of vigabatrin treatment.

2.1.9 Labeling and Post-Marketing Risk Management Plan

Dr. Boehm has recommended some changes to the Sponsor's proposed labeling and that labeling is being reviewed by the Division. Vision loss will be addressed in the REMS.

3 Conclusions

Dr. Boehm has not identified any issues in his review of the safety data that would prevent approval of Sabril. In addition to the recommended labeling changes suggested by Dr. Boehm, I reiterate the following recommendations:

1. Comparative safety data from the CPS database should be included in the IS labeling.
2. Any ongoing or planned vigabatrin clinical trials should incorporate monitoring of relevant hematologic parameters and should incorporate hematologic testing during post-treatment washout in order to assess rate of recovery from reduction of hemoglobin and hematocrit.
3. It would be useful to carefully evaluate edema risk in ongoing or planned clinical trials in pediatrics.
4. The Sponsor should collect data that address the effect of vigabatrin on growth and development.
5. Since the long term consequences of vigabatrin-related weight gain in terms of cardiac and metabolic risk are not known, this type of metabolic data (such as lipids and glucose) should be included in future studies of reasonable duration.
6. The Sponsor should closely follow up any spontaneous reports of liver injury and should submit any serious livery injury cases as 15 day reports.

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Sally Yasuda

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INTERDISCIPLINARY

CLINICAL REVIEW

Application Type	NDA
Submission Number	022-006
Submission Code	N 000
Letter Date	12/28/08
Stamp Date	12/31/08
PDUFA Goal Date	6/30/08
Reviewer Name	Gerard Boehm, MD, MPH
Review Completion Date	7/7/08
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

TABLE OF CONTENTS

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 (b) (6) days and was receiving a vigabatrin dose of 195 mg/kg for 3 consecutive weeks. On (b) (6) 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).*

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 (b) (6) 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 (b) (6) 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 (b) (6). 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 (b) (6) 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 1ocal 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 l00 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.

Patient 02-02-02: Patient was male (d.o.b.: (b) (6)), having an age of IS onset of 29 months (date: (b) (6)). 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: (b) (6)). 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.: (b) (6)) and presented with IS 5.5 months after birth (date: (b) (6)). 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 (b) (6) thus 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 (b) (6) 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 (b) (6)) This Caucasian female born on (b) (6) 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 (b) (6), 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 (b) (6) 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,

On (b) (6), 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 (b) (6). 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 (b) (6)6. 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 (b) (6), 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 (b) (6) 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 (b) (6), 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 (b) (6) 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 (b) (6)) This Caucasian male born on (b) (6) 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 (b) (6), 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 (b) (6) 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 (b) (6). 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 (b) (6) 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 (b) (6). 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.

On (b) (6), 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 (b) (6) 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 (b) (6). 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

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 (b) (6) 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 (b) (6), 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 (b) (6). The subject recovered from the infantile spasms on (b) (6) and from the hypertension on (b) (6). 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[a]**	**>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 OVAT1A 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.
[a] 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 (b) (4) 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. (b) (4) 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. (b) (4) 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	Eyelid ptosis	Retinal disorder
	Blindness cortical	Hypermetropia	Visual acuity reduced
	Cataract	Mydriasis	
Investigations	Alanine aminotransferase increased	Diagnostic procedure	Red blood cell count increased
	Biopsy kidney	Gamma glutamyltransferase increased	Urine analysis abnormal
	Blood albumin abnormal	Hepatic enzyme increased	Visual tract testing abnormal
	Blood albumin decreased	Liver function test abnormal	Weight decreased
	Blood corticotrophin abnormal	Neurological examination abnormal	Weight increased
	Blood potassium decreased	Protein total decreased	White blood cell count increased
	Body temperature increased	Pupillary light reflex tests abnormal	White blood cells urine positive
	Cytoscopy	Red blood cell count decreased	
Injury, Poisoning and Procedural Complicaitons	Arthropod bite	Head injury	Skin laceration
	Cephalhaematoma	Hip fracture	Surgical procedure repeated
	Drug toxicity	Injury	Thermal burn
	Excoriation	Joint dislocation	Upper limb fracture
	Fall	Mouth injury	Vaccination complication
	Feeding tube complication	Near drowning	Ventriculoperitoneal shunt malfunction
	Femoral neck fracture	Post procedural pain	
	Femur fracture	Shunt occlusion	
Musculoskeletal and Connective Tissue Disorders	Back pain	Muscle twitching	Musculoskeletal stiffness
	Exostosis	Muscle spasms	Neck pain
	Hip deformity	Muscular weakness	Osteopenia
	Kyphoscoliosis	Musculoskeletal discomfort	Scoliosis
Blood and Lymphatic System Disorders	Iron deficiency anemia	Monocytosis	Neutropenia
	Leukocytosis	Nephrogenic anemia	Thrombocythemia
Ear and Labyrinth Disorders	Deafness	Middle ear effusion	Tympanic membrane hyperaemia
	Hypoacusis	Tympanic membrane disorder	
Immune System Disorders	Allergy to arthropod bite	Hypersensitivity	Seasonal allergy
	Drug hypersensitivity	Immunisation reaction	
	Food allergy	Milk allergy	
Surgical and Medical Procedures	Brain operation	Fundoplication	Surgery
	Brain tumor operation	Gastrintestinal tube insertion	

	Drug delivery device implantation	Hospitalization	
Cardiac Disorders	Atrioventricular block second degree	Cardio-respiratory arrest	Ventricular extrasystoles
	Bradycardia	Tachycardia	Ventricular tachycardia
	Cardiac arrest	Cyanosis	Wolff-Parkinson-White syndrome
Congenital, Familial and Genetic Disorders	Bronchial cyst	Epidermal naevus	Tuberous sclerosis
	Cleft palate	Hip dysplasia	
	Cryptorchism	Talipes	
Renal and Urinary Disorders	Glomerulonephritis focal	Ketonuria	Proteinuria
	Glycosuria	Lekocyturia	
	Haematuria	Nephrolithiasis	
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/

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7/7/2008 01:05:53 PM
MEDICAL OFFICER

Sally Yasuda
7/8/2008 02:59:06 PM
BIOPHARMACEUTICS