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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biostatistics

Statistical Review and Evaluation
CLINICAL STUDIES

NDA/Serial Number:	NDA 20427 / S-011 & NDA 22006 / S-012 (Efficacy Supplements)
Drug Name:	Sabril® (vigabatrin)
Indication(s):	Pediatric Refractory Complex Partial Seizures
Applicant:	Lundbeck, Inc.
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Keywords: *Clinical studies, NDA review, statistical review, endpoint analysi/, multi-center, rank ANCOVA*

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1. EXECUTIVE SUMMARY

1.1. CONCLUSIONS AND RECOMMENDATIONS

Study 118 demonstrated that VGB 100 mg/kg/day was statistically significantly superior to placebo based on the change of the patient mean monthly frequency of CPS plus partial seizures secondarily generalized at the end of study compared to baseline (p-value = 0.0142). VGB 20 mg/kg/day and 60 mg/kg/day were not statistically significantly different from placebo (p-value = 0.8622 and 0.8140, respectively). Since a few patients (i.e., one or two patients) were randomized to each treatment group within each study site, no comparison within study sites was made in Study 118. The descriptive results of the post-hoc interim analyses of CPEN study also support that a 6-month of treatment with VGB is adequate to prevent recurrence of spasms after cessation of treatment.

In conclusion, the efficacy evidence supports the use of VGB as adjunctive therapy for pediatric patients 10 to 17 years of age with CPS who have inadequately responded to alternative treatments.

1.2. BRIEF OVERVIEW OF REVIEWED CLINICAL STUDIES

Study 118 was a multicenter, randomized, double-blind, placebo-controlled, parallel group study in pediatric patients between the ages of 3 and 16 years, and was conducted with a 10-week baseline phase, a 6-week titration phase, and a 8-week maintenance phase. Enrollment into the study was discontinued early due to an administrative reason (i.e., based on Amendment#5, and it is discussed in the review); and approximately 63% of the protocol-specified total enrollment of 200 patients was achieved in 25 study sites within USA. That is, there were 126 patients randomized to treatment groups [32 placebo (PLB), 30 vigabatrin (VGB) 20 mg/kg/day, 32 VGB 60 mg/kg/day, and 32 VGB 100 mg/kg/day] and 108 patients completed the study (28 PLB, 26 VGB 20 mg/kg/day, 27 VGB 60 mg/kg/day, and 27 VGB 100 mg/kg/day).

The primary objective of this study was to determine the efficacy of VGB at doses of 20, 60, and 100 mg/kg/day compared to placebo when added to currently prescribed antiepileptic drug (AED) in pediatric patients having uncontrolled complex partial seizures with or without secondary generalization. The primary efficacy endpoint was the change in mean monthly (i.e., 28 days) frequency of complex partial seizures plus partial seizures secondarily generalized during the 8 weeks of the maintenance phase compared to the last 8 weeks of the baseline phase.

The primary efficacy analyses were based on the Intent-to-treat (ITT) patient population. The ITT population included any patient taking at least one dose of study medication and having any post-baseline efficacy data. The primary efficacy parameter was the change in patient mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized (CPS = IB + IC). The rank of mean monthly frequency of CPS was analyzed using a Rank Analysis of Covariance (ANCOVA) model with ranked baseline CPS as the covariate and factors for treatment and investigative site.

Dealings with Dropouts / Missing Data

For the primary efficacy end point, the monthly seizure rate during the maintenance period was calculated over the number of days with non-missing seizure data in the maintenance period. No explicit imputation of missing data was made, but this approach was implicitly equivalent to using the average seizure rate during the days with non-missing seizure data to impute the seizure rate for days after study discontinuation and days with missing seizure data. As a sensitivity analysis of the primary end, the sponsor analyzed the percent reduction in drop seizures from baseline to the first 4 weeks, middle 4 weeks, and last 4 weeks of the maintenance period.

CPEN Study

The CPEN study was a multicenter, randomized, double-blind, parallel-group, placebo-controlled trial to assess the improvement of developmental outcome of children treated for infantile spasms (IS) with add-on flunarizine or placebo.

A statistical analysis plan (SAP) for a post-hoc interim analysis for the CPEN study was created. The SAP was a descriptive type statistical analysis plan. There was no statement of any statistical hypothesis testing in the SAP. The primary objective of the interim analysis was to evaluate the relapse rate of VGB responders following discontinuation of VGB treatment for a duration of 6 months. VGB responders were defined as patients with spasm cessation (evaluated by the Week 4 visit Spasm Diary), the absence of hypsarrhythmic EEG pattern (evaluated by Week 4 visit EEG), and who are treated with VGB for a duration of 6 months. Relapse was defined as return of spasms or hypsarrhythmias. The relapse evaluation was restricted to the time-span between Month 6 visit and Month 12 visit – the first 6 months following discontinuation of VGB – as confirmed by the 12 month visit EEG.

1.3. STATISTICAL ISSUES AND FINDINGS

Dealing with missing data in Seizure frequency trials is a statistical challenge. The primary efficacy end point is often defined as the weekly/monthly seizure rate during the double-blind period / maintenance period, and the rate is calculated over the number of days with non-missing seizure data in the maintenance period. Suppose a subject is dropped out from the trial after 4 days of randomization, his/her weekly/monthly rate of seizure frequency will be calculated based on the available data for the four days. This approach of dealing with missing data may not be different from the last observation carried forward (LOCF) approach. Since the seizure data are count-data and the primary endpoint is the weekly/monthly rate of seizure, the other approaches (e.g., MMRM approach) are not appropriate to analyze such data. A research on the missing data in presence rate of seizure per week/month is necessary to carry out.

2. INTRODUCTION

2.1 OVERVIEW

The sponsor has submitted a Supplemental New Drug Application (sNDA) to respond to an amended Pediatric Written Request (PWR) (Amendment # 1) issued by the Agency on 18 April 2013 for the SABRIL New Drug Application (NDA). SABRIL (vigabatrin) was approved on August 21, 2009 for the treatment of refractory complex partial seizures in adults.

The sponsor has submitted several studies in this sNDA. In the filing meeting, it is decided that two studies (Study 118 and CPEN Study) need to be considered in the statistical review of this sNDA. In this review, the CPEN Study will be reviewed after reviewing the study 118. Study 118 was a multicenter, randomized, double-blind, placebo-controlled, parallel group study in pediatric patients between the ages of 3 and 16 years, and was conducted with a 10-week baseline phase, a 6-week titration phase, and a 8-week maintenance phase.

Enrollment into the study was discontinued early due to an administrative reason. The sponsor made an amendment#5 for the enrollment discontinuation. The amendment#5 was occurred 1 year and 11 months after patient enrollment was initiated. Under the amendment#5, dated march 27, 1997, patient enrollment was stopped on March 31, 1997 due to a minor stability problem with the blinded study medication in the dose adjustment phase of long-term Open-Label study 0201. All patients who completed Visit 1 of Study 0118 prior to March 1, 1997 completed the study as it was written prior to the amendment#5.

Based on previous vigabatrin studies, it was assumed that 15% of the placebo patients versus 40% of the vigabatrin patients would be classified as responders (≥ 50% reduction in complex partial seizures), and under these response rates, 50 patients per treatment group (total 200 patients) were necessary to provide 80% power to declare significance at alpha=0.05 using a two-tailed test. However, due to the amendment#5, approximately 63% of the protocol-specified total enrollment of 200 patients was achieved from 25 study sites within USA. There were 126 patients randomized to treatment (32 placebo (PLB), 30 vigabatrin (VGB) 20 mg/kg/day, 32 VGB 60 mg/kg/day, and 32 VGB 100 mg/kg/day) and 108 patients completed the study (28 PLB, 26 VGB 20 mg/kg/day, 27 VGB 60 mg/kg/day, and 27 VGB 100 mg/kg/day). Table 1 lists the description of the study.

The primary objective of this study was to determine the efficacy of VGB at doses of 20, 60, and 100 mg/kg/day compared to placebo when added to currently prescribed antiepileptic drug (AED) in pediatric patients having uncontrolled complex partial seizures with or without secondary generalization. The primary efficacy endpoint was the change in mean monthly (28 days) frequency of complex partial seizures plus partial seizures secondarily generalized during the 8 weeks of the maintenance phase compared to the last 8 weeks of the baseline phase.

Table 1. Description of Double-Blind Clinical Efficacy Study 118

Study ID/ Type of Study/	Objectives(s) of the Study	Study Design & Type of Control	Test Product(s); Dosage Regimen; Route of Administration	No of Subs	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
118/ Efficacy and safety	To determine the efficacy and safety of VGB at doses of 20, 60, and 100 mg/kg/day when compared to placebo when added to currently prescribed AED therapy in pediatric patients having uncontrolled complex partial seizures with or without secondary generalization.	MC, R, DB, parallel, with 10-week Baseline Phase, 6-week Titration Phase, and 8-week Maintenance Phase	Placebo solution VGB solution 20 mg/kg/day VGB solution 60 mg/kg/day VGB solution 100 mg/kg/day Route: Oral	32 30 32 32	Pediatric patients with uncontrolled complex partial seizures with or without secondary generalization between the ages of 3 and 16, inclusive.	14 weeks (6 weeks titration and 8 weeks maintenance)

Source: Study report

The secondary efficacy parameters were the number of therapeutic successes, change in the patient mean monthly frequency of seizure episodes by seizure type (i.e., simple partial [IA], complex partial [IB], partial with secondary generalization [IC]), the change in patient mean monthly frequency of seizure-free days, global evaluation of efficacy by the investigator and caregiver, and the mean proportion of complex partial seizures (lB) that secondarily generalize (IC).

The primary efficacy analyses were based on the Intent-to-treat (ITT) patient population. The ITT population included any patient taking at least one dose of study medication and having any post-baseline efficacy data. The primary efficacy parameter was the change in patient mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized (CPS = IB + IC). The rank of mean monthly frequency of CPS was analyzed using a Rank Analysis of Covariance (ANCOVA) model with ranked baseline CPS as the covariate and factors for treatment and investigative site.

The proportion of therapeutic successes was tested for treatment group differences using a Cochran Mantel Haenszel test, adjusting for site differences. Analyses of simple partial seizures, complex partial seizures, and partial seizures with secondary generalization were conducted using the same model used to analyze patient mean monthly frequency of CPS. Analysis of the mean proportion of complex partial seizures (lB) that secondarily generalize (IC) was conducted using the ANCOVA model on the untransformed data.

In the study protocol, there was no statement regarding multiplicity adjustment of testing the doses. Subgroup analyses on the primary efficacy measure would be done on age, race, and gender.

Dealings with Dropouts / Missing Data

For the primary efficacy end point, the monthly frequency of CPS rate during the maintenance period was calculated over the number of days with non-missing seizure data in the maintenance period. No explicit imputation of missing data was made, but this approach was implicitly equivalent to using the average seizure rate during the days with non-missing seizure data to impute the seizure rate for days after study discontinuation and days with missing seizure data. As a sensitivity analysis of the primary endpoint, the sponsor analyzed the percent reduction in CPS from baseline to the first 4 weeks, middle 4 weeks, and last 4 weeks of the maintenance period.

Disposition of Subjects

Of the 126 patients who were randomized, 108 patients (85.7%) completed the study. Seven patients dropped out because of adverse events (1 PLB, 2 VGB 60 mg/kg/day, 4 VGB 100 mg/kg/day), 6 patients dropped out because of increased seizure frequency/intensity (1 PLB, 2 VGB 20 mg/kg/day, 2 VGB 60 mg/kg/day and 1 VGB 100 mg/kg/day), 2 PLB patients withdrew consent, 1 patient met the exclusion criteria (1 VGB 20 mg/kg/day), l patient in the VGB 60 mg/kg/day group was discontinued due to protocol violation and 1 patient in the VGB 20 mg/kg/day group was discontinued because of other reasons.

2.2 DATA SOURCE

The study reports and SAS data sets are available at
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3. STATISTICAL EVALUATION

3.1 DEMOGRAPHIC AND BASELINE DISEASE CHARACTERISTICS

Table 2 lists the demographic characteristics of the randomized subjects. There were no differences in randomization into the treatment groups with respect to race, sex, age, weight, age of onset of epilepsy, and years since an onset of epilepsy.

Table 2. Baseline Characteristics of the randomized patients.

Baseline Characteristic	*Treatment*			
	PLB (N=32)	20 mg/kg/day VGB (N=30)	60 mg/kg/day VGB (N=32)	100 mg/kg/day VGB (N=32)
Sex Males Females	 16 (.50.0%) 16 (50 0%)	 14 (46.7%) 16 (53 3%)	 17 (53.1%) 15 (46 9%)	 12 (37.5%) 20 (62 5%)
Race Asian Black Caucasian Multiracial	 0(0%) 2 (6.3%) 29 (90.6%) 1 (3.1%)	 0 (0%) 2 (6.7%) 28 (93.3%) 0(0%)	 1(3.1%) 2 (6.3%) 29 (90.6%) 0 (0%)	 1 (3.1%) 1 (3.1%) 28 (87.5%) 2 (6.3%)
Age (years) Median	 9.0	 12.5	 12.5	 8.5
Weight (kg) Median	 32.4	 51.7	 48.8	 33.3
Age at Onset of Epilepsy (years) Median	 3.0	 3.0	 3.8	 2.3
Years Since Onset of Epilepsy Median	 5.2	 6.2	 7.6	 5.4
Frequency of CPS (No./28 days) Median	 22.0	 16.5	 9.3	 13.3

Source: Study report

3.2 EFFICACY EVALUATION

Sponsor's reported Analyses results

Table 3 lists the primary efficacy results of the primary endpoint the median change in CPS frequency. The pair-wise comparison of VGB 100 mg/kg/day to PLB was statistically significant (p-value = 0.0142) but VGB 20 mg/kg/day and 60 mg/kg/day were not statistically different from PLB (p-values = 0.8622 and 0.8140, respectively). These p-values are more congruent with the median values that show similar changes for PLB, VGB 20 mg/kg/day, and VGB 60 mg/kg/day versus a much larger change for VGB 100 mg/kg/day. The median changes in CPS frequency were -2.00, -2.5, and -5.00 seizures per 28 days in the VGB 20 mg/kg/day group, VGB 60 mg/kg/day group, and VGB 60 mg/kg/day group, respectively. When all data collected after baseline were included in the analysis, similar results were obtained (Table 4).

Table 3. Change from Baseline to End of Study in Frequency of CPS in Study 118 for the Intent-to-Treat Population

Study Phase	PLB N = 32	VGB		
		20 mg N = 30	60 mg N = 32	100 mg N = 32
Baseline median	22.00	16.51	9.25	13.25
End of study median	17.75	10.25	7.50	4.00
Change median	-2.75	-2.00	-2.50	-5.00
p-value for diff. from PLB		0.8622	0.8140	0.0142

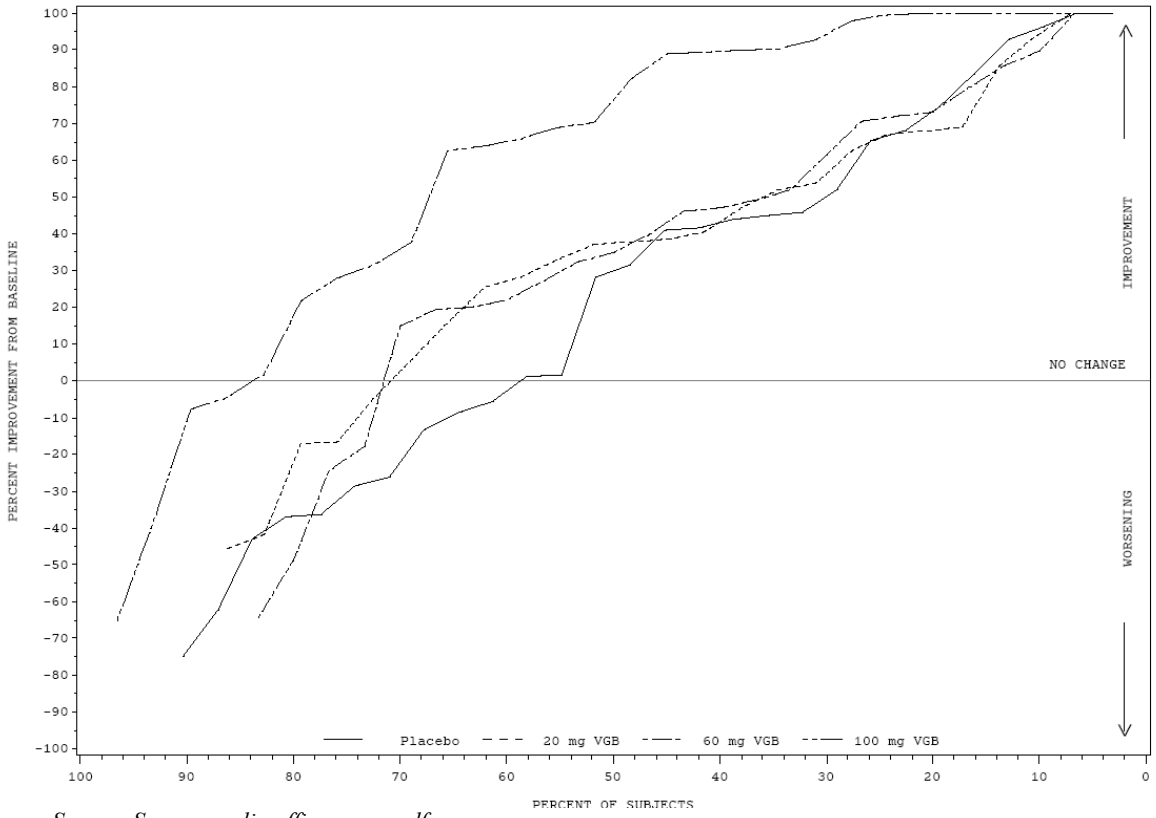
ANCOVA = analysis of covariance;
Baseline includes data collected during the Baseline Phase
End of study includes data collected during the last 8 weeks of the Study
P-value based on Rank ANCOVA model with factors for treatment and site with ranked Baseline seizure frequency as covariate.
Source: Summary-clin-efficacy-cps.pdf.

Table 4. Change from Baseline to End of Study in Frequency of CPS Using All Available Post-Baseline Data – Intent-to-Treat Population- Study 118

Study Phase	PLB N = 32	VGB		
		20 mg N = 30	60 mg N = 32	100 mg N = 32
Baseline median	22.00	16.51	9.25	13.25
End of study median	16.95	10.95	5.89	6.82
Change median	-2.13	-2.23	-2.25	-5.27
p-value for difference from PLB		0.760	0.338	0.015

ANCOVA = analysis of covariance;
Baseline includes data collected during the Baseline Phase
P-value based on Rank ANCOVA model with factors for treatment and site with ranked Baseline seizure frequency as covariate.
Source: Summary-clin-efficacy-cps.pdf.

Figure 1. Continuous Responder Curves Based on Percent Reduction From Baseline in CPS – ITT Population



Source: Summary-clin-efficacy-cps.pdf

Figure 1 lists the continuous responder curves (i.e., cumulative distribution of frequency) based on percent reduction from baseline in CPS. The figure also supported the efficacy findings obtained from the Rank ANCOVA analysis. That is, the continuous responder curve for VGB 100 mg/kg/day group was higher from the curve for PLB group.

Table 5 lists the number and percent of patients achieving therapeutic success in the ITT population of the study 118. The percent of patients achieving therapeutic success was statistically significantly larger in the VGB 100 mg/kg/day group than the PLB group (56.25% and 31.25% respectively). When all data collected after baseline were included in the analysis, similar results were also obtained (Table 5).

Table 5. Number and Percent of Patients Achieving Therapeutic Success in Study 118 – Intent-to-Treat Population

Parameter	PLB N = 32	VGB		
		20 mg N = 30	60 mg N = 32	100 mg N = 32
End of study N (%) of patients achieving success p-value for difference from PLB	10 (31.25)	11 (36.67) 0.5043	12 (37.50) 0.3816	18 (56.25) 0.0351
Including all post-Baseline data N (%) of patients achieving success p-value for difference from PLB	6 (18.75)	13 (43.33) 0.0510	11 (34.38) 0.2750	18 (56.25) 0.0012

ANCOVA = analysis of covariance;
Baseline includes data collected during the Baseline Phase
End of study includes data collected during the last 8 weeks of the Study
P-value based on ANCOVA model with factors for treatment and site with ranked Baseline seizure frequency as covariate.
Source: Summary-clin-efficacy-cps.pdf.

Table 6 lists the global efficacy evaluations by caregiver and investigator in Study 118 for the intent-to-treat population. The distribution of caregiver evaluations was statistically significantly different between the VGB 100 mg/kg/day and PLB groups (p-value = 0.0139). The percent of patients evaluated by the caregiver as significantly improved at the final visit was larger in the VGB 100 mg/kg/day group than in the PLB group (43.8% and 16.1%, respectively). Results for the investigator evaluations were similar to those for caregiver evaluations.

Table 6. Global Efficacy Evaluations by Caregiver and Investigator in Study 118 – Intent-to-Treat Population

Parameter	PLB N = 32	VGB		
		20 mg N = 30	60 mg N = 32	100 mg N = 32
Caregiver evaluation at Final Visit, n (%) Significantly improved Slightly improved No change Slightly worse Significantly worse p-value for diff from PLB	n = 31 5 (16.1) 8 (25.8) 12 (38.7) 2 (6.5) 4 (12.9)	n = 28 12 (42.9) 7 (25.0) 7 (25.0) 1 (3.6) 1 (3.6) 0.1726	n = 32 11 (34.4) 9 (28.1) 6 (18.8) 3 (9.4) 3 (9.4) 0.2482	n = 32 14 (43.8) 11 (34.4) 3 (9.4) 2 (6.3) 2 (6.3) 0.0139
Investigator evaluation at Final Visit, n (%) Significantly improved Slightly improved No change Slightly worse Significantly worse p-value for difference from PLB	n = 32 7 (21.9) 7 (21.9) 13 (40.6) 1 (3.1) 4 (12.5)	n = 29 11 (37.9) 8 (27.6) 8 (27.6) 1 (3.5) 1 (3.5) 0.4630	n = 32 11 (34.4) 11 (34.4) 7 (21.9) 1 (3.1) 2 (6.3) 0.2172	n = 32 14 (43.8) 10 (31.3) 4 (12.5) 3 (9.4) 1 (3.1) 0.0266

P-value based on test for Mantel-Haenszel test for general association.
Source: Summary-clin-efficacy-cps.pdf

Table 7. Change from Baseline to End of Study in Frequency of Complex Partial Seizures (IB) in Study 118 for the Intent-to-Treat Population

Study Phase	PLB N = 32	VGB		
		20 mg N = 30	60 mg N = 32	100 mg N = 32
Baseline median	13.50	10.54	8.25	9.50
End of study median	14.50	10.00	6.50	1.75
Change median	-2.02	-1.74	-2.44	-6.11
p-value for diff. from PLB		0.558	0.902	0.029

ANCOVA = analysis of covariance; Baseline includes data collected during the Baseline Phase;
End of study includes data collected during the last 8 weeks of the Study
P-value based on ANCOVA model with factors for treatment and site with ranked Baseline seizure frequency as covariate.
Source: study report.

Separate analyses were performed for the complex partial (IB), and partial seizures secondarily generalized (IC). Analyses for each seizure type were performed using all intent-to-treat patients. Table 7 lists the change from Baseline to End of Study in Frequency of IB. There was a statistically significant difference in monthly average IB seizures between the VGB 100 mg/kg/day and placebo groups (p-value= 0.029). VGB 20 mg and VGB 60 mg were no statistically significant different from placebo with respect to the monthly average frequency of IB seizures. However, the median reduction in the IB seizure frequency appeared to increase with increasing VGB dose.

The analysis of partial seizures secondarily generalized (IC) was performed on the intent-to-treat population. Only 34% of the ITT population experienced partial seizures secondarily generalized during the study: 27 patients experienced IC seizures at both Baseline and during Maintenance, 11 patients experienced IC seizures at Baseline only, and 5 patients experienced IC seizures during Maintenance only. All medians were zero for all treatment groups. There were no statistically significant differences between the treatment groups with respect to the number or frequency of partial secondarily generalized seizures.

Only 6% of the ITT population experienced simple partial seizure flurries during the study: 1 patient experienced simple partial seizure flurries at both Baseline and during Maintenance, 4 patients experienced simple partial seizure flurries at Baseline only, and 2 patients experienced simple partial seizure flurries during Maintenance only. Only 13% of the ITT population experienced complex partial seizure flurries during the study: 6 patients experienced complex partial seizure flurries at both Baseline and during Maintenance, 8 patients experienced complex partial seizure flurries at Baseline only, and 3 patients experienced complex partial seizure flurries during Maintenance only. All medians were zero for all treatment groups.

Only 2% of the ITT population experienced episodes of partial status epilepticus during the study: 2 patients experienced episodes of partial status epilepticus at Baseline only and 1 patient experienced episodes of partial status epilepticus during Maintenance only. Only 1 patient in the ITT population experienced episodes of generalized status epilepticus at both Baseline and during Maintenance. All medians were zero for all treatment groups.

Table 8 summarizes the results of the ITT analysis of seizure-free days. All three VGB treatment groups experienced larger increases in the median number of seizure-free days per 28 days than the placebo group. There was no statistically significant difference between the VGB groups and PLB group in the median number of seizure-free days per 28 days.

Table 8. Analysis of Number of Seizure-Free Days-Study 118, Intent-to-Treat Population

Study Phase	PLB N = 32	VGB		
		20 mg N = 30	60 mg N = 32	100 mg N = 32
Baseline median	17.5	14.90	20.00	16.04
End of study median	19.71	18.64	22.5	24.85
Change median	1.04	1.22	1.95	4.00
p-value for diff. from PLB		0.3915	0.6295	0.1085

ANCOVA = analysis of covariance;
Baseline includes data collected during the Baseline Phase
End of study includes data collected during the last 8 weeks of the Study
P-value based on ANCOVA model with factors for treatment and site with ranked Baseline seizure frequency as covariate.
Source: study report.

3.3. FDA Reviewer's Data Analyses and Comment

This reviewer re-analyzed the efficacy data of the study according to the protocol specified statistical analysis plan and found that the statistical findings are consistent with the sponsor's reported efficacy findings. In analyzing seizure frequency data from AED trials, it is also a common practice to consider a parametric ANCOVA on the log-transformed data as protocol specified primary statistical analysis method. The sponsor did not include this analysis in the study report. Therefore, as a sensitivity analysis, this reviewer did a parametric ANCOVA analysis considering the log-transformed monthly (28 days) frequency of CPS during the 8 weeks of the maintenance phase as dependent measure and the log-transformed (28 days) frequency of CPS during the last 8 weeks of baseline as a covariate and treatment group and study sites as factors in the model. The pair-wise comparison of VGB 100 mg/kg/day to PLB was statistically significant (p-value = 0.0169) but VGB 20 mg/kg/day and 60 mg/kg/day were not statistically different from PLB (p-values = 0.8417 and 0.9447, respectively). The p-values obtained from the sensitivity analysis were very similar to the p-values obtained from the protocol specified statistical analysis (i.e., Rank ANCOVA analysis). Since there was no statement regarding multiplicity adjustment of testing the doses in the protocol, a closed testing procedure (i.e., testing the highest dose first) might be applicable for multiplicity adjustment. Considering the closed testing procedure for multiplicity adjustment, the primary analysis confirmed that VGB 100 mg/kg/day was statistically significantly efficacious in treating pediatric patients having uncontrolled complex partial seizures with or without secondary generalization. The sensitivity analysis also supported the efficacy findings obtained from the primary analysis.

Dealings with Dropouts or Missing Data

To evaluate the impact of missing data in the efficacy results of the study, ranked ANCOVA analyses on the primary efficacy endpoint - percent reduction in average monthly rate of CPS

were conducted considering (i) baseline compared to 6 weeks tritration period, (ii) baseline compared first 4 weeks of maintenance period and (iii) baseline compared last 4 weeks of the maintenance period of IITT Population. The monthly CPS rates during the tritration and maintenance periods were calculated over the number of days with non-missing CPS data in the tritration and maintenance periods. VGB 100 mg group was statistically significantly superior to the placebo group for percent reduction in average monthly rate of CPS from baseline to the first 4 weeks, and last 4 weeks of the maintenance period (Table 9). VGB 20 mg and VGB 60mg were not statistically significantly superior to the PLB group for percent reduction in average monthly rate of drop seizures from baseline to the first 4 weeks and last 4 weeks of the maintenance period. These findings supported that the missing data due to dropouts of patients had no major impact on the findings obtained from the primary analysis of the study.

Table 9. Percent Reduction in Monthly (i.e., 28 days) Rate of Complex Partial Seizures (Baseline Compared to 6 weeks Titration, First 4 Weeks of Maintenance and Last Four Weeks of Maintenance) Study 118 - ITT Population

		VGB Dose Level		
Period	Placebo (N=32)	20 mg/kg/day (N=30)	60 mg/kg/day (N=32)	100 mg/kg/day (N=32)
6 weeks titration period	N=32	N=30	N=32	N=32
Baseline median seizure rate	21.21	16.25	9.25	13.50
Titration period median seizure rate	14.90	10.62	5.25	9.33
Median percent reduction in seizure rate	2.34	45.89	37.84	53.09
p-value: comparison to placebo		0.2731	0.0673	0.0836
First 4 weeks of maintenance period	N=31	N=29	N=31	N=29
Baseline median seizure rate	19.00	14.00	8.50	13.00
Maintenance period median seizure rate	14.00	12.00	6.00	2.00
Median percent reduction in seizure rate	16.92	31.25	36.05	69.14
p-value: comparison to placebo		0.9249	0.7740	0.0026
Last 4 weeks of maintenance period	N=31	N=25	N=29	N=27
Baseline median seizure rate	19.00	18.49	8.00	14.00
Maintenance period median seizure rate	16.00	8.84	6.59	2.55
Median percent reduction in seizure rate	17.65	32.12	38.11	76.86
p-value: comparison to placebo		0.6889	0.7561	0.0020

P - values are based on ranked ANCOVA.
Baseline includes data collected during the last 8 weeks of the baseline period.
Source: Amendment to Pending Supplement – Response to Agency Request for Information 01 July 2013.
EDR Location: \\CDSESUB1\EVSPROD\NDA020427\0046

4. SUBGROUP ANALYSIS

Table 10 lists the mean monthly frequencies by age groups (Age: 3 to < 6, ≥ 6 to < 12, ≥ 12 to < 17 years) and gender on the mean and change in patient mean monthly frequency of CPS for the ITT patients. There were a few patients within each subgroup. There were no clinically important differences in the efficacy of VGB groups among the subpopulations. Majorities of the patients were Caucasian (91%), and hence no subgroup analyses were done on race.

Table 10. Change from Baseline to End of Study in Frequency of CPS for Study 118 by Age and Gender Groups – Intent-to-Treat Population

Study Phase	PLB N = 32	*VGB*		
		20 mg/kg/day N = 30	60 mg/kg/day N = 32	100 mg/kg/day N = 32
Age Group (years)				
3 to < 6	n = 8	n = 5	n = 1	n = 10
Baseline median	33.31	34.11	1.00	19.25
End of study median	21.25	11.00	1.56	5.50
Change median	-4.80	-10.50	0.56	-4.75
≥ 6 to < 12	n = 14	n = 8	n = 12	n = 11
Baseline median	20.50	40.50	9.00	28.53
End of study median	17.75	17.25	7.50	2.00
Change median	-1.25	-7.25	-2.28	-15.00
≥ 12 to < 17	n = 10	n = 17	n = 19	n = 11
Baseline median	20.75	7.50	12.50	9.00
End of study median	7.75	9.50	8.00	2.50
Change median	-3.02	-1.00	-3.00	-3.00
Gender				
Female	n = 16	n = 16	n = 15	n = 20
Baseline median	16.00	14.51	11.00	13.25
End of study median	15.75	10.00	8.00	4.00
Change median	-6.00	-1.50	-2.50	-3.75
Male	n = 16	n = 14	n = 17	n = 12
Baseline median	23.00	25.25	5.50	11.75
End of study median	17.75	13.06	2.50	7.32
Change median	-1.00	-3.00	-2.50	-8.25

Source: Study report

5. A POST-HOC INTERIM ANALYSIS OF CPEN STUDY

In the Type C meeting dated June 8, 2012, the agency asked the sponsor to submit a post-hoc interim analysis results of the data from an ongoing Canadian Pediatric Epilepsy Network (CPEN) study to evaluate the relapse rate of VGB responders following discontinuation of the patients successfully treated with VGB for 6 months. The findings could be informative with regard to adequate duration of VGB treatment to future patients with infantile spasms.

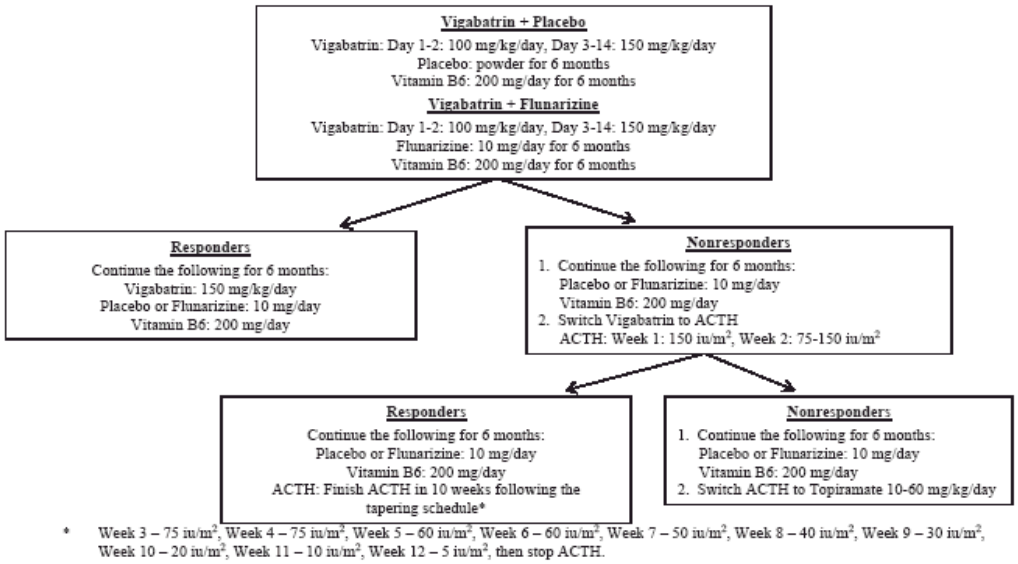
The sponsor created a statistical analysis plan (SAP) for a post-hoc interim analysis for the CPEN study. The SAP was a descriptive type statistical analysis plan. There was no statement of any statistical hypothesis testing in this SAP. The primary objective of the interim analysis was to evaluate the relapse rate of VGB responders following discontinuation of VGB treatment for a duration of 6 months. VGB responders were defined as patients with spasm cessation (evaluated by the Week 4 visit Spasm Diary), the absence of hypsarrhythmic EEG pattern (evaluated by Week 4 visit EEG), and who are treated with VGB for a duration of 6 months. Relapse was defined as return of spasms or hypsarrhythmias. The relapse evaluation was restricted to the time-span between Month 6 visit and Month 12 visit – the first 6 months following discontinuation of VGB – as confirmed by the 12 month visit EEG.

The CPEN study was a multicenter, randomized, double-blind, parallel-group, placebo-controlled trial to assess the improvement of developmental outcome of children treated for infantile spasms (IS) with add-on flunarizine or placebo.

A total of 80 infants who had new onset of IS and EEG-recorded hypsarrhythmia or modified hypsarrhythmia were planned for enrollment in the CPEN study. During period 1 (first two weeks of treatment), all patients recruited into the study received VGB 100 mg/kg/day, which was increased to 150mg/kg/day by the third day and continued at that dose for the remaining two-week period. At the onset of treatment with VGB, subjects were randomized to receive add-on flunarizine or placebo. Vitamin B6 was also given with VGB as the standard therapy. The vitamin was given at a dose of 200 mg per day for a total period of 6 months. That is, randomized patients were allocated to Group A: VGB and placebo or Group B: VGB and flunarizine (10 mg/day). Sample size calculations were not done for the post-hoc interim relapse analysis. In the post-hoc interim relapse analysis, 69 patients (68 received at least 1 dose of VGB) were included.

If patients did not respond to VGB treatment at the end of Week 2, they were then switched to sACTH while placebo [Group C: sACTH and placebo] or flunarizine [Group D: sACTH and flunarizine (10 mg/day)]. If patients did not respond to sACTH treatment at the end of Week 4 (2 weeks after switching to sACTH), they were then switched to topiramate while placebo [Group E: topiramate and placebo] or flunarizine [Group F: topiramate and flunarizine (10 mg/day)] was maintained. Figure 2 lists the study design of this study.

Figure 2 Study Design



Source: Study report

Observed data were analyzed; no imputation procedure was used for imputing the missing data. Data for the sACTH and topiramate and other AED therapies groups are presented for information purposes only. Efficacy analyses were based on the FAS population- all randomized patients who took at least one dose of VGB and had valid baseline assessments and had at least one valid post-baseline assessments of the primary efficacy measure.

Efficacy Assessments include (i) Seizure Records at the end of weeks 2, 4, 6-months and 12-month, and (ii) An EEG, with 1-hour wake/sleep studies, was performed at Weeks 2, 4, 6-months and 12- month.

The primary efficacy endpoint in the post-hoc interim analysis was the relapse rate of VGB responders following discontinuation of VGB. VGB responders were defined as patients with spasm cessation (evaluated by the Week 4 spasm diary), the absence of hypsarrhythmic EEG pattern (evaluated by Week 4 EEG), and who were treated with VGB for a duration of 6 months. Relapse was defined as return of spasms or hypsarrhythmias. The relapse evaluation was restricted to the first 6 months following discontinuation of VGB (between Month 6 and Month 12; i.e., 6 months following discontinuation of VGB) as confirmed by the 12 month EEG.

An alternative method was also used to evaluate the response rate and relapse rate of VGB following discontinuation of VGB. In the alternative method, VGB responders were defined as patients with the absence of hypsarrhythmic EEG pattern (evaluated EEG at Week 2, Week 4, or Month 6) and who were treated with VGB for a duration of 6 months, and relapse was defined as return of hypsarrhythmias at Month 12. If Month 12 EEG data were missing and Month 24 EEG data were present, relapse was evaluated using Month 24 EEG data instead.

Patient Disposition

Among the 68 VGB patients who were included in the post-hoc interim relapse analysis, 1 patient died between Week 1 and Week 2, 38 patients responded to VGB at the end of Week 2, and 29 patients did not respond to VGB at the end of Week 2. The 29 nonresponders were switched to sACTH at the end of Week 2. Of these 29 patients, 23 patients responded to sACTH and 6 patients did not respond to sACTH at the end of Week 4 (2 weeks after switching to sACTH) and were switched to topiramate and other AED therapies.

Of the 39 VGB -treated patients, the majority (33 patients; 84.6%) completed the interim analysis. Of the remaining 6 patients, 2 patients (5.1%) withdrew from the study at the time of the interim analysis and 4 patients (10.3%) had no month 12 or month 24 EEG data.

Baseline Demographics

Among the 68 enrolled patients treated with VGB, demographic characteristics were similar across treatment groups. The majority of VGB-treated patients were male (61.5%) and of European ethnicity (53.8%). The mean age of VGB-treated patients at baseline was 6.9 months and ranged from 2 months to 14 months. The mean weight and height of VGB-treated patients were 8.27 kg and 69.19 cm, respectively. The mean time to an onset of spasms was 1.34 months.

Efficacy Evaluation

Table 11 lists a summary of responder rate at Week 4 and relapse rate at Month 12 for the FAS population. Twenty-eight of the 35 VGB-treated patients (80.0%) became spasm- and hypsarrhythmia-free within 4 weeks of receiving VGB and one of these 28 patients (3.6%) had hypsarrhythmia relapse at 12 months (6 months following discontinuation of VGB).

Table 11. Primary Summary of Responder Rate at Week 4 and Relapse Rate at Month 12-FAS population

Study Visit	VGB N = 38	sACTH N = 23	Topiramate and Other AED Therapies	Total N = 67
Responders at 4 weeks Responder Non Responder Not Classified	n = 35 28 (80.0%) 2 (5.7%) 5 (14.3%)	n = 22 12 (54.5%) 9 (40.9%) 1 (4.5%)	n = 6 0 6 (100%) 0	n = 63 40 (63.5%) 17 (27.0%) 6 (9.5%)
12 month visit; 6 months following discontinuation of VGB Relapsed Responder Relapse Rate	n = 1 1/28 (3.6%)	n = 0 0/12	n = 0 0/0	n = 1 1/40 (2.5%)

Source: Study Report

In an alternative analysis of response rate and relapse rate, VGB responders were defined as patients with the absence of hypsarrhythmic EEG pattern (evaluated by Week 2, Week 4, or Month 6 EEG) and who were treated with VGB for 6 months. Relapse was defined as return of hypsarrhythmia at Month 12. If Month 12 visit EEG data were missing and Month 24 visit EEG data were present, relapse was evaluated using Month 24 visit EEG data instead. Thirty seven of 38 VGB-treated patients (80.0%) became spasm- and hypsarrhythmia-free within 4 weeks of receiving VGB and one of these 28 patients (3.6%) had a hypsarrhythmia relapse at 12 months (6 months following discontinuation of VGB).

Table 12. Summary of Responder Rate (Absence of Hypsarrhythmic EEG Pattern [Evaluated by Weeks 2, 4, or month 6 EEG]) and Relapse Rate (Return of Hypsarrhythmia at Month 12 or Month 24)- FAS population

Study Visit	VGB N = 38	sACTH N = 23	Topiramate and Other AED Therapies	Total N = 67
Responders at week 2, week 4, or month 6 visits Responder Non Responder Not Classified	n = 38 37 (97.4%) 0 1 (2.6%)	n = 23 22 (95.7%) 1 (4.3%) 0	n = 6 5 (83.3%) 1 (16.7%) 0	n = 67 64 (95.5%) 2 (3.0%) 1 (1.5%)
Months 12 or 24 months [i.e., 6 or 18 months following discontinuation of VGB, respectively] Relapsed Responder Relapse Rate	n = 0 0/37	n = 0 0/22	n = 1 1/5 (20.0%)	n = 1 1/64 (1.6%)

Source: Study Report

FDA Reviewer's Data Analyses and Comment

This reviewer re-analyzed the CPEN study data according to the protocol specified statistical analysis plan and found that the statistical findings are consistent with the sponsor's reported efficacy findings.

6. SUMMARY AND CONCLUSIONS

The statistical findings of Study 118 demonstrated that VGB 100 mg/kg/day was statistically significantly superior to placebo for the patient mean monthly frequency of CPS at the end of study compared to baseline (p-value = 0.0142). VGB 20 mg/kg/day and 60 mg/kg/day were not statistically different from placebo (p-value = 0.8622 and 0.8140, respectively). The descriptive results of the post-hoc interim analyses of CPEN study also support that 6 months of treatment with VGB is adequate to prevent recurrence of spasms after cessation of treatment.

In conclusion, the efficacy evidence supports the use of VGB 100 mg/kg/day as adjunctive therapy for pediatric patients 10 to 17 years of age with CPS who have inadequately responded to alternative treatments.

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/s/

OHIDUL I SIDDIQUI
09/26/2013

KUN JIN
09/26/2013
I concur with the review.

HSIEN MING J HUNG
10/01/2013