CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA /Serial Number:	22-006
Drug Name:	Vigabatrin (Sabril®)
Indication:	Infant Spasms
Applicant:	Ovation Pharmaceuticals
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Key Words: Infantile spasm, Responder rate, Chi-square test, ANCOVA, Interim analysis

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

For Study 1-A, based on the primary efficacy results, it appears that there is a positive signal of treatment effect of vigabatrin for subjects with new onset infantile spasm. However, it is very difficult to make sound statistical inference due to the concerns (explained in Section 1.3) with Statistical Analysis Plan and issues in sample size increases and interim analyses.

Study 71754-W-019 did not demonstrate an effect of vigabatrin on infantile spasms, based on the pre-specified primary endpoint, the average percent change in daily spasm frequency, assessed during a predefined two-hour window. When this efficacy variable was based on data collected over the 24-hour window, there appears to be a treatment difference in favor of vigabatrin.

1.2 Brief Overview of Clinical Studies

This submission includes two well-controlled efficacy studies, Study 1-A and Study 71754-W-019, hereafter referred to as Study 1A and Study W019, respectively (The open label study 097WFR03 is not included in this review).

Study 1A was a multicenter, randomized, single-blind study of 14 to 21 days duration comparing two doses (high dose and low dose) of vigabatrin with an open-label, flexible dosing, long-term follow-up in subjects younger than 2 years of age with new onset infantile spasms (IS). Investigators were aware of treatment assignments while caregivers and non-investigator electroencephalographers were blinded. Two hundred and twenty-seven (227) subjects were enrolled into the study from 9 sites in the United States.

Study 1A was comprised of two phases. During the initial controlled phase, subjects were randomized to receive either low-dose (18 to 36mg/kg/day) or high-dose (100 to 148mg/kg/day) vigabatrin in a single-blind manner for 14 to 21 days. Study drug was titrated over 7 days, followed by a constant dose for 7 days. If the subject became spasm-free on or before day 14, another 7 days of constant dose was administered. The second phase was an open-label, dose-ranging, long-term follow-up (up to 3 years).

Study W019 was a randomized, double-blind, placebo-controlled, parallel group study, with an open follow-up, to investigate the safety and efficacy of vigabatrin monotherapy in children (up to the age of 18 months) with infantile spasms. This study enrolled 40 subjects from seven European countries (UK, Canada, France, Netherlands, Finland, Hungary and Serbia).

Study W019 was designed with 3 phases. Phase 1 was a 2 to 3 day pretreatment period. Subjects successfully completing this baseline period were then randomized to placebo or vigabatrin. The second phase was a 5 day double-blind period, during which subjects initially received a dose of 50mg/kg/day vigabatrin or placebo. If the spasms continued, the patients were titrated to a maximum of 150mg/kg/day. At the end of the double-blind phase, subjects entered phase 3, a 6-month open evaluation period of vigabatrin treatment.

1.3 Statistical Issues and Findings

1.3.1 STUDY 1A

Study 1A was sponsored by the Vigabatrin Infantile Spasm (IS) Study Group (VISSG), an unincorporated association of physicians and medical researchers dedicated to the study of IS. The 1A clinical study was conducted under an investigator-sponsored IND (47,707) beginning in January 1996. There was no industry sponsor involved in the conduct of this study, although Aventis Pharmaceuticals did provide a grant to Dr. Roy Elterman in the amount of $144,500.00 on March 17, 2000 to cover certain costs. Aventis also provided vigabatrin clinical study supplies for study 1A at no cost to the 9 participating VISSG investigators. Ovation Pharmaceuticals acquired an exclusive license to the Study 1A data per an agreement with Dr. Roy Elterman in April, 2002. Subsequently, Ovation acquired the North American rights to vigabatrin from Aventis in March 2004. It was only after this latter acquisition that Ovation began data monitoring and verification at the VISSG study sites.

The primary efficacy endpoint was the proportion of subjects achieving spasm cessation for 7 consecutive days beginning within the first 14 days of therapy and confirmed by caregiver assessment and via CCTV EEG monitoring within 3 days of the seventh day of spasm freedom. It was analyzed by Chi-square test to compare the proportions of subjects in the high- and low-dose vigabatrin treatment groups who were free of spasms.

Totally, 227 subjects were enrolled into the study. The first subject enrolled on January 22, 1996 and the last subject completed the study on April 2, 2002. Three analyses were performed with the data collection cut-off date May 31, 1997, February 28, 1999 and April 02, 2002.

Specifically, for the final analysis, 221 subjects were analyzed for efficacy (114 received low-dose vigabatrin and 107 received high-dose vigabatrin). Primary efficacy analysis showed that 11% (25/221) of the subjects were spasm-free: 16% (17/107) of the subjects in the high-dose treatment group and 7% (8/114) of subjects in the low-dose treatment group. The difference between treatment groups was statistically significant (Chi-square test, p=0.0375).

Based on the primary efficacy results, it appears that there is a positive signal of treatment effect of vigabatrin for subjects with new onset infantile spasm. However, it is very difficult to make sound statistical inference due to concerns in Statistical Analysis Plan and issues in sample size increases and interim analyses.

Statistical Analysis Plan

In the Clinical Study Report, the sponsor states that, the final data analysis was in accordance with the Statistical Analysis Plan (SAP) included as Appendix 16.1.15. In the response to the Agency's request, the sponsor states that this SAP was signed-off in October 2004 and not submitted to IND 47, 707 as the IND had been placed on inactive status prior to the creation of the SAP; the sponsor also states that Dr. Roy Elterman verified for Ovation that Aventis did not

develop an SAP for Study 1A, but Drs. Elterman and Shields included statistical methods in both the first and second interim Clinical Study Report that were used in efficacy analyses. However, it is not clear to this reviewer what impact of the first and second interim analysis was on the development of this SAP (i.e., Appendix 16.1.15) and on the final analysis.

Issues in Sample Size Increases

According to the Clinical Study Report, Study 1A was initially planned as a compassionate use study to allow physicians to distribute study drug while a New Drug Application (NDA) for vigabatrin was under FDA review. According to the original efficacy assumptions, 37-40 subjects needed to be enrolled. The protocol allowed for a maximum of 60 subjects. However, the study was redesigned as a high/low-dose comparative trial and a minimum of 44 subjects were to be enrolled. Furthermore, the sponsor states that, due to a delay in the expected marketing approval, the protocol was amended to include up to 150 subjects and further amended to allow up to 250 subjects. There was no additional power analysis conducted to determine the final two sample size increases; the adjustment was made to allow physicians to continue to administer drug while awaiting FDA approval. From the Clinical Study Report, totally 227 subjects were enrolled to Study 1A. It seems that the sample size for Study 1A was never fixed, and when the study was initiated, there was no pre-specified plan regarding how many subjects were to be enrolled and under what circumstance the sample size was to be increased.

Issues in Interim Analyses

According to the Clinical Study Report, three analyses (two interim analyses and one final analysis) were performed on the collected data. The results of the second interim analysis were published in *Neurology* in 2001. There are three issues associated with interim analyses:

- Firstly, it seems that the two interim analyses were not pre-specified and the p-value for final analysis was not adjusted for the two interim analyses.
- Secondly, the results of the second analysis were published in *Neurology* in October, 2001 and the last subject completed the study in April, 2002. The impact of the publication of the results of this interim analysis on the trial conduct and final analysis is unknown.
- Thirdly, it is not clear whether the participating sites had conducted any type of analyses before the first interim analysis.

1.3.2 STUDY W019

For Study W019, the primary efficacy variable was the average percent change in daily spasm frequency, assessed during a predefined two-hour window, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final two days of the period.

This primary efficacy variable was analyzed for ITT population using ANCOVA with Treatment and Geographical location as factors and Baseline spasm count as covariate. Based on this primary efficacy variable, the results in the two treatment groups are similar, with eight patients

in each group (40% placebo group and 47% vigabatrin group) achieving a greater than 70% improvement (i.e. reduction in spasm frequency), and three patients in each treatment group (15% of placebo and 18% of vigabatrin patients) achieving 40 to 69% improvement during the 2-hour time window. This treatment difference was not statistically significant (p=0.562).

When this efficacy variable was based on data collected over the 24-hour window, there appears to be a treatment difference in favor of vigabatrin. The sponsor explains this is due to the fact that the spasms did not occur at the same intensity every day as expected by the choice of the two hour window; but this is a post hoc analysis.

2 INTRODUCTION

2.1 Overview

Infantile spasms (IS) constitute a rare and refractory type of childhood epilepsy. Subjects with IS frequently have neurological deficits. Mental retardation is present in 70 to 90% of subjects with IS, with the majority of these subjects having severe-to-profound retardation. Mortality rates for infants with IS are high; these rates have been estimated to be 5 to 30%, with 10 to 33% of these deaths occurring before age 3.

The most commonly used therapies for the treatment of IS are ACTH and prednisone. Although a substantive proportion of patients treated with these drugs respond initially, the risk of relapse is high. Other therapies that have been used in efforts to treat IS include sodium valproate, benzodiazepines, and some newer AEDs. However, the efficacy of these agents has not been established. Moreover, clinical experience suggests they are not very effective and can cause significant adverse effects.

Vigabatrin was developed for the treatment of epilepsy and is indicated, in many countries throughout the world, for the treatment of resistant partial epilepsies, with and without secondary generalization, and for the management of infantile spasms (IS). Vigabatrin use has been limited by the occurrence of ophthalmologic abnormalities, including a specific VGB-induced retinal injury [visual field defects (VFD)].

This NDA submission includes two well-controlled efficacy studies, Study 1A and Study W019.

Study 1A was a multicenter, randomized, single-blind study of 14 to 21 days duration comparing two doses (high dose and low dose) of vigabatrin with an open-label, flexible dosing, long-term follow-up in subjects younger than 2 years of age with new onset infantile spasms (IS). Investigators were aware of treatment assignments while caregivers and non-investigator electroencephalographers were blinded. Two hundred and twenty-seven (227) subjects were enrolled into the study from 9 sites in the United States.

Study 1A was comprised of two phases. During the initial controlled phase, subjects were randomized to receive either low-dose (18 to 36mg/kg/day) or high-dose (100 to 148mg/kg/day)

vigabatrin in a single-blind manner for 14 to 21 days. Study drug was titrated over 7 days, followed by a constant dose for 7 days. If the subject became spasm-free on or before day 14, another 7 days of constant dose was administered. The second phase was an open-label, dose-ranging, long-term follow-up (up to 3 years).

Study W019 was a randomized, double-blind, placebo-controlled, parallel group study, with an open follow-up, to investigate the safety and efficacy of vigabatrin monotherapy in children (up to the age of 18 months) with infantile spasms. This study enrolled 40 subjects from seven European countries (UK, Canada, France, Netherlands, Finland, Hungary and Serbia).

Study W019 was designed with 3 phases. Phase 1 was a 2 to 3 day pretreatment period. Subjects successfully completing this baseline period were then randomized to placebo or vigabatrin. The second phase was a 5 day double-blind period, during which subjects initially received a dose of 50mg/kg/day vigabatrin or placebo; if the spasms continued, the patients were titrated to a maximum of 150mg/kg/day. At the end of the double-blind phase, subjects entered phase 3, a 6-month open evaluation period of vigabatrin treatment.

2.2 Data Sources

The sponsor's original electronic submission was stored in the directory of \\Fdswa150\nonectd\N22006\N_000\2007-12-28 of the center's electronic document room.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 PROTOCOL 1A

3.1.1.1 Brief History of Study 1A

Study 1A was sponsored by the Vigabatrin Infantile Spasm (IS) Study Group (VISSG), an unincorporated association of physicians and medical researchers dedicated to the study of IS. The 1A clinical study was conducted under an investigator-sponsored IND (47,707) beginning in January 1996. There was no industry sponsor involved in the conduct of this study, although Aventis Pharmaceuticals did provide a grant to Dr. Roy Elterman in the amount of $144,500.00 on March 17, 2000 to cover certain costs. Aventis also provided vigabatrin clinical study supplies for study 1A at no cost to the 9 participating VISSG investigators. Ovation Pharmaceuticals acquired an exclusive license to the Study 1A data per an agreement with Dr. Roy Elterman in April, 2002. Subsequently, Ovation acquired the North American rights to vigabatrin from Aventis in March 2004. It was only after this latter acquisition that Ovation began data monitoring and verification at the VISSG study sites.

Reviewer Comments:
This brief history is an excerpt from Ovation's response. Since the final Clinical Study Report was provided by Ovation Pharmaceuticals, in this review document, the sponsor and the Clinical Study Report refer to "Ovation Pharmaceuticals" and the final Clinical Study Report by Ovations Pharmaceuticals, respectively.

3.1.1.2 Study Objectives

The objective of this study was to evaluate the safety and efficacy of vigabatrin in children less than 2 years of age with new onset infantile spasm.

3.1.1.3 Study Design

This was a multicenter, randomized, single-blind study of 14 to 21 days duration comparing two doses (high dose and low dose) of vigabatrin with an open-label, flexible dosing, long-term follow-up in subjects with new onset IS. Investigators were aware of treatment assignments while caregivers and non-investigator electroencephalographers were blinded. Two hundred and twenty-seven (227) subjects were enrolled into the study from 9 sites in the United States.

3.1.1.4 Efficacy Measures

The primary endpoint of this study was the proportion of subjects who were free of spasms for 7 consecutive days beginning within the first 14 days of vigabatrin therapy and confirmed by caregiver assessment and via CCTV EEG monitoring within 3 days of the seventh day of spasm freedom.

The secondary efficacy endpoints of the study were to assess spasm freedom without the use of CCTV EEG, based only on caregiver assessment of spasm frequency in response to direct questioning regarding spasm frequency or as recorded in the seizure diary. The endpoints were:

- the proportion of subjects who were free of spasms for 7 consecutive days and remained spasm free for the duration of the study;
- the time to spasm cessation for subjects who were free of spasms for 7 consecutive days and remained spasm free for the duration of the study;
- the proportion of subjects who were free of spasms for 7 consecutive days during the study;
- the time to spasm cessation for subjects who were free of spasms for 7 consecutive days during the study;
- the proportion of subjects classified by etiology who were free of spasms according to the primary efficacy criteria;
- the proportion of subjects classified by etiology who were free of spasms for 7 consecutive days and remained spasm free for the duration of the study;
- the time to spasm cessation by etiology for subjects who were free of spasms for 7 consecutive days and remained spasm free for the duration of the study;

- the proportion of subjects classified by etiology who were free of spasms for 7 consecutive days during the study;
- the time to spasm cessation by etiology for subjects who were free of spasms for 7 consecutive days during the study;
- the proportion of subjects who were free of spasms according to the primary criteria, adjusting for whether or not the subject was taking AEDs at baseline;
- the number of spasm clusters per subject over the course of the study period;
- physician global assessment;
- caregiver global assessment.

3.1.1.5 Statistical Analysis Plan

Reviewer's Comments:

In the Clinical Study Report, the sponsor states that, the final data analysis was in accordance with the Statistical Analysis Plan (SAP) included as Appendix 16.1.15. In the response to the Agency's request, the sponsor states that this SAP was signed-off in October 2004 and not submitted to IND 47, 707 as the IND had been placed on inactive status prior to the creation of the SAP; the sponsor also states that Dr. Roy Elterman verified for Ovation that Aventis did not develop an SAP for Study 1A, but Drs. Elterman and Shields included statistical methods in both the first and second interim Clinical Study Report that were used in efficacy analyses. Table 1 is an excerpt from sponsor's response comparing the determination of responder in primary efficacy analysis and method for primary efficacy analysis.

Table 1 Comparison of Statistical Methods for Study 1A Interim and Final Analyses

Topic	Study 1A Report	Method / Comments
Determination of responder in primary efficacy analysis	First (Elterman/Shields)	CRF check box for spasm free (yes/no) and date and outcome (fixed categories) of EEG.
	Second (Elterman/Shields)	Same as in first interim report.
	Final (Ovation)	Algorithm incorporating CRF check box for spasm free, counts of spasm clusters, dates of visits, and date and outcome (fixed categories) of EEG.
	Summary of differences	Ovation used an algorithm to determine more stringently whether the subject was a responder per the primary criteria.
Method for analysis of primary efficacy analysis	First (Elterman/Shields)	Fisher's exact test
	Second (Elterman/Shields)	Mantel Haenszel chi-square test
	Final (Ovation)	Pearson chi-square test
	Summary of differences	The Aventis analysis in the first interim report used Fisher's exact test to handle small cell counts in the analysis by etiology. It is surmised that for consistency the same test was also used for the primary efficacy analysis. It is not known why the analysis in the second Aventis report used the Mantel Haenszel chi-square; possibly larger sample sizes accommodated the asymptotic test. The Ovation analysis had a larger sample size and number of responders, so that the Pearson chi-square test provided a valid inferential method. There is very little difference between the Mantel-Haenszel and Pearson chi-square statistic.

Source: Sponsor's Response on June 18, 2008

The following analysis methods for primary and secondary endpoints as well as the selected changes in the planned analysis were excerpted from the Clinical Study Report and the available Statistical Analysis Plan (Appendix 16.1.15 of the Clinical Study Report).

Primary Efficacy Analysis

The primary endpoint of this study was the proportion of subjects who were free of spasms for 7 consecutive days beginning within the first 14 days of vigabatrin therapy and confirmed by caregiver assessment and via CCTV EEG monitoring within 3 days of the seventh day of spasm freedom. This primary endpoint was analyzed using a Chi-square test on modified ITT population.

Secondary Efficacy Analyses

Chi-square tests, logistic regression, Kaplan-Meier estimates, negative binomial regression, and repeated measures analysis of variance were used to analyze secondary endpoints.

Changes in the Planned Analysis (Selected)

In the approved statistical analysis plan for the assessment of the primary efficacy endpoint, subjects were considered responders if the subject became spasm free on or before day 21 after randomization. This was based on the criterion that subjects must be spasm free for 7 consecutive days beginning within the first 14 days of treatment (e.g., 14 days plus 7 days). However, the last day a subject may be spasm free and still be considered a responder was actually day 20 after randomization (e.g., day 14 is the first day of the 7 consecutive day period of spasm freedom). As a result, a subject should have been considered a responder only if he/she became spasm free on or before day 20 after randomization. The analysis was conducted according to these corrected criteria.

Following approval of the statistical analysis plan, it was decided that due to the number of missing dates of last spasm, for the primary and secondary efficacy analysis, when a subject was designated as spasm free and a date of last spasm was not provided, visit date minus 7 would be used as a proxy for date of last spasm (i.e. visit date would be considered the 7th day of spasm freedom). Additionally, for the primary, secondary and ad hoc analysis, if the response to the question “Is patient infantile spasms free (by criteria)?” was “no” or not answered and the number of clusters since last visit was equal to 0 then the subject would be considered spasm free by criteria.

Reviewer’s Comments:

This reviewer asked the sponsor to provide a sensitivity analysis for the aforementioned method for the primary efficacy analysis. The sponsor’s response states that a sensitivity analysis for the method described above (if the response to the question “Is patient spasms free by primary criteria?" was "no" or not answered and the number of clusters since last visit was equal to 0 then the subject would be considered "NOT spasm free”) demonstrates no impact on the primary endpoint results for Study 1A. There were no additional subjects considered spasm free using the criteria of "Is patient infantile spasms free (by criteria)" with "no" or not answered and the number of clusters since last visit was equal to 0”.

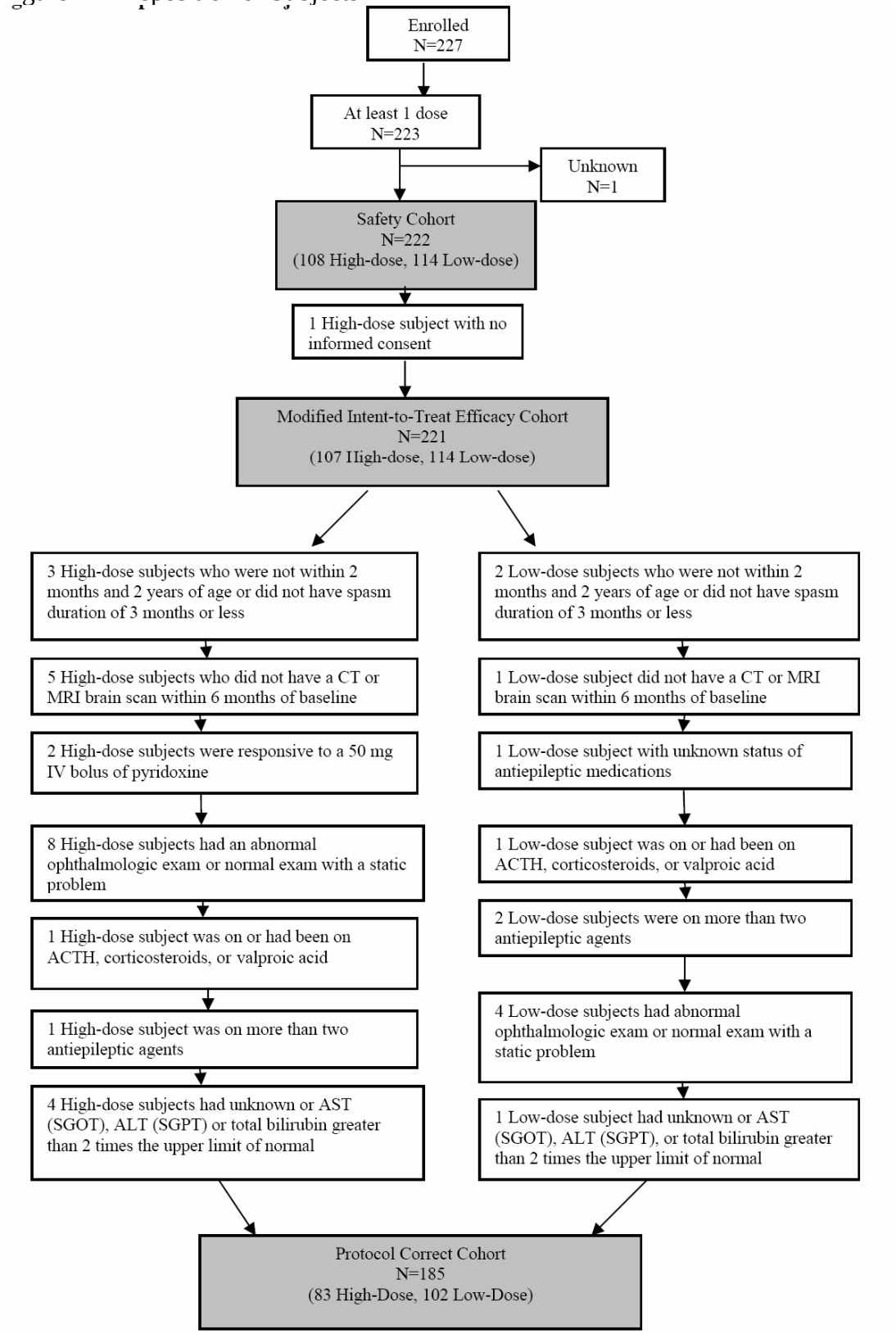
3.1.1.6 Patient Disposition and Demographic Characteristics

Patient Disposition

Two hundred and twenty-seven (227) subjects were randomized between January 22, 1996 and August 14, 2001. Figure 1 shows the disposition of these subjects. One of the 227 subjects was erroneously randomized and never officially enrolled. Of the 226 enrolled subjects, one subject became spasm free before the first visit and did not receive study drug, and two other subjects had no record of receiving vigabatrin. Of the 223 subjects that received at least one dose of study drug, the data for 1 subject did not include a treatment arm or enough information to determine a dose group, and thus the subject was removed from the analyses.

The safety cohort of subjects was made up of 222 subjects that were randomized and received at least 1 dose of vigabatrin (108 high-dose and 114 low-dose). Of these subjects, one high-dose subject did not have an informed consent. Therefore, 221 subjects met the criteria of the modified ITT cohort (107 high-dose and 114 low-dose) that was used for the efficacy analysis in this clinical study report.

Figure 1 Disposition of Subjects



Source: Figure 10-1 of sponsor's Clinical Study Report

Demographic Characteristics

Baseline characteristics for modified ITT population are summarized in Table 2.

Table 2 Baseline Characteristics

Characteristic	Statistic/ Category	High-dose (N=107)	Low-dose (N=114)	Total (N=221)
Age (yrs)[1]	N	102	112	214
	Mean±SD	0.6 ± 0.3	0.6 ± 0.3	0.6 ± 0.3
	Range	0.1 − 1.7	0.1 − 1.7	0.1 − 1.7
	Median	0.6	0.6	0.6
Gender	Male	45 (42.1)	63 (55.3)	108 (48.9)
	Female	61 (57.0)	50 (43.9)	111 (50.2)
	Missing	1 (0.9)	1 (0.9)	2 (0.9)
Race	African-American/Black	15 (14.0)	11 (9.7)	26 (11.8)
	Asian-American	3 (2.8)	0 (0)	3 (1.4)
	Caucasian/White	76 (71.0)	84 (73.7)	160 (72.4)
	Other	13 (12.2)	19 (16.7)	32 (14.5)
Weight (kg)[1]	N	106	112	218
	Mean±SD	7.9 ± 2.1	8.0 ± 2.0	8.0 ± 2.0
	Range	4.0 − 15.0	3.7 − 13.6	3.7 − 15.0
	Median	7.7	8.0	7.8
Etiology	Cryptogenic	27 (25.2)	30 (26.3)	57 (25.8)
	Symptomatic-Other	60 (56.1)	66 (57.9)	126 (57.0)
	Symptomatic-Tuberous Sclerosis	20 (18.7)	18 (15.8)	38 (17.2)

Source: Excerpt from Table 11.2a of sponsor's Clinical Study Report

The percentages of male subjects were 42% and 55% for high dose and low dose, respectively. With respect to age, race, weight and etiology, the treatment groups appeared generally similar.

3.1.1.7 Sponsor's Primary Efficacy Results

The primary efficacy analysis of this study compared the proportions of subjects in the high- and low-dose vigabatrin treatment groups who were free of spasms by both caregiver assessment and CCTV EEG confirmation within 3 days of the seventh day of spasm freedom. These subjects were considered to be primary responders to vigabatrin therapy. Based on these primary criteria, 11% (25/221) of the subjects were spasm free with CCTV EEG confirmation within 3 days, 16% (17/107) of the subjects in the high-dose treatment group and 7% (8/114) of subjects in the low-dose treatment group. The results are presented in Table 3.

Table 3 Treatment Comparison on Spasm Cessation via Primary Criteria

Treatment	Number (%) of Subjects with Spasm Cessation	Number (%) of Subjects with Spasm Non-Cessation	χ^2 Test Statistic	*P* Value
High-dose (N=107)	17 (15.9)	90 (84.1)		
Low-dose (N=114)	8 (7.0)	106 (93.0)		
			4.33	.0375
Total (N=221)	25 (11.3)	196 (88.7)		

Note: Primary criteria were based on caregiver assessment plus required CCTV EEG confirmation.

Source: Table 11.4a of sponsor's Clinical Study Report

3.1.1.8 Sponsor's Secondary Efficacy Results (Selected)

Spasm Cessation for 7 Consecutive Days and Remained Spasm Free During Study Period via Secondary Criteria

The first secondary efficacy analysis was the comparison of the proportions of subjects in the high- and low-dose vigabatrin treatment groups who were free of spasms for 7 consecutive days and remained spasm free for the duration of the study period based on caregiver assessment (secondary criteria).

In this analysis, 60% (132/221) of the subjects in the modified ITT cohort were spasm free, 68% (73/107) in the high-dose group and 52% (59/114) in the low-dose group. The results are summarized in Table 4.

Table 4 Treatment Comparison on Spasm Cessation for 7 Consecutive Days and Remained Spasm Free During Study Period via Secondary Criteria

Treatment	Number (%) of Subjects with Spasm Cessation N (%)	Number (%) of Subjects with Spasm Non-Cessation N (%)
High-dose (N=107)	73 (68.2)	34 (31.8)
Low-dose (N=114)	59 (51.8)	55 (48.3)
Total (N=221)	132 (59.7)	89 (40.3)

Source: Excerpt from Table 11.4b of sponsor's Clinical Study Report

Spasm Cessation for 7 Consecutive Days during Study Period via Secondary Criteria

The second secondary efficacy analyses was the comparison of the proportions of subjects in the high- and low-dose vigabatrin treatment groups who were spasm free for 7 consecutive days during the study period based on caregiver assessment, allowing for relapse.

In this analysis, 77% (171/221) of the subjects in the modified ITT efficacy cohort were spasm free, 78% (84/107) in the high-dose group and 76% (87/114) in the low-dose group. Table 5 summarizes the results.

Table 5 Treatment Comparison on Spasm Cessation for 7 Consecutive Days during Study Period via Secondary Criteria

Treatment	Number (%) of Subjects with Spasm Cessation	Number (%) of Subjects with Spasm Non-Cessation
High-dose (N=107)	84 (78.5)	23 (21.5)
Low-dose (N=114)	87 (76.3)	27 (23.7)
Total (N=221)	171 (77.4)	50 (22.6)

Source: Excerpt from Table 11.4c of sponsor's Clinical Study Report

3.1.2 PROTOCOL W019

3.1.2.1 Study Objectives

Primary Objective
To determine the safety and efficacy of vigabatrin, as compared to placebo, as the initial monotherapy in children with newly diagnosed and previously untreated infantile spasms.

Secondary Objective (Follow up - Open phase only)
To provide information on the duration of response to treatment by assessing both relapse rate and time to relapse.

3.1.2.2 Study Design

This was a randomized, double-blind, placebo-controlled, parallel group study, with an open follow-up, to investigate the safety and efficacy of vigabatrin monotherapy in children (up to the age of 18 months) with infantile spasms.

Study W019 was designed with 3 phases. Phase 1 was a 2 to 3 day pretreatment period. Subjects successfully completing this baseline period were then randomized to placebo or vigabatrin. The second phase was a 5 day double-blind period, during which subjects initially received a dose of 50mg/kg/day vigabatrin or placebo. If the spasms continued, the patients were titrated to a maximum of 150mg/kg/day. At the end of the double-blind phase, subjects entered phase 3, a 6-month open evaluation period of vigabatrin treatment.

3.1.2.3 Efficacy Measures

Spasm Count
A detailed history of the timing and number of spasms per day was obtained from the parents of each patient to ascertain the point during the day when the majority of spasms occurred for that patient. For each patient, a two-hour intensive monitoring period was then scheduled to coincide with the predicted peak in spasms. During this two-hour period, all spasms were recorded. Although the two-hour sampling time was different for each child, once a child was entered into the study, the sampling times for that individual remained constant throughout the baseline and the double-blind period. For the remainder of the 24-hour period, spasms were recorded as and when they were observed.

The primary efficacy variable was the percent change in the average frequency of spasms, assessed during a predefined two-hour window, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final two days of the period.

The secondary efficacy variables were:

- the average percent change in daily spasm frequency, assessed over the whole 24-hour period, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final two days of the period;

- the average percent change in daily spasm frequency, assessed during a predefined two-hour window, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final day of the period;

- the average percent change in daily spasm frequency, assessed over the whole 24-hour period, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final day of the period;

- the number of patients achieving cessation of spasms on the final day of the double-blind period, as assessed over the whole 24 hour period;

- the average percent change in frequency of clusters assessed during a predefined two-hour window, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final two days of the period;

- the average percent change in frequency of clusters, as assessed over whole 24 hour period, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final two days of the period;

- the average percent change in the duration of clusters from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final two days of the period;

- proportion of patients showing disappearance of hypsarrhythmia on final day of double-blind period;

- investigator's overall assessment of efficacy on final day of double-blind period;

- efficacy (i.e. total cessation, decrease or none/worse) in patients diagnosed as having symptomatic spasms compared with those diagnosed as having cryptogenic spasms on final day of double-blind period as assessed over whole 24-hour period.

3.1.2.4 Statistical Analysis Plan

The primary efficacy variable was the percent change in the average frequency of spasms, assessed during a predefined two-hour window, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final two days of the period. This primary efficacy endpoint (log transformed in analysis) was analyzed using

ANCOVA for ITT population with treatment and geographical location as factors and baseline spasm count as a covariate.

3.1.2.5 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

Forty (40) patients were screened, randomized and included in both the safety and ITT populations. Six patients were excluded from the 'protocol correct' analysis, which therefore included 34 patients (16 vigabatrin and 18 placebo patients). The primary population for determining efficacy was the ITT, the protocol correct analysis was used to confirm the ITT findings. No patients withdrew from the study during the double-blind phase.

Demographic and Baseline Characteristics

The demographic data are summarized in Table 6 and Table 7. The two treatment groups appeared generally similar with respect to demographic characteristics.

Table 6 Demographic Summary at Baseline I (ITT)

	Treatment					
	Placebo		VGB		Total	
	N	%	N	%	N	%
Gender						
male	11	55	8	40	19	48
female	9	45	12	60	21	53
Total	20	100	20	100	40	100
Race						
caucasian	17	85	18	90	35	86
black	1	5	0	0	1	3
mixed	2	10	1	5	3	8
other	0	0	1	5	1	3
Total	20	100	20	100	40	100
Patient Status						
out patient	6	30	7	35	13	33
normally hospitalized	14	70	13	65	27	68
normally institutionalized	0	0	0	0	0	0
Total	20	100	20	100	40	100

Source: Table 5a of sponsor’s Clinical Study Report

Table 7 Demographic Summary at Baseline II (ITT)

	Treatment		
	Placebo	VGB	Total
Age at onset (months)			
n	20	20	40
missing	0	0	0
mean	6	7	6
median	6	6	6
sd	3	3	3
minimum	0	1	0
maximum	11	17	17
Age at study (months)			
n	20	20	40
missing	0	0	0
mean	8	8	8
median	8	7	8
sd	3	4	3
minimum	4	5	4
maximum	17	20	20
Height (cm)			
n	19	19	38
missing	1	1	2
mean	71	68	70
median	72	68	69
sd	8	6	7
maximum	58	57	58
minimum	91	81	91
Weight (kg)			
n	20	20	40
missing	0	0	0
mean	8	8	8
median	8	8	8
sd	2	1	2
minimum	4	5	4
maximum	13	10	13

Source: Table 5b of sponsor's Clinical Study Report

Pre-study clinical characteristics are summarized in Table 8. The two treatment groups appeared generally similar with respect to pre-study clinical characteristics, except epileptic history (three placebo patients (15%) had epileptic history compared to 9 patients (45%) in vigabatrin group.)

Table 8 Clinical Characteristics (ITT)

	Treatment					
	Placebo		VGB		Total	
	N	%	N	%	N	%
Family history of epilepsy/febrile convulsions						
not known	0		1		1	
no	15	75	16	84	31	79
yes	5	25	3	16	8	21
Total	20	100	20	100	40	100
Perinatal complications						
no	11	55	9	45	20	50
yes	9	45	11	55	20	50
Total	20	100	20	100	40	100
Epileptic history						
no	17	85	11	55	28	70
yes	3	15	9	45	12	30
Total	20	100	20	100	40	100
Development status normal						
no	18	90	17	85	35	88
yes	2	10	3	15	5	13
Total	20	100	20	100	40	100
Denver Test						
missing	3		1		4	
normal	2	12	1	5	3	8
suspect	15	88	14	74	29	81
untestable	0	0	4	21	4	11
Total	20	100	20	100	40	100

Source: Table 6 of sponsor's Clinical Study Report

3.1.2.6 Sponsor's Primary Efficacy Results

The primary efficacy variable was the percentage change in the average frequency of spasms as assessed from the two-hour intensive monitoring window, from baseline to the end of the double-blind period, where the end of the double-blind period was defined as the last two days of that treatment period. This primary efficacy variable (log-transformed) was analyzed using ANCOVA for ITT population. This analysis is summarized in Table 9.

The results in the two treatment groups are similar, with eight patients in each group (40% placebo group and 47% vigabatrin group) achieving a greater than 70% improvement (i.e. reduction in spasm frequency), and three patients in each treatment group (15% of placebo and 18% of vigabatrin patients) achieving 40 to 69% improvement during the 2-hour time window. However, in the placebo group eight patients (40%) had no improvement or worsened as compared to four patients (24%) in the vigabatrin group. This treatment difference was not statistically significant (p=0.562).

Table 9 Percentage Change in Average Frequency of Spasms – Double-blind Phase (over Final 2 Days) (ITT)

	% improvement	Treatment: Placebo N	Placebo %	VGB N	VGB %	Total N	Total %	P-value*
2 hour								
	missing	0		3		3		
	>=70	8	40	8	47	16	43	
	40-69	3	15	3	18	6	16	
	1-39	1	5	2	12	3	8	
	<=0	8	40	4	24	12	32	
Total		20	100	20	100	40	100	
#	mean	59.5%		45.6%		$ 0.768		
	95% CI	(30%-117%)		(24%-88%)		(0.305-1.929)		0.562
24 hour								
	>=70	3	15	8	40	11	28	
	40-69	3	15	3	15	6	15	
	1-39	4	20	5	25	9	23	
	<=0	10	50	4	20	14	35	
Total		20	100	20	100	40	100	
#	mean	83.0%		31.1%		$ 0.374		
	95% CI	(43%-159%)		(17%-58%)		(0.155-0.902)		0.030

* Taken from final model from log analyses

The mean and 95% CI's for this primary variable are taken from the final log model over the complete distribution, estimated by $[(nspasm_{78} +1)/(nspasm_{123} +1)] * 100\%$

$ Relative risk with their corresponding CI's of VGB/Placebo from the final log model

Source: Table 13 of sponsor's Clinical Study Report

3.1.2.7 Sponsor's Secondary Efficacy Analyses (Selected)

24-hour Period - Baseline to Final Two Days (Double-blind Phase)

For the 24 hour monitoring window the differences between the treatment groups were greater than for the two-hour window. Eight vigabatrin patients (40%) compared to three placebo patients (15%) reported a greater than 70% improvement and 10 (50%) placebo patients as compared with four (20%) vigabatrin patients having either no improvement or a worsening. The results were presented in Table 9.

Cessation of Spasms (Double-Blind Phase)

The number of patients achieving complete cessation of spasms at the end of the double-blind phase is summarized in Table 10 and Table 11. When cessation of spasm was taken as no spasm at all on the final day of the double-blind period, seven (35%) vigabatrin patients compared to two (10%) placebo patients showed complete cessation of spasms on the final day.

Table 10 Number of Patients with Complete Cessation of Spasms (0 or 1 Spasms) on Final Day in 24-hour Window – Double-blind Phase (ITT)

	Treatment					
Complete cessation*	Placebo		VGB		Total	
	N	%	N	%	N	%
No	17	85	11	55	28	70
Yes	3	15	9	45	12	30
Total	20	100	20	100	40	100

* Includes 3 patients who had 1 isolated spasm as defined in the analysis plan

Source: Excerpt from Table 15a of sponsor's Clinical Study Report

Table 11 Number of Patients with Complete Cessation of Spasms (0 Spasms) on Final Day in 24-hour Window – Double-blind Phase (ITT)

	Treatment					
Complete Cessation*	Placebo		VGB		Total	
	N	%	N	%	N	%
No	18	90	13	65	31	78
Yes	2	10	7	35	9	23
Total	20	100	20	100	40	100

* Here defined as complete absence of spasms

Source: Excerpt from Table 15b of sponsor's Clinical Study Report

3.1.3 REVIEWER'S ANALYSIS/COMMENTS FOR STUDY 1A

This reviewer confirmed the efficacy results presented in this review for Study 1A.

Based on the primary efficacy results, it appears that there is a positive signal of treatment effect of vigabatrin for subjects with new onset infantile spasm. However, it is very difficult to make sound statistical inference due to the concerns with Statistical Analysis Plan and issues in sample size increases and interim analyses; details are elaborated below.

3.1.3.1 Concerns in Statistical Analysis Plan

In the Clinical Study Report, the sponsor states that, the final data analysis was in accordance with the Statistical Analysis Plan (SAP) included as Appendix 16.1.15. In the response to the Agency's request, the sponsor states that this SAP was signed-off in October 2004 and not

submitted to IND 47, 707 as the IND had been placed on inactive status prior to the creation of the SAP; the sponsor also states that Dr. Roy Elterman verified for Ovation that Aventis did not develop an SAP for Study 1A, but Drs. Elterman and Shields included statistical methods in both the first and second interim Clinical Study Report that were used in efficacy analyses. However, it is not clear to this reviewer what impact of the first and second interim analysis was on the development of this SAP (i.e., Appendix 16.1.15) and on the final analysis.

3.1.3.2 Issues in Sample Size Increases

According to the Clinical Study Report, Study 1A was initially planned as a compassionate use study to allow physicians to distribute study drug while a New Drug Application (NDA) for vigabatrin was under FDA review. According to the original efficacy assumptions, 37-40 subjects needed to be enrolled. The protocol allowed for a maximum of 60 subjects. However, the study was redesigned as a high/low-dose comparative trial and a minimum of 44 subjects were to be enrolled. Furthermore, the sponsor states that, due to a delay in the expected marketing approval, the protocol was amended to include up to 150 subjects and further amended to allow up to 250 subjects. There was no additional power analysis conducted to determine the final two increases in sample size; the adjustment was made to allow physicians to continue to administer drug while awaiting FDA approval. The dates for original protocol and subsequent amendments are listed below:

- Original protocol: 8/9/1995
- Amendment 1: 9/27/1995
- Amendment 2: 11/14/1995
- Amendment 3: 6/14/1996
- Amendment 4: 1/27/1997 (sample size was increased to 150 subjects)
- Amendment 5: 10/3/2000 (sample size was increased to 250 subjects)
- Amendment 5': 10/3/2000, version date is 1/26/2001

Based on the Clinical Study Report, totally 227 subjects were enrolled to Study 1A.

It seems that the sample size for Study 1A was never fixed, and when the study was initiated, there was no pre-specified plan regarding how many subjects were to be enrolled and under what circumstance the sample size was to be increased.

3.1.3.3 Issues in Interim Analyses

According to the Clinical Study Report, three analyses were performed on the collected data. The sponsor states that the first analysis was performed in response to the FDA's request for information on pediatric use of vigabatrin to be included in the proposed package insert. A second analysis, requested by Aventis Pharmaceuticals Inc, was performed to fulfill a request from the FDA. The results of this analysis were published in *Neurology* in 2001. The following table summarizes the results of the two interim analyses and final analysis by the sponsor, as well as the results for the first 40 and 44 subjects by this reviewer.

Table 12 Summary of Analyses for Study 1A

	Reviewer's Analysis		Sponsor's Analysis			
	First 40	First 44	1st Interim	2nd Interim (a)	2nd Interim (b)[2]	Final
Cut-off date	9/11/1996[1]	9/27/1996[1]	5/31/1997[4]	2/28/1999	2/28/1999	4/2/2002
No. of subjects randomized	-	-	89	179	179	227
No. of Subjects Included in Analysis	40 MITT	44 MITT	62 Efficacy Evaluable	142 Efficacy Evaluable	142 Efficacy Evaluable	221 (MITT)
Responder rate for low dose	0% (0/21)	0% (0/22)	15% (5/33)	11% (8/75)	5% (4/75)	7 % (8/114)
Responder rate for high dose	11% (2/19)	14% (3/22)	28% (8/29)	36% (24/67)	15% (10/67)	16% (17/107)
P-value[3]	0.2192	0.2326	0.349	P<0.001	P=0.0883	0.0375[5]

Source: Reviewer's Analysis and sponsor's Reports.

[1]: The 40th and 44th MITT subject were enrolled into the study on September 11, 1996 and September 27, 1996, respectively.

[2:] The number of responders were provided by the sponsor upon request (please see the paragraph below for details); this reviewer used Fisher's Exact test to generate the p-value.

[3]: P-values are nominal p-values;
Fisher's Exact test were used by this review to analyze the data for the first 40 and 44 subjects and the 2nd interim analysis (b), due to some small cell counts.
The sponsor used Fisher's Exact Test, Mantel Haenszel Chi-square test, and Pearson Chi-square test for the 1st interim analysis, the 2nd interim analysis (a) and the final analysis, respectively.

[4]: Interim analysis report indicates the cut-off date was June 30, 1997.

[5]: The p-value is 0.0544, based on Fisher's Exact Test.

The results for the second interim analysis (a) was excerpted from sponsor's 2nd interim analysis report dated 1 Feb 2000. However, since noticing that the number of responders for high dose group was decreased from 24 to 17 from the second interim analysis (a) to the final analysis, this reviewer raised this question to the sponsor and the sponsor states that the definition of a responder is the same but for the final analysis the responder definition was applied in a more conservative manner (please refer to Table 1 for details). This reviewer asked the sponsor to re-produce the results of the responder rate for the second interim analysis according to this "more conservative manner". The results are presented as 2nd Interim Analysis (b), in which the sponsor provided the number of responders by dose group and this reviewer used Fisher's Exact Test to generate the p-value.

There are three issues associated with interim analyses.

Firstly, it seems that the two interim analyses were not pre-specified and the p-value for the final analysis was not adjusted for the two interim analyses.

Secondly, the results of the second analysis were published in *Neurology* in October, 2001 and the last subject completed the study in April, 2002. The impact of the publication of the results of this interim analysis on the trial conduct and final analysis is unknown.

Thirdly, it is not clear whether or not any type of analysis was conducted for this study before the first interim analysis. By the time of Protocol Amendment 4 in which the sample size was increased from 44 to 150, 64 subjects had been enrolled into the study. This means, before Amendment 4, Study 1A had enrolled more subjects than the planned sample size of 44 subjects. However, it is not clear whether the sponsor conducted any type of analysis before Amendment 4 and first interim analysis. Below is sponsor's response to this reviewer's question "Before the first interim analysis, was there any type of analysis conducted on the data for Study 1A?"

> *Ovation conferred with Dr. Elterman and he confirmed that there was no compilation of results from the participating sites or analyses until issuance of the first interim analysis (i.e. first interim clinical study report).*

From this response, it is still not clear whether the participating sites had conducted any type of analyses before the first interim analysis.

3.1.4 REVIEWER'S ANALYSIS/COMMENTS FOR STUDY W019

This reviewer confirmed the efficacy results presented in this review for Study W019.

In Study W019, the primary efficacy variable was the percentage change in the average frequency of spasms as assessed from the two-hour intensive monitoring window, from baseline to the end of the double-blind period, where the end of the double-blind period was defined as the last two days of that treatment period. For this pre-specified primary endpoint, the difference between the vigabatrin group and placebo group was not statistically significant (p=0.562). When this efficacy variable was based on data collected over the 24-hour window, there appears to be a treatment difference in favor of vigabatrin. The sponsor explains this is due to the fact that the spasms did not occur at the same intensity every day as expected by the choice of the two hour window; but this is a post hoc analysis.

3.2 Evaluation of Safety

Please read Drs. Gerard Boehm's and Ronald Farkas' review for safety assessment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

4.1.1 STUDY 1A

Responder rate is summarized by subgroups and treatment group in Table 13.

Table 13 Responder Rate by Subgroups and Treatment Group

Subgroup	High-Dose Vagabatrin	Low-Dose Vagabatrin
Age <=0.6 yrs	17% (9/52)	14% (8/59)
Age>0.6 yrs	13% (7/52)	0% (0/55)
Male	16% (7/45)	3% (2/63)
Female	16% (10/61)	12% (6/50)
White	18% (14/76)	8% (7/84)
Black	7% (1/15)	9% (1/11)
Asian	33% (1/3)	0% (0/0)
Other	8% (1/13)	0% (0/19)

Source: Reviewer's Analysis

It appears that the point estimates of responder rate were in the same direction across the patient subgroups investigated.

4.1.2 STUDY W019

Study W019 did not demonstrate an effect of vigabatrin on infantile spasms, based on the pre-specified primary endpoint. Therefore, the subgroup analysis was omitted.

4.2 Other Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 STUDY 1A

Study 1A was sponsored by the Vigabatrin Infantile Spasm (IS) Study Group (VISSG), an unincorporated association of physicians and medical researchers dedicated to the study of IS. The 1A clinical study was conducted under an investigator-sponsored IND (47,707) beginning in January 1996. There was no industry sponsor involved in the conduct of this study, although Aventis Pharmaceuticals did provide a grant to Dr. Roy Elterman in the amount of $144,500.00 on March 17, 2000 to cover certain costs. Aventis also provided vigabatrin clinical study supplies for study 1A at no cost to the 9 participating VISSG investigators. Ovation Pharmaceuticals acquired an exclusive license to the Study 1A data per an agreement with Dr. Roy Elterman in April, 2002. Subsequently, Ovation acquired the North American rights to vigabatrin from Aventis in March 2004. It was only after this latter acquisition that Ovation began data monitoring and verification at the VISSG study sites.

The primary efficacy endpoint was the proportion of subjects achieving spasm cessation for 7 consecutive days beginning within the first 14 days of therapy and confirmed by caregiver assessment and via CCTV EEG monitoring within 3 days of the seventh day of spasm freedom. It was analyzed by Chi-square test to compare the proportions of subjects in the high- and low-dose vigabatrin treatment groups who were free of spasms.

Totally, 227 subjects were enrolled into the study. The first subject enrolled on January 22, 1996 and the last subject completed the study on April 2, 2002. Three analyses were performed with the data collection cut-off date May 31, 1997, February 28, 1999 and April 02, 2002.

Specifically, for the final analysis, 221 subjects were analyzed for efficacy (114 received low-dose vigabatrin and 107 received high-dose vigabatrin). Primary efficacy analysis showed that 11% (25/221) of the subjects were spasm-free: 16% (17/107) of the subjects in the high-dose treatment group and 7% (8/114) of subjects in the low-dose treatment group. The difference between treatment groups was statistically significant (Chi-square test, p=0.0375).

Based on the primary efficacy results, it appears that there is a positive signal of treatment effect of vigabatrin for subjects with new onset infantile spasm. However, it is very difficult to make sound statistical inference due to concerns in Statistical Analysis Plan and issues in sample size increases and interim analyses.

Statistical Analysis Plan

In the Clinical Study Report, the sponsor states that, the final data analysis was in accordance with the Statistical Analysis Plan (SAP) included as Appendix 16.1.15. In the response to the Agency's request, the sponsor states that this SAP was signed-off in October 2004 and not submitted to IND 47, 707 as the IND had been placed on inactive status prior to the creation of the SAP. The sponsor also states that Dr. Roy Elterman verified for Ovation that Aventis did not

develop an SAP for Study 1A, but Drs. Elterman and Shields included statistical methods in both the first and second interim Clinical Study Report that were used in efficacy analyses. However, it is not clear to this reviewer what impact of the first and second interim analysis was on the development of this SAP (i.e., Appendix 16.1.15) and on the final analysis.

Issues in Sample Size Increases

According to the Clinical Study Report, Study 1A was initially planned as a compassionate use study to allow physicians to distribute study drug while a New Drug Application (NDA) for vigabatrin was under FDA review. According to the original efficacy assumptions, 37-40 subjects needed to be enrolled. The protocol allowed for a maximum of 60 subjects. However, the study was redesigned as a high/low-dose comparative trial and a minimum of 44 subjects were to be enrolled. Furthermore, the sponsor states that, due to a delay in the expected marketing approval, the protocol was amended to include up to 150 subjects and further amended to allow up to 250 subjects. There was no additional power analysis conducted to determine the final two sample size increases; the adjustment was made to allow physicians to continue to administer drug while awaiting FDA approval. From the Clinical Study Report, totally 227 subjects were enrolled to Study 1A. It seems that the sample size for Study 1A was never fixed, and when the study was initiated, there was no pre-specified plan regarding how many subjects were to be enrolled and under what circumstance the sample size was to be increased.

Issues in Interim Analyses

According to the Clinical Study Report, three analyses (two interim analyses and one final analysis) were performed on the collected data. The results of the second interim analysis were published in *Neurology* in 2001. There are three issues associated with interim analyses:

- Firstly, it seems that the two interim analyses were not pre-specified and the p-value for final analysis was not adjusted for the two interim analyses.
- Secondly, the results of the second analysis were published in *Neurology* in October, 2001 and the last subject completed the study in April, 2002. The impact of the publication of the results of this interim analysis on the trial conduct and final analysis is unknown.
- Thirdly, it is not clear whether the participating sites had conducted any type of analyses before the first interim analysis.

5.1.2 STUDY W019

For Study W019, the primary efficacy variable was the average percent change in daily spasm frequency, assessed during a predefined two-hour window, from baseline to the end of the double-blind study period, where end of the double-blind study period is defined as the final two days of the period.

This primary efficacy variable was analyzed for ITT population using ANCOVA with Treatment and Geographical location as factors and Baseline spasm count as covariate. Based on this primary efficacy variable, the results in the two treatment groups are similar, with eight patients in each group (40% placebo group and 47% vigabatrin group) achieving a greater than 70%

improvement (i.e. reduction in spasm frequency), and three patients in each treatment group (15% of placebo and 18% of vigabatrin patients) achieving 40 to 69% improvement during the 2-hour time window. This treatment difference was not statistically significant (p=0.562).

When this efficacy variable was based on data collected over the 24-hour window, there appears to be a treatment difference in favor of vigabatrin. The sponsor explains this is due to the fact that the spasms did not occur at the same intensity every day as expected by the choice of the two hour window; but this is a post hoc analysis.

5.2 Conclusions and Recommendations

For Study 1-A, based on the primary efficacy results, it appears that there is a positive signal of treatment effect of vigabatrin for subjects with new onset infantile spasm. However, it is very difficult to make sound statistical inference due to the concerns (explained in Section 1.3) with Statistical Analysis Plan and issues in sample size increases and interim analyses.

Study 71754-W-019 did not demonstrate an effect of vigabatrin on infantile spasms, based on the pre-specified primary endpoint, the average percent change in daily spasm frequency, assessed during a predefined two-hour window. When this efficacy variable was based on data collected over the 24-hour window, there appears to be a treatment difference in favor of vigabatrin.

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