CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-006

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	20-427, 22-006
Brand Name	Sabril®
Generic Name	Vigabatrin
Sponsor	Ovation Pharmaceuticals
Indication	NDA 20-427: Treatment of Complex Partial Seizures (CPS) with or without Secondary Generalization in Adults NDA 22-006: Treatment of infantile spasm (IS) from birth to 2 years of age
Dosage Form	Tablets (NDA 20-427) and Solution (NDA 22-006)
Drug Class	Antiepileptic
Therapeutic Dosing Regimen	Up to 3.0 g/day (1.5 g bid) in adults with CPS (NDA 20-427) Up to 150 mg/kg/day for IS (NDA 22-006)
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	Up to 6.0 g qd have been studied
Submission Number and Date	N 000 BZ, October 31, 2008
Review Division	DNP/HFD120

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QT prolongation effect of vigabatrin (3.0 g and 6.0 g) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between vigabatrin (3.0 g and 6.0 g) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidance. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 2, indicating that assay sensitivity was established.

In this randomized, blinded, four-period crossover study, 60 healthy subjects received vigabatrin 3.0 g, vigabatrin 6.0 g, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Vigabatrin (3.0 g and 6.0 g) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Vigabatrin 3.0 g	6	1.0	(-1.2, 3.3)
Vigabatrin 6.0 g	12	1.3	(-0.9, 3.5)
Moxifloxacin 400 mg*	2	10.5	(8.3, 12.8)

* Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 7.4 ms.

The supratherapeutic dose (6.0 g) produces mean C_{max} values 1.8-fold higher than the mean C_{max} for the therapeutic dose (3.0 g, tablets) in NDA 20-427 and 5.6- and 3.0-fold higher than the mean C_{max} for the 50 mg/kg/day oral solution administered to infants and children. The C_{max} for the highest therapeutic dose in infants (150 mg/kg) is not expected to exceed the concentrations observed from the 6.0-g dose in adults. The concentrations in adults (in study OV-1033) do not exceed those for the predicted worst case scenario (5-g therapeutic dose administered to patients with severe renal disease yields a 3.5-fold increase over the maximum studied exposure).

Dose adjustment is recommended for patients of any age with renal impairment (see section 2.2 of the label). Vigabatrin is renally eliminated and concentrations are not expected to change with co-administration of other drugs. Exposure response analysis did not indicate a positive increase in QT prolongation with increasing exposure to vigabatrin. Even if doses exceed 1.5 g (up to 5.0 g for therapy) in adults or 150 mg/kg in children with severe renal disease and exposures exceed the maximum studied, it is not anticipated to alter the QT interval based on the lack of increasing slope in the exposure-response data.

2 PROPOSED LABEL

The sponsor did not include a description of study results in the proposed label. The following text is our suggestions for labeling. We defer all labeling decisions to the clinical review team.

12.2 Pharmacodynamics
Effects on Electrocardiogram

There is no indication of a QT/QTc prolonging effect of SABRIL in single doses up to (b) (4) In a randomized, placebo-controlled, crossover study, 58 healthy subjects were administered a single oral dose of SABRIL (3 g and 6 g) and placebo. Peak concentrations for 6.0 g SABRIL were approximately 2-fold higher than the peak concentrations following the 3.0 g single oral dose.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Vigabatrin (VGB) is an irreversible inhibitor of γ-aminobutyric acid -transaminase (GABA-T). The sponsor is seeking approval for the following indications:

NDA 20-427: Adjunctive therapy for adult patients with refractory complex partial seizures (CPS) who have inadequately responded to alternative treatments and for whom the potential benefits outweigh the potential risk of developing the peripheral Visual Field Defect (VFD)

NDA 22-006: Monotherapy for pediatric patients with Infantile Spasms (IS) for whom the potential benefits outweigh the potential risk of developing the peripheral Visual Field Defect (VFD)

3.2 MARKET APPROVAL STATUS

Vigabatrin was approved for marketing in the United Kingdom and Ireland in 1989, and is currently approved in more than 60 countries. Approved indications for vigabatrin include adjunctive treatment of partial epilepsy in subjects who have not responded adequately to other antiepileptic drugs (AEDs) and monotherapy for the treatment of IS.

3.3 PRECLINICAL INFORMATION

Source: Pharmacology Written Summary, CTD 2.6.2, 15 September 2006 and IB dated 20 July 2007

> *"In vitro effects of Vigabatrin on cloned hERG channels expressed in mammalian cells:*
>
> "The objective of this study was to analyze the *in vitro* effects of vigabatrin on cloned hERG channels expressed in HEK293 cells using the patch clamp technique. Vigabatrin was exposed to three cells each (n = 3) at nominal target concentrations of 100 and 300 µg/mL at physiological temperature (35 ± 2ºC). The highest concentration tested corresponds to approximately 4 times the maximum plasma concentration. Actual concentrations delivered to cells ranged from 79.1 to 82.8 µg/mL (from a target of 100 µg/mL) and from 251 to 253µg/mL (from a target of 300 µg/mL)
>
> "Vigabatrin at concentrations up to approximately 250 µg/mL did not produce significant inhibition of hERG currents (0.4% to 0.8% inhibition), which was not different (*P*>0.05) from control (Mean ± SEM) 0.1 ± 0.4% inhibition; n = 3. In contrast, under identical conditions, the positive control, terfenadine (a compound known to associated with clinical *TdP*) at 60 nM inhibited hERG currents by 74.6 ± 4.7% (Mean ± SD) in two cells (n = 2).
>
> *"Effect of Vigabatrin on Action Potentials in Isolated Rabbit Cardiac Purkinje Fibers:*
>
> The *in vitro* effects of vigabatrin on action potentials (AP) from a set of four isolated rabbit cardiac Purkinje fibers (n = 4) were evaluated at concentrations ranging from 10 to 300 µg/ml. Some prolongation of the APD was observed (APD_{60} was prolonged 9.8 to 18.9% and APD_{90} was prolonged (5.8% to 11.2%) upon exposure to vigabatrin. The prolongation of APD was not statistically significant (P > 0.05) when compared to that observed by exposing a set of Purkinje fibers (n = 4) to the vehicle in a time-matched fashion. In addition, no significant changes in the resting membrane potential (RMP), action potential

amplitude (APA), and rate of conduction (V_{max}) were observed upon exposure to vigabatrin up to 300 µg/mL. In contrast, the positive control article (50 µM *dl*-sotalol) caused significant prolongation of the APD (APD_{60} increased ~ 80% and APD_{90} increased ~ 68%) indicating the sensitivity of the test system to detect APD prolongation."

"Generally no effect was observed on BP, intra-ventricular pressure, heart rate, cardiac output or ECG in doses of 50-200 mg/kg iv. or 140 mg/kg po in the dog. One dog in one study had a prolonged 20 mm drop in BP."

3.4 PREVIOUS CLINICAL EXPERIENCE

Source: Investigators Brochure dated 20 July 2007 (recent Summary of Clinical Safety was not available)

"To date, vigabatrin has been administered to more than 4000 subjects in epilepsy trials, including more than 400 pediatric subjects and over 200 infants. This section includes safety information on vigabatrin reported from multiple sources through 17 June 2005. The information contains safety data from clinical studies of the adult and pediatric (non- IS) epilepsy subjects and pediatric subjects with IS. In addition, safety information obtained from post-marketing sources, including Europe and Canada (where vigabatrin is already approved), and safety data reported in the published literature are included.

"A total of 63/4853 (1.3%) subjects died during a study. Reported events contributing to death of a subject include the following: seizure (22), sudden unexplained death in epilepsy (18), respiratory events (4), aspiration (3), cancer (3), cardiovascular events (3), coronary atherosclerosis (3), drowning (2), hypoxia (2), myocardial infarction (2), and trauma (2). The remaining causes of death had a frequency of 1 in the combined dataset. No causal relationship between treatment with VGB and any patient death could be identified.

"Sudden and Unexplained Death in Epilepsy Patients (SUDEP) - In US and primary non- US clinical studies of 4075 vigabatrin-treated patients, 15 patients were reported to have sudden and unexplained deaths (estimated minimum 7091 patient-years of exposure). This represents an incidence of 1.9 deaths per thousand patient-years. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of SUDEP in patients with epilepsy not receiving vigabatrin (ranging from 0.5/1000 for the general population of epilepsy patients, to 4/1000 for recently studied clinical trial populations similar to the population in the clinical development program for vigabatrin, to 5/1000 for patients with refractory epilepsy). The estimated SUDEP rate in patients receiving vigabatrin was similar to that observed in patients receiving other AEDS who underwent clinical testing in a similar population at about the same time.

"A total of 936 subjects from all primary US and secondary non-US clinical epilepsy studies reported at least one serious adverse event (19.76%). The highest incidences of SAEs were nervous system disorder related; visual field defect was reported in 324 subjects (6.84%).

"In the non-clinical, clinical, and post marketing experience, there has been no signal suggesting that vigabatrin prolongs the QT interval."

Reviewer's Comment: The sponsor reports that the incidence of SUDEP is similar to what is reported with other AEDs. On review of the Safety section (4.4) there are isolated cases of ventricular tachycardia, ventricular fibrillation, cardiac arrest and cardiogenic shock. It is hard to come to any conclusions regarding these events without comparing the incidence of the same in patients on other AEDs.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of vigabatrin's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under (b) (4). The sponsor submitted the thorough QT study report OV-1033 for vigabatrin, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Double-Blind, Double-Dummy, Randomized, Comparative, Positive and Placebo Controlled, Crossover Design Trial to Assess the Effects of Vigabatrin on Cardiac Repolarization Following a Therapeutic and Supratherapeutic Dose in Healthy Volunteers

4.2.2 Protocol Number

OV-1033

4.2.3 Study Dates

5 February 2007 – 12 March 2007

4.2.4 Objectives

Primary

- To evaluate the effect of vigabatrin on Fridericia's corrected QTc interval (QTcF) following a single oral dose in healthy adult subjects

Secondary

- To evaluate the effect of vigabatrin on Bazett's corrected interval (QTcB) and the individual corrected interval (QTcI) in healthy adult subjects
- To evaluate vigabatrin dose and plasma exposure on the cardiac repolarization (QTc interval)

4.2.5 Study Description

4.2.5.1 Design

This was a single-dose, double-blind, double-dummy, randomized, positive and placebo controlled crossover design study in healthy male and female subjects between the ages of 18 to 45 years. The washout period was 2 days between doses.

Reviewer's Comment: The study was not conducted at steady-state. The half-life is 7 hours while the dosing interval is 12 hours. A study done at steady-state would yield more clinically relevant exposures given the intended chronic administration.

4.2.5.2 Controls

The sponsor used both placebo and positive (400 mg moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were double blinded. In order to maintain blindness of the treatment assignments, over-encapsulated moxifloxacin tablets and moxifloxacin placebo tablets were identical in appearance. Vigabatrin solution and placebo solution were identical as well.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Sixty subjects were randomly and equally allocated to four treatment regimens using a typical Williams Square 4x4 cross-over design. Fifteen subjects were assigned to each of the four sequences as listed in Table 2.

Table 2: Crossover Design Treatment Sequences

Sequence	Day 1	Day 4	Day 7	Day 10
1	A	B	C	D
2	B	D	A	C
3	C	A	D	B
4	D	C	B	A

Treatment A: 3.0 g vigabatrin solution +1 moxifloxacin placebo tablet
Treatment B: 6.0 g vigabatrin solution +1 moxifloxacin placebo tablet
Treatment C: Moxifloxacin tablet (over-encapsulated) 400 mg +vigabatrin placebo solution
Treatment D: Moxifloxacin placebo tablet +vigabatrin placebo solution

4.2.6.2 Sponsor's Justification for Doses

"The doses of vigabatrin selected for this study were 3.0 g and 6.0 g. The standard therapeutic dose range for refractory complex partial epilepsy in adults is 1.0 to 3.0 g/day, administered in divided doses twice daily (bid). The usual recommended therapeutic dose for adult patients with refractory complex partial seizures is 1.5 g bid, and doses up to 3.0 g bid have been used in clinical trials and in clinical practice, although this dose was not statistically superior in efficacy to the 3.0 g/day dose and was

associated with an increased incidence of AEs in clinical trials. However, 3.0 g bid administered chronically is relatively well tolerated. The maximum recommended therapeutic dose for patients with infantile spasms is 150 mg/kg/day. The doses currently being tested for (b) (4) are 0.5, 1.5, and 2.5 g bid. To support continued (b) (4) the proposed doses tested in the current study were an anticipated therapeutic dose of 3.0 g, and an anticipated supratherapeutic dose of 6.0 g (which equates to an approximate dose exposure of 12.0 g/day).

"No maximum tolerated dose of vigabatrin has been established. However, there is substantial clinical safety data accumulated during the chronic administration of up to 3.0 g bid and single dose safety data on doses up to 4.0 g. Two studies by another Sponsor administered up to 4.0 g orally as a single dose. In one study, 24 healthy male volunteers participated in a 4-way crossover study of vigabatrin pharmacokinetics. In this study, 4 g was well tolerated. No SAEs were reported and no subject had to discontinue the study. The most frequent AE was headache, which occurred in 2 subjects at the 4.0 g dose."

Reviewer's Comment: The supratherapeutic dose (6.0 g, tablet) selected for this study is not adequate to cover the entire range of possible clinical exposures when considering no dose adjustment for subjects with renal impairment. The pharmacokinetics are linear across all studied doses. Vigabatrin is almost entirely excreted unchanged in the urine. Therefore, pharmacokinetic drug-drug interactions are not expected to affect vigabatrin concentrations. However, dose reduction is recommended for patients with renal impairment. The greatest increase in vigabatrin AUC for a dose of 0.75 g (tablets) was 4.5-fold for patients with severe renal disease. The expected therapeutic dose-range is 1.5–5.0 g in adults (NDA 20-427) and no more than 150 mg/kg in children (NDA 22-006). Without dose reduction, patients with severe renal disease may exhibit exposures greater than that produced by the studied supratherapeutic dose of 6.0 g in patients with normal renal function.

Further increases in exposure may be expected from chronic dosing every 12 hours. SABRIL in study OV-1033 was given as a single dose. However, the rise in concentrations based on accumulation is not expected to be as great as that due to renal impairment.

4.2.6.3 Instructions with Regard to Meals

Subjects fasted overnight before each study drug administration.

Reviewer's Comment: A food effect study for vigabatrin was conducted. The effects of dosing in the fed versus fasted state were minimal. Total drug exposure did not change; however, the C_{max} decreased 30% and the T_{max} (7 hours in fasted) was delayed an additional hour (8 hours in fed state). The choice to conduct the study in the fasted state meant a higher range of exposures to test the QT prolongation response to vigabatrin.

4.2.6.4 ECG and PK Assessments

On Days 1, 4, 7, and 10, subjects received doses of vigabatrin, moxifloxacin, or placebo according to the randomization schedule. Subjects fasted overnight before each study drug administration. Washout days occurred on Days 2 and 3, 5 and 6, 8 and 9, and 11 and 12. Digital ECGs from the Holter recorder were collected before dosing (–1.5, –1.0,

–0.5, and 0 hours) and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 16, and 22 hours after dosing on Days 1, 4, 7, and 10. Blood samples for pharmacokinetic analyses were collected before dosing (0 hour) and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 16, 23, 36, and 48 hours after dosing on Days 1, 4, 7, and 10.

Reviewer's Comment: The timing of ECGs is thorough and almost comprehensive of the 24-hour time period post dose. Studying out to 22 hours post-dose appears acceptable as there are no trends in the data at these later time points.

4.2.6.5 Baseline

Baseline value is defined as the ECG measurements before dose on the same day.

4.2.7 ECG Collection

The continuous 12-lead ECG data were extracted from the Holter recorder flash cards within a 6-minute window that started at the specified nominal time point. The subjects were kept at rest in a semi-recumbent position for 5-to-10 minutes prior to each acquisition.

All the study electrocardiograms used for the analysis were transmitted over a secured internet interface via the (b) (4) to a centralized ECG core laboratory (b) (4) and subsequently extracted from the H-12 Plus ambulatory electrocardiograph recorder flashcards (study electrocardiograms for analysis) and were analyzed manually utilizing the same validated digital techniques of E-Scribe™ system and the Veritas™ algorithm.

The ECGs were interpreted by Cardiologists at (b) (4) in a blinded fashion without knowledge of therapy or sequence including the active control. The QT intervals were measured using a high resolution manual on-screen caliper method.

The initial measurements were performed by cardiovascular technicians using the derived median representative beat method, preferentially in lead II. Exceptions included excessive artifact, wandering, and poor T wave amplitude in lead II in which case V5 was measured. The measurements were confirmed or re-adjusted by the cardiologist.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 60 subjects (30 males, 30 females), 19–45 years of age, with a normal baseline ECG and BMI between 18-30 kg/m^2 were enrolled in the study and 58 subjects completed all 4 treatment periods. Two subjects discontinued in period 4 due to AEs.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

A repeated measures mixed effects linear model was used to test the primary hypothesis, using PROC MIXED procedure in SAS software v9.1.3, where the outcome ΔQTcF is the change from baseline in the predose-subtracted value of QTcF. For each time point, the mean predose-corrected difference between each vigabatrin dose and placebo,

estimated from the above model ΔQTcF, are presented along with a two-sided 90% upper confidence bound on the difference.

Table 3 presents the mean differences in ΔQTcF between each vigabatrin dose and placebo at each time point postdose. The largest one sided 95% upper bound of mean difference of 3.0 g vigabatrin from placebo in ΔQTcF was 3.0 ms occurred at 6 hours after dose. The largest upper bound for 6.0 g vigabatrin is 3.3 ms at 12 hours after dose. The results indicate no clinically relevant effect on the QT/QTc interval.

Table 3: Mean Change from Baseline QTcF for each Vigabatrin Dose vs. Placebo

	LS Means			Vigabatrin 3.0 g - Placebo		Vigabatrin 6.0 g - Placebo	
Hours Postdose	Placebo (N=59)	Vigabatrin 3.0 g (N=59)	Vigabatrin 6.0 g (N=60)	Difference	95% Upper Bound	Difference	95% Upper Bound
0.25	3.90	0.87	1.92	-3.04	-0.75	-1.98	0.30
0.5	-0.79	-3.07	-2.46	-2.28	-0.00	-1.67	0.61
0.75	-3.76	-5.91	-6.14	-2.15	0.13	-2.38	-0.10
1	-4.69	-5.65	-6.61	-0.96	1.33	-1.92	0.37
2	-2.27	-4.96	-4.71	-2.69	-0.41	-2.44	-0.17
3	1.38	-1.66	-2.11	-3.04	-0.76	-3.49	-1.22
4	1.16	0.24	0.02	-0.92	1.37	-1.13	1.16
6	-4.07	-3.38	-5.52	0.69	2.98	-1.46	0.83
8	-6.26	-7.17	-6.70	-0.92	1.37	-0.44	1.85
12	-1.39	-1.90	-0.40	-0.51	1.78	0.99	3.28
16	6.92	5.10	6.69	-1.82	0.46	-0.23	2.05
22	6.11	6.40	4.47	0.29	2.57	-1.65	0.65

Source: sponsor's table 14.6.4.1.1

4.2.8.2.2 Secondary Analyses

The secondary endpoints were the changes from the period-specific baseline in QTcB (ΔΔQTcB) and in QTcI (ΔΔQTcI). The largest one-sided upper 95% confidence bound on ΔΔQTcB occurred at 6 hours postdose for the 3.0-g group (6.4 ms) and at 12 hours postdose for the 6.0-g group (6.3 ms). The largest one-sided upper 95% confidence bound on ΔΔQTcI occurred at 6 hours postdose for the 3.0-g group (3.7 ms) and at 12 hours postdose for the 6.0-g group (4.3 ms). All upper 95% confidence limits were below 10 ms.

4.2.8.2.3 Assay Sensitivity

Table 4 presents the QTc interval comparison of moxifloxacin to placebo at each time point. The one-sided lower 95% confidence bound on ΔQTcF (95%CI) exceeded 5 ms at 2 hours postdose (7.88 ms) and 3 hours postdose (5.32 ms), hence, the assay sensitivity hypothesis is rejected in favor of moxifloxacin demonstrating an increase in ΔΔQTcF >5 ms.

Table 4: Mean Change from Baseline QTcF for Moxifloxacin Dose vs. Placebo

Hours Postdose	Moxifloxacin 400 mg (N=59)	Placebo (N=59)	Difference	95% Lower Bound
0.25	1.68	3.97	-2.29	-4.73
0.5	2.85	-0.73	3.58	1.14
0.75	0.82	-3.70	4.52	2.09
1	2.49	-4.62	7.11	4.68
2	8.11	-2.20	10.31	7.88
3	9.20	1.45	7.75	5.32
4	7.92	1.23	6.69	4.25
6	1.32	-4.00	5.32	2.88
8	-0.19	-6.19	6.00	3.56
12	3.58	-1.32	4.90	2.46
16	11.35	6.98	4.37	1.93
22	8.38	6.18	2.20	-0.25

Source: sponsor's table 14.6.5.1

Reviewer's Comments: The sponsor did not adjust results for multiple comparisons. The results with Bonferroni adjustment are in section 5.2.1.2.

4.2.8.2.4 Categorical Analysis

The number and percent of subjects with postdose QTc > 450 ms are summarized in Table 5. The proportions of subjects with any postdose QTcF > 450 ms at any time were 1.7%, 3.4%, and 1.7% for the placebo, 3.0-g, and 6.0-g treatment groups, respectively. The proportions of subjects with any postdose QTcB > 450 ms at any time were 11.9%, 10.2%, and 10.0% for the placebo, 3.0-g, and 6.0-g treatment groups, respectively. The proportions of subjects with any postdose QTcI > 450 ms at any time were 5.1%, 5.1%, and 10.0% for the placebo, 3.0-g, and 6.0-g treatment groups, respectively.

There was one subject with QTcI > 480 ms in the vigabatrin 3.0-g treatment group. There were no additional subjects with QTcF or QTcB > 480 ms and no subjects had a QTcF, QTcB, or QTcI > 500 ms.

Table 5: Summary of Subjects with Maximum QTcF, QTcB, QTcl Intervals by Category and Treatment

Category	Placebo (N=59)	Vigabatrin 3.0 g (N=59)	Vigabatrin 6.0 g (N=60)
QTcF (msec)			
>450	1 (1.7%)	2 (3.4%)	1 (1.7%)
>480	0 (0.0%)	0 (0.0%)	0 (0.0%)
>500	0 (0.0%)	0 (0.0%)	0 (0.0%)
QTcB (msec)			
>450	7 (11.9%)	6 (10.2%)	6 (10.0%)
>480	0 (0.0%)	0 (0.0%)	0 (0.0%)
>500	0 (0.0%)	0 (0.0%)	0 (0.0%)
QTcI (msec)			
>450	3 (5.1%)	3 (5.1%)	6 (10.0%)
>480	0 (0.0%)	1 (1.7%)	0 (0.0%)
>500	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: sponsor's Table 14.6.7.1

Table 6 presents the number and percent of subjects with increases from the predose baseline in QTc > 30 ms. The proportions of subjects with increases from the predose baseline in QTcF > 30 ms were 0.0%, 3.4%, and 1.7% for the placebo, 3.0-g, and 6.0-g treatment groups, respectively. The proportions of subjects with increases from the predose baseline in QTcB > 30 ms were 6.8%, 13.6%, and 10.0% for the placebo, 3.0-g,

and 6.0-g treatment groups, respectively. The proportions of subjects with increases from the predose baseline in QTcI > 30 ms were 6.8%, 5.1%, and 3.3% for the placebo, 3.0-g, and 6.0-g treatment groups, respectively. There were no subjects with increases from predose baseline in QTc > 60 ms.

Table 6: Summary of Subjects with Maximum Change from Baseline in QTcF, QTcB, and QTcl Intervals by Category and Treatment

Category	Placebo (N=59)	Vigabatrin 3.0 g (N=59)	Vigabatrin 6.0 g (N=60)
QTcF (msec)			
>30	0 (0.0%)	2 (3.4%)	1 (1.7%)
>60	0 (0.0%)	0 (0.0%)	0 (0.0%)
QTcB (msec)			
>30	4 (6.8%)	8 (13.6%)	6 (10.0%)
>60	0 (0.0%)	0 (0.0%)	0 (0.0%)
QTcI (msec)			
>30	4 (6.8%)	3 (5.1%)	2 (3.3%)
>60	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: sponsor's Table 14.6.7.2

4.2.8.3 Safety Analysis

There were no deaths, SAEs. As mentioned earlier 2 subjects discontinued due to AEs. One subject experienced hypersensitivity (event diagnosis: allergic reaction) after receiving 400 mg moxifloxacin and 1 subject (Randomization no. 0051) experienced costochondritis after receiving placebo.

Adverse events reported by the highest numbers of subjects included contact dermatitis (32 subjects; 53.3%) and dizziness (9 subjects; 15.0%).

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 7 (vigabatrin tablets in adults), Table 8 (moxifloxacin in adults), and Table 9 (vigabatrin oral solution in pediatrics). C_{max} and AUC values from healthy adults in the thorough QT study were 2-fold higher following administration of 6.0 g vigabatrin compared with 3.0 g vigabatrin in adults (the intended clinical dose) and 3-fold higher following administration of 50 mg/kg oral solution in children (the intended starting dose for NDA 22-006).

Table 7: Arithmetic Mean (%CV) of Pharmacokinetic Parameters of Vigabatrin

	Treatment	
Pharmacokinetic Parameter (unit)	3.0 g Vigabatrin N = 57	6.0 g Vigabatrin N = 57
AUC0-lqc (µg•h/mL)	419 (15)	854 (16)
AUC0-inf (µg•h/mL)	423 (15)	860 (16)
Cmax (µg/mL)	107 (19)	196 (22)
Tmax (h)[a]	0.85 (0.6–2.1)	1.10 (0.6–2.1)
t1/2 (h)	7.0 (15)	7.2 (13)
CL/F (L/h)	7.3 (15)	7.2 (16)
Vd/F (L)	73.8 (21)	74.6 (21)

%CV = percent coefficient of variation
Note: Pharmacokinetic parameters were calculated from actual sampling times.
[a] Median (Range)

(Source: Sponsor's QT Study OV-1033 Report)

Table 8: Arithmetic Mean (%CV) of Pharmacokinetic Parameters of Moxifloxacin

	Treatment
Pharmacokinetic Parameter (unit)	400 mg Moxifloxacin N = 57
AUC0-lqc (µg•h/mL)	30.4 (20)
AUC0-inf (µg•h/mL)	32.4 (20)
Cmax (µg/mL)	2.29 (26)
Tmax (h)[a]	2.10 (0.6–4.1)
t1/2 (h)	12.1 (14)
CL/F (L/h)	12.9 (21)
Vd/F (L)	223 (23)

%CV = percent coefficient of variation
Note: Pharmacokinetic parameters were calculated from actual sampling times.
[a] Median (Range)

(Source: Sponsor's QT Study OV-1033 Report)

Table 9: Arithmetic Mean (%CV) of Pharmacokinetic Parameters of Vigabatrin in Children and Infants After a Single Dose of 50 mg/kg Oral Solution

Pharmacokinetic Parameters	Infants		Children	
	S(+)	R(-)	S(+)	R(-)
Tmax (hr)	2.85 ± 1.61	2.35 ± 1.87	1.36 ± 0.96	1.28 ± 0.58
Cmax (mcg/mL)	13.90 ± 4.53	21.00 ± 6.60	23.80 ± 12.20	41.3 ± 13.9
$t_{1/2}$ (hr)	5.65 ± 1.52	2.87 ± 1.03	5.47 ± 1.93	5.68 ± 2.86
$AUC_{0-\infty}$ (mcg/mLxhr)	90.9 ± 27.9	106.00 ± 28.5	117.00 ± 26.00	147.00 ± 34.00
Cl/F (L/hr/kg)	0.591 ± 0.165	0.498 ± 0.110	0.446 ± 0.103	0.355 ± 0.082
Vd/F (L/kg)	4.630 ± 1.120	2.01 ± 0.68	3.480 ± 1.230	2.770 ± 1.190

(Source: Sponsor's QT Study OV-1033 Report)

4.2.8.4.2 Exposure-Response Analysis

The sponsor did not conduct an exposure-response analysis.

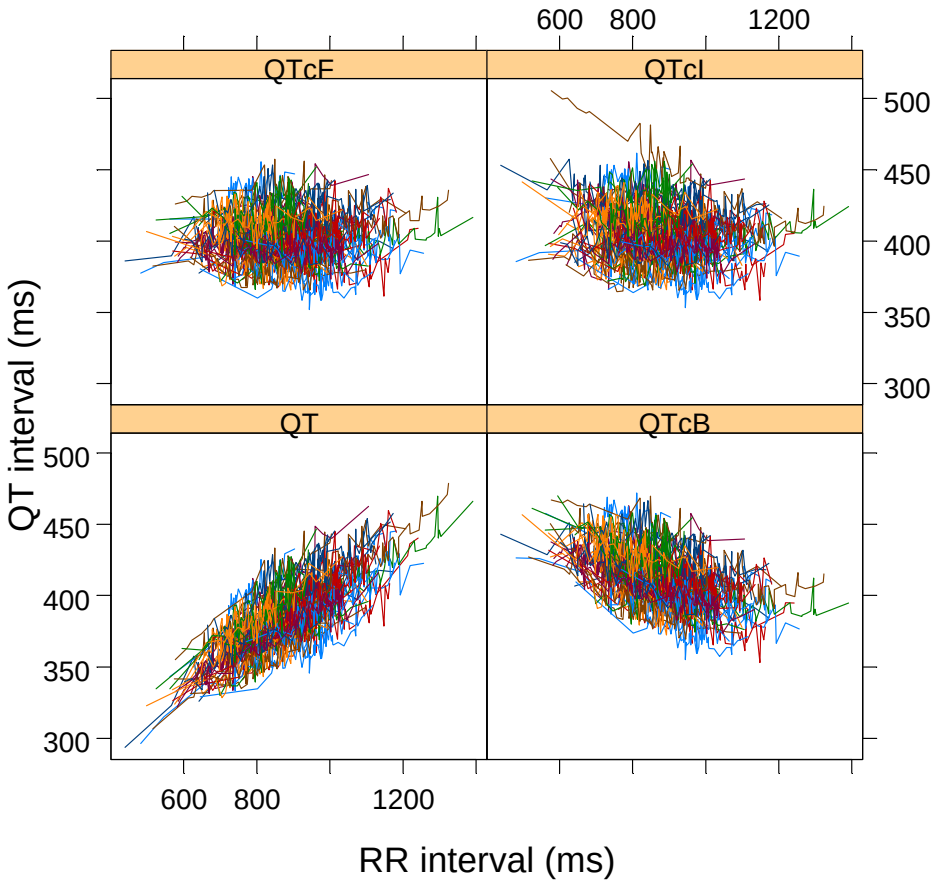
Reviewer's Analysis: A plot of ΔΔQTc vs. drug concentrations is presented in ***Figure 4****.*

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The observed QT-RR interval relationship is presented in Table 10 together with the Bazett's (QTcB), Fridericia (QTcF).

Figure 1: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



We evaluated the linear relationships between different correction methods (QTcB, QTcI and QTcF) and RR. We used the average sum of squared slopes as the criterion. The smaller this value is, the better the correction. Based on the results listed in the following table, QTcF is the best correction method with the lowest average sum of squared slope. Therefore, this statistical reviewer used QTcF as the primary outcome for the statistical analysis.

Table 10: **Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

Correction Method	Vigabatrin 3.0 g (N=59)	Vigabatrin 6.0 g (N=59)	Placebo (N = 58)	Moxifloxacin (N=58)	ALL (N=60)
QTcB	0.0059	0.0046	0.0043	0.0061	0.0046
QTcF	0.0022	0.0021	0.0018	0.0032	0.0013
QTcI	0.0026	0.0020	0.0023	0.0036	0.0016

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Vigabatrin

The statistical reviewer used mixed model to analyze the ΔΔQTcF effect. The model includes treatment, time points, period and gender as fixed effects and subject as a random effect. Interactions between treatment and time points were used to construct the LS means. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

Table 11: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group of Vigabatrin 3.0 g

	Vigabatrin 3.0 g		Placebo		ΔΔQTcF	
Time/(hr)	Mean	Std Err.	Mean	Std Err.	Mean	90% CI
0.25	1.1	1.1	3.8	1.1	-2.7	(-4.9, -0.5)
0.5	-2.8	1.1	-0.9	1.1	-1.9	(-4.1, 0.3)
0.75	-5.7	1.1	-3.9	1.1	-1.8	(-4.0, 0.4)
1	-5.4	1.1	-4.8	1.1	-0.6	(-2.8, 1.6)
2	-4.7	1.1	-2.4	1.1	-2.3	(-4.5, -0.1)
3	-1.4	1.1	1.2	1.1	-2.7	(-4.9, -0.5)
4	0.5	1.1	1.1	1.1	-0.6	(-2.8, 1.6)
6	-3.1	1.1	-4.2	1.1	1.0	(-1.2, 3.3)
8	-6.9	1.1	-6.4	1.1	-0.6	(-2.8, 1.6)
12	-1.7	1.1	-1.5	1.1	-0.2	(-2.4, 2.1)
16	5.3	1.1	6.8	1.1	-1.4	(-3.6, 0.8)
22	6.6	1.1	6.0	1.1	0.7	(-1.6, 2.9)

Table 12: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group of Vigabatrin 6.0 g

	Vigabatrin 6.0 g		Placebo		ΔΔQTcF	
Time/(hr)	Mean	Std Err.	Mean	Std Err.	Mean	90% CI
0.25	2.2	1.1	3.8	1.1	-1.6	(-3.8, 0.6)
0.5	-2.2	1.1	-0.9	1.1	-1.3	(-3.5, 0.9)
0.75	-5.9	1.1	-3.9	1.1	-2.0	(-4.2, 0.2)
1	-6.4	1.1	-4.8	1.1	-1.6	(-3.8, 0.6)
2	-4.5	1.1	-2.4	1.1	-2.1	(-4.3, 0.1)
3	-1.9	1.1	1.2	1.1	-3.1	(-5.3, -0.9)
4	0.3	1.1	1.1	1.1	-0.8	(-3.0, 1.4)
6	-5.3	1.1	-4.2	1.1	-1.1	(-3.3, 1.1)
8	-6.5	1.1	-6.4	1.1	-0.1	(-2.3, 2.1)
12	-0.2	1.1	-1.5	1.1	1.3	(-0.9, 3.5)
16	6.9	1.1	6.8	1.1	0.1	(-2.1, 2.3)
22	4.7	1.1	6.0	1.1	-1.2	(-3.5, 1.0)

The largest upper bounds of the 2-sided 90% CI for the mean difference between vigabatrin 3.0 g and placebo, and between vigabatrin 6.0 g and placebo were 3.3 ms at 6 hour and 3.5 ms at 12 hour, respectively.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same model to analyze moxifloxacin and placebo data at time 1-4 after dose. The whole time course for ΔΔQTcF of nine time points after dose is displayed in Figure 2. The largest unadjusted 90% lower confidence interval is 8.3 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 7.4 ms at two hour after dose, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

Table 13: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group of 400mg Moxifloxacin at Time Point 1-4

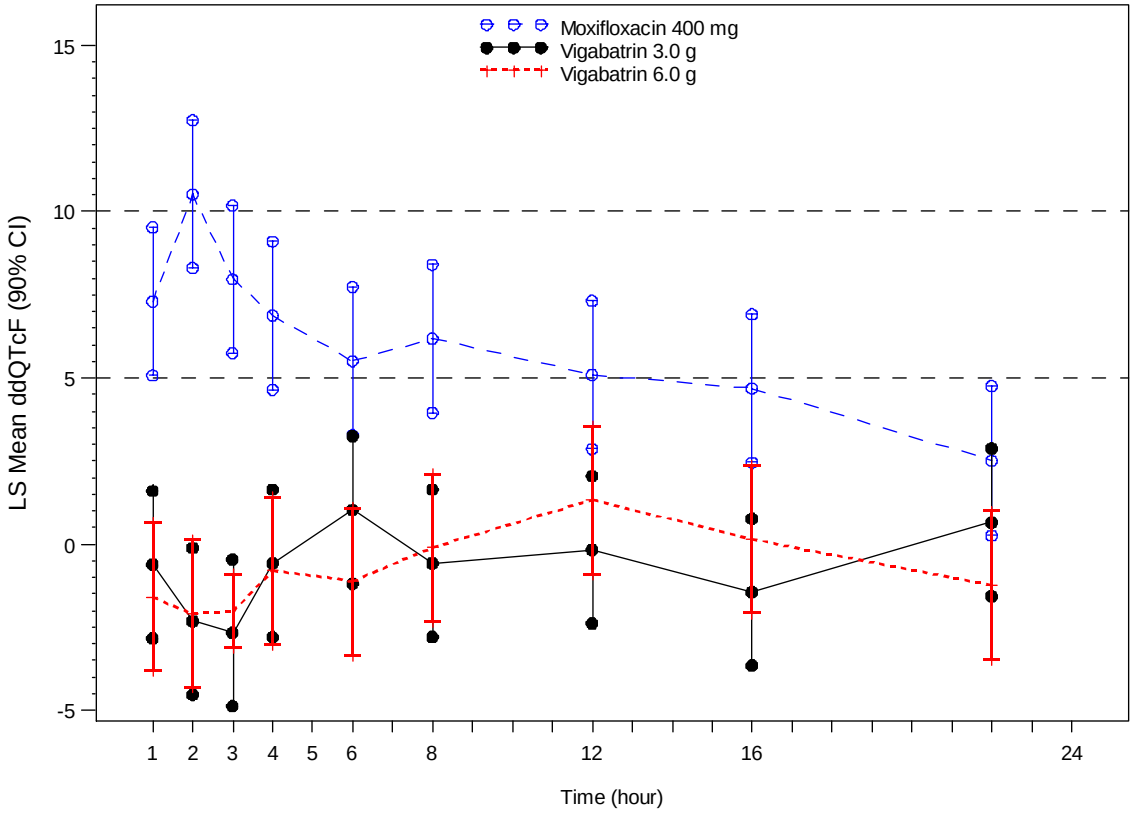
	Moxifloxacin		Placebo		ΔΔQTcF		
Time/(hr)	Mean	Std Err.	Mean	Std Err.	Diff LS Mean	Unadjusted 90% CI	Adjusted 90% CI
1	2.5	1.1	-4.8	1.1	7.3	(5.1, 9.5)	(4.2, 10.2)
2	8.1	1.1	-2.4	1.1	10.5	(8.3, 12.8)	(7.4, 13.3)
3	9.2	1.1	1.2	1.1	8.0	(5.8, 10.2)	(4.8, 10.8)
4	7.9	1.1	1.1	1.1	6.9	(4.7, 9.1)	(3.8, 9.7)

*Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

5.2.1.3 Graph of ΔΔQTcF over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

Figure 2: Mean and 90% CI ΔΔQTcF Timecourse



(Note: CIs are all unadjusted including moxifloxacin)

5.2.1.4 Categorical Analysis

Table 14 lists the number of subjects as well as the number of observations whose absolute QTcF values are ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 14: Categorical Analysis of QTcF

	Total N		Value<=450 ms		450 ms<Value<=480 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Baseline	60	234	60 (100%)	234 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	58	690	56 (96.6%)	685 (99.3%)	2 (3.4%)	5 (0.7%)
Placebo	58	679	57 (98.3%)	678 (99.9%)	1 (1.7%)	1 (0.1%)
Vigabatrin 3.0 g	59	706	57 (96.6%)	704 (99.7%)	2 (3.4%)	2 (0.3%)
Vigabatrin 6.0 g	59	706	58 (98.3%)	705 (99.9%)	1 (1.7%)	1 (0.1%)

Table 15 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

Table 15: Categorical Analysis of ΔQTcF

	Total N		Value<=30 ms		30 ms<Value<=60 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Moxifloxacin 400 mg	58	690	57 (98.3%)	689 (99.9%)	1 (1.7%)	1 (0.1%)
Placebo	58	679	58 (100%)	679 (100%)	0 (0.0%)	0 (0.0%)
Vigabatrin 3.0 g	59	706	57 (96.6%)	704 (99.7%)	2 (3.4%)	2 (0.3%)
Vigabatrin 6.0 g	59	706	58 (98.3%)	705 (99.9%)	1 (1.7%)	1 (0.1%)

5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 16. The largest upper limits of 90% CI for the PR mean differences between vigabatrin 3.0 g and placebo and vigabatrin 6.0 g and placebo are 6.1 ms and 4.6 ms, respectively.

Table 16: Analysis Results of ΔΔPR by Treatment Group

	Vigabatrin 3.0 g		Vigabatrin 6.0 g	
Time/(hr)	**LS Mean**	**90% CI**	**LS Mean**	**90% CI**
0.25	0.3	(-2.0, 2.6)	-2.1	(-4.3, 0.2)
0.5	-2.1	(-4.4, 0.1)	-2.0	(-4.3, 0.2)
0.75	-0.9	(-3.2, 1.3)	-1.1	(-3.4, 1.1)
1	-2.6	(-4.8, -0.3)	-3.8	(-6.0, -1.5)
2	1.4	(-0.9, 3.6)	-2.0	(-4.3, 0.3)
3	-0.4	(-2.6, 1.9)	-1.3	(-3.5, 1.0)
4	-0.2	(-2.5, 2.0)	-2.3	(-4.5, -0.0)
6	0.8	(-1.5, 3.1)	-0.5	(-2.7, 1.8)
8	0.7	(-1.6, 3.0)	-1.5	(-3.8, 0.7)
12	-0.6	(-2.9, 1.7)	-0.8	(-3.0, 1.5)
16	1.5	(-0.8, 3.7)	2.3	(0.1, 4.6)
22	3.8	(1.5, 6.1)	1.8	(-0.5, 4.1)

The outlier analysis results for PR are presented in Table 17 for those with PR > 200 ms for the study drug.

Table 17: Categorical Analysis for Observations PR >200 ms under Treatment

Treatment Group	ID	Time 0.25	Time 0.5	Time 0.75	Time 1	Time 2	Time 3	Time 4	Time 12	Time 16	Time 22	Baseline
Vigabatrin 3.0 g	052											(b) (4)
Vigabatrin 3.0 g	100											
Vigabatrin 3.0 g	112											
Vigabatrin 6.0 g	042											
Vigabatrin 6.0 g	052											
Vigabatrin 6.0 g	066											
Vigabatrin 6.0 g	100											
Vigabatrin 6.0 g	106											
Vigabatrin 6.0 g	112											

5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 18. The largest upper limits of 90% CI for the QRS mean differences between vigabatrin 3.0 g and placebo and vigabatrin 6.0 g and placebo are 1.1 ms and 0.6 ms, respectively. There is no subject who experienced absolute QRS interval greater than 120 ms in any treatment group.

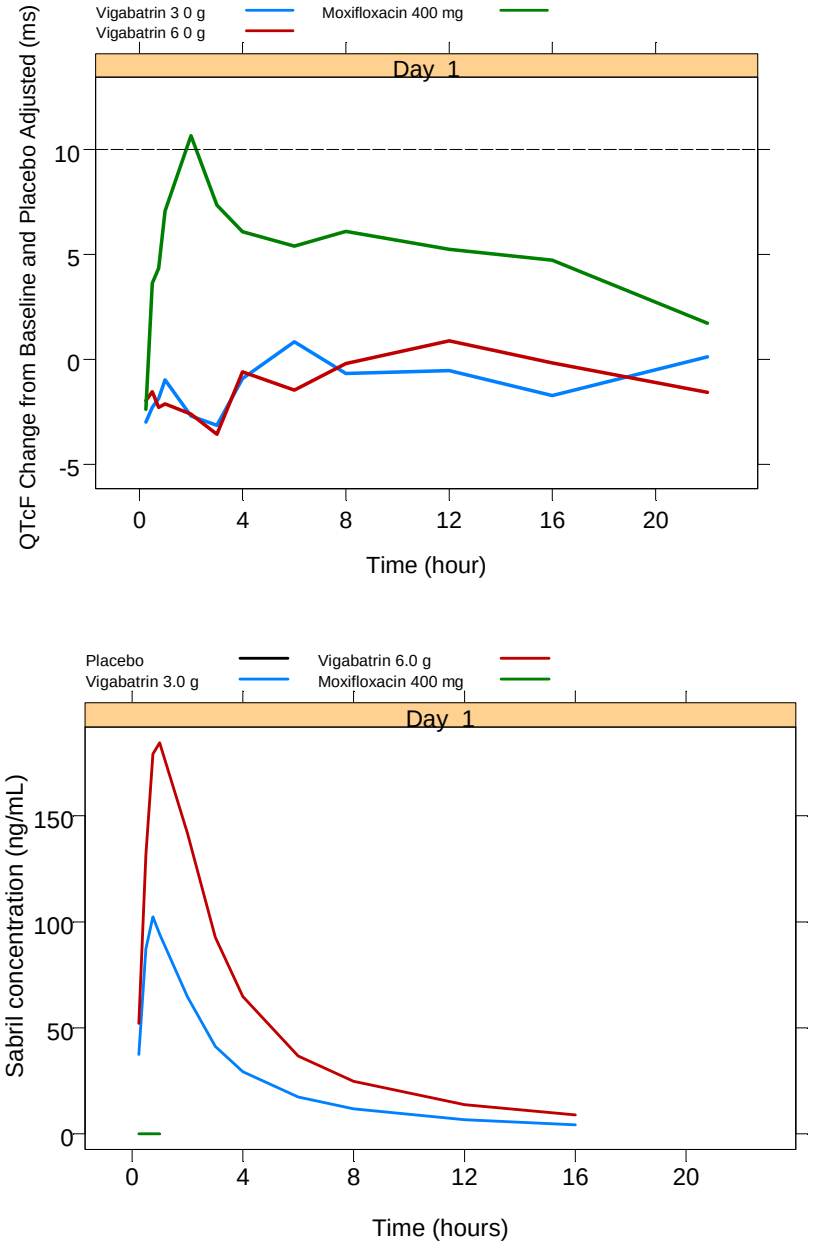
Table 18: Analysis Results of ΔΔQRS by Treatment Group

	Vigabatrin 3.0 g		Vigabatrin 6.0 g	
Time/(hr)	**LS Mean**	**90% CI**	**LS Mean**	**90% CI**
0.25	-0.2	(-0.9, 0.5)	-0.2	(-0.9, 0.5)
0.5	-0.5	(-1.1, 0.2)	-0.9	(-1.5, -0.2)
0.75	-0.9	(-1.6, -0.2)	-1.2	(-1.9, -0.5)
1	-0.2	(-0.9, 0.4)	-0.8	(-1.5, -0.1)
2	-0.7	(-1.3, 0.0)	-0.2	(-0.9, 0.5)
3	-0.2	(-0.9, 0.5)	-0.6	(-1.3, 0.1)
4	0.3	(-0.4, 1.0)	-0.1	(-0.8, 0.6)
6	0.4	(-0.3, 1.1)	-0.3	(-1.0, 0.4)
8	-0.0	(-0.7, 0.7)	-0.2	(-0.9, 0.5)
12	-0.6	(-1.3, 0.1)	-0.4	(-1.1, 0.3)
16	0.3	(-0.4, 1.0)	-0.1	(-0.8, 0.6)
22	0.4	(-0.2, 1.1)	-0.6	(-1.3, 0.1)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

5.3.1 QTcF and Vigabatrin Concentration Time Profiles

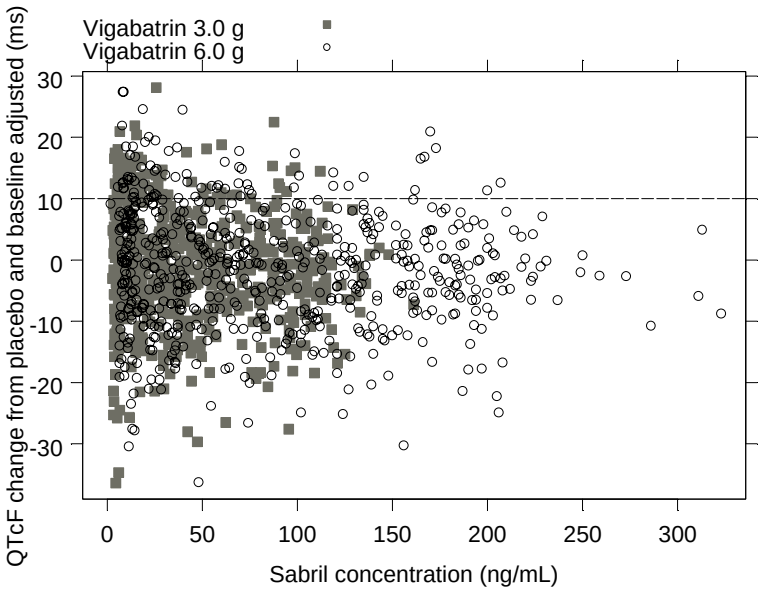
Figure 3: Mean Δ QTcF (change from baseline) (top), ΔΔ QTcF (placebo-adjusted change from baseline) (middle), Vigabatrin concentration (bottom) time profiles for Vigabatrin 3.0 g (blue line), Vigabatrin 6.0 g (red line), Moxifloxacin (green line), and Placebo (black line).



5.3.2 Sabril Concentration-QTcF Analysis

The relationship between ΔΔ QTcF and Sabril concentrations is visualized in Figure 4 with no evident exposure-response relationship.

Figure 4: ΔΔ QTcF vs. Sabril concentration.



No exposure response was evidenced from the range of vigabatrin exposures. Even if doses exceed 1.5 g (up to 5.0 g for therapy) in patients with severe renal disease and exposures exceed the maximum studied, it is not anticiptated to increase the QT interval based on the lack of increasing slope in the exposure-response data.

5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. The representative median beat was used for interval measurements, with less than 0.4% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There were no clinically relevant effects on the PR and QRS intervals. As reported in the statistical reviewer's analysis, seven out of the nine subjects who had an absolute PR interval over 200 ms after study drug had the same at baseline. The remaining two subjects had a baseline PR interval of over 190 ms. No subject had an absolute QRS interval of over 120 ms.

5.4.4 MGPS Datamining Analysis

The reviewer conducted an MGPS datamining analysis of the AERS database for AEs related to QT prolongation with vigabatrin. The signal scores (EBGM values) for sudden death and significant ventricular arrhythmias were below 2, indicating incidence rate similar to background rate in the general population. There were no reports of TdP.

Configuration: CBAERS BestRep (S) **Run :** Generic (S) **Run ID:** 338
Dimension: 2 **Selection Criteria:** Generic name(Vigabatrin) + PT(...)
3 rows Sorted by Generic name, EBGM desc

Generic name	Level 1	Level 2	PT	HLT	HLGT	SOC	N	EBGM	EB05	EB95	PRR
Vigabatrin	Fatty Acid Derivatives	Nerv	Convulsion	Seizures and seizure disorders NEC	Seizures (incl subtypes)	Nerv	11	2.51	1.51	3.97	5.17
Vigabatrin	Fatty Acid Derivatives	Nerv	Sudden death	Death and sudden death	Fatal outcomes	Genrl	2	1.81	0.588	4.55	11.0
Vigabatrin	Fatty Acid Derivatives	Nerv	Cardiac arrest	Ventricular arrhythmias and cardiac arrest	Cardiac arrhythmias	Card	3	1.56	0.610	3.45	2.78

ID:	338
Type:	MGPS
Name:	Generic (S)
Description:	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information
Project:	CBAERS Standard Runs
Configuration:	CBAERS BestRep (S)
Configuration Description:	CBAERS data; best representative cases; suspect drugs only; with duplicate removal
As Of Date:	12/19/2008 00:00:00
Item Variables:	Generic name, PT
Stratification Variables:	Standard strata
Highest Dimension:	2
Minimum Count:	1
Calculate PRR:	Yes
Calculate ROR:	Yes
Base Counts on Cases:	Yes
Use "All Drugs" Comparator:	No
Apply Yates Correction:	Yes
Stratify PRR and ROR:	No
Fill in Hierarchy Values:	Yes
Exclude Single Itemtypes:	Yes
Fit Separate Distributions:	Yes
Save Intermediate Files:	No
Created By:	(b) (4)
Created On:	12/28/2008 11:42:06 EST
User:	Suchitra Balakrishnan
Source Database:	Source Data: CBAERS data from Extract provided by CBER as of 12/19/2008 00:00:00 loaded on 2008-12-25 01:45:19.0

Dimension: 2 **Selection Criteria:** Generic name(Vigabatrin) + PT(Cardiac arrest, Convulsion, Sudden cardiac death, Sudden death, Torsade de pointes, Ventricular arrhythmia, Ventricular fibrillation, Ventricular flutter, Ventricular tachyarrhythmia, Ventricular tachycardia)
SELECT * FROM OutputData 338 WHERE (DIM=2 AND ((P1='D' AND ITEM1 IN ('Vigabatrin') AND P2='E' AND ITEM2 IN ('Cardiac arrest','Convulsion','Sudden cardiac death','Sudden death','Torsade de pointes','Ventricular arrhythmia','Ventricular fibrillation','Ventricular flutter','Ventricular tachyarrhythmia','Ventricular tachycardia')))) ORDER BY ITEM1,EBGM desc

These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Table 1. Highlights of Clinical Pharmacology	
Description	**Result**
Therapeutic Dose	The maximum dose to be used in the (b) (4) clinical studies will be 5 g/day (2.5 g BID). The maximum recommended dose for treatment of refractory complex partial seizures is 3 g/day (1.5 g BID), although up to 6 g/day has been used in clinical trials.
Maximum Tolerated Dose	The MTD is not established in humans. The NOAEL is 0.5 mg BID for multiple doses.
Principle Adverse Events	In U.S. and primary non-U.S. clinical epilepsy studies of 4,077 vigabatrin-treated patients, the most commonly observed (≥5%) adverse events associated with the use of vigabatrin in combination with other AEDs were headache (18.3%), somnolence (17.1%), fatigue (16.4%), dizziness (15.3%), convulsion (11.1%), nasopharyngitis (10.2%), weight increased (10.2%), upper respiratory tract infection (9.9%), visual field defect (8.7%), depression (8.2%), tremor (7.1%), nystagmus (7%), nausea (6.9%), diarrhea (6.7%), memory impairment (6.7%), insomnia (6.6%), irritability (6.6%), coordination abnormal (6.5%), vision blurred (6.3%), diplopia (6.2%), vomiting (6.1%), influenza (6%), pyrexia (5.6%), rash (5.6%), and constipation (5%). Because patients were also treated with other AEDs, it is not possible to determine whether these adverse events can be ascribed to vigabatrin alone, or to the combination of vigabatrin and other AEDs. The adverse events most commonly associated with vigabatrin treatment discontinuation in ≥1% of patients were convulsion (1.4%) and depression (1.5%).
Maximum Dose Tested	
Single Dose	4 g
Multiple Dose	6 g/day (3 g BID)
Exposure Achieved at Maximum Tested Dose	
Single Dose	4.0 g; C_{max} = 134.6 µg/mL (32.5%), AUC_{0-inf} = 588.5 µg*h/mL
Multiple Dose	2.0 g BID; C_{max} = 64.0 µg/mL (21.9%), $AUC_{0-12, ss}$ = 284.7µg*h/mL
Range of Linear PK	• 0.5 to 4.0 g (0.5, 1.0, 2.0, 4.0 g); single oral dose; • 0.5 and 2.0 g BID (1.0 and 4.0 g/day); multiple oral dosing for 5 days
Accumulation at Steady State	~1.26 (AUC_{0-inf}/AUC_{0-12}; BID dose)
Metabolites	VGB is not metabolized.
Absorption	
Absolute/Relative Bioavailability	Relative BA = 1.03
Tmax	~1 hr

Table 1. Highlights of Clinical Pharmacology	
Description	**Result**
Distribution	
Vd	Vigabatrin is widely distributed throughout the body; mean steady-state volume of distribution is 1.1 L/Kg (CV=20%).
% bound	Vigabatrin does not bind to plasma proteins.
Elimination	Renal, unchanged
Terminal ½ Life	7.42 (11.5%)
CL/F or Cl	93.6 mL/min (22%); 4.0 g single dose
Intrinsic Factors	
Age	The renal clearance of vigabatrin in healthy elderly patients (≥ 65 years of age) was 36% less than those in healthy younger patients. This finding is confirmed by population PK analysis of patient data from a U.S. controlled clinical trial.
Sex	No gender differences were observed for the pharmacokinetic parameters of vigabatrin in patients.
Race	A cross study comparison between 24 Caucasian and 8 Japanese patients who received 1, 2, and 4 g of vigabatrin indicated that the AUC, Cmax, and half-life were similar for the two populations, but the mean renal clearance of Caucasian patients was 16% higher than that of Japanese patients.
Hepatic & Renal Impairment	Mean AUC values increased approximately 32% and 253% and terminal half-life values increased from 8.1 hours to 12.1, and 23.4 hours in patients with mild to moderate (creatinine clearance of 40-79 mL/min) and severe (creatinine clearance of 10-39 mL/min) renal impairment, respectively. Vigabatrin is not metabolized. Therefore, the pharmacokinetics of vigabatrin in patients with impaired liver function have not been studied.
Extrinsic Factors	
Drug Interactions	Other than phenytoin, there are few known drug interactions with vigabatrin. Based on population pharmacokinetics, carbamazepine, clorazepate, primidone, and sodium valproate appear to have no effect on plasma concentrations of vigabatrin. Vigabatrin had no effect on plasma concentrations of clorazepate and primidone during controlled clinical studies. During concurrent vigabatrin treatment, population pharmacokinetic analysis of average plasma concentrations at end of study were compared with average plasma concentrations at baseline. Phenobarbital from phenobarbital or primidone was reduced by an average of 8% to 16%, and sodium valproate plasma concentrations were reduced by an average of 8%. These reductions did not appear to be clinically relevant. Phenytoin A 16% to 20% average reduction in total phenytoin plasma levels was reported in controlled clinical studies. *In*

Table 1. Highlights of Clinical Pharmacology	
Description	Result
Drug Interactions (cont)	*vitro* drug metabolism studies established that decreased phenytoin concentrations upon addition of vigabatrin therapy is likely due to induction of cytochrome P450 2C enzymes in some patients. Uniform phenytoin dose adjustment cannot be recommended. As always, dose adjustment of phenytoin or any other concomitant AED should be considered if clinically indicated, and not by pre-determined serum levels. Clonazepam In a study of 12 healthy volunteers, clonazepam (0.5 mg) co-administration had no pharmacokinetic effect on vigabatrin (1.5 g twice daily), nor did vigabatrin produce uniform effects on the pharmacokinetics of clonazepam. Alcohol Co-administration of ethanol (0.6 g/kg) with vigabatrin (1.5 g twice daily) indicated that neither drug influences the pharmacokinetics of the other. Oral Contraceptives In a double–blind, placebo–controlled study using a combination oral contraceptive containing 30 µg ethinyl estradiol and 150 µg levonorgestrel, vigabatrin (3 g/day) did not modify the in vivo indices of hepatic microsomal enzyme activity and did not interfere significantly with the cytochrome P450 isoenzyme (CYP3A) – mediated metabolism of the contraceptive tested. Additionally, no significant difference in pharmacokinetic parameters (elimination half–life, AUC, C_{max}, apparent oral clearance, time to peak, and apparent volume of distribution) between vigabatrin and placebo were found for ethinyl estradiol and levonorgestrel. Based on this study, vigabatrin is unlikely to affect the efficacy of steroid oral contraceptives.
Food Effect	The effects of a high fat meal on the pharmacokinetics of vigabatrin were minimal in a study of 24 healthy males administered a single oral dose of 1.0 g vigabatrin with and without a high fat meal. The absorption of vigabatrin co-administered with food was delayed in comparison to the fasted state, but the extent of absorption as measured by AUC was unchanged. The AUC values for the fasted and fed groups were 127 µg.h/mL and 117 µg.h/mL, respectively. Cmax was 30% lower and Tmax was about 2 times longer in the fed state versus the fasted state- 20.9 µg/mL and 2.14 hours versus 31.2 µg/mL and 1.00 hours, respectively. The half-life was extended in the fed group (9.15 hours) versus the fasted group (7.15 hours), but the renal clearance and the percentage of dose excreted in the urine values between the two groups were not different A food effect study involving administration of vigabatrin to healthy volunteers under fasting and fed conditions indicated that the Cmax was decreased by 33% while AUC remained unchanged under fed conditions.

Table 1. Highlights of Clinical Pharmacology	
Description	Result
Expected high Clinical Exposure Scenario	The major expected adverse events from the supratherapeutic dose are transient headache and drowsiness. Given linear pharmacokinetics, the supratherapeutic dose to be used in the TQT study of 6 g is 2.4 times the maximum single dose (2.5 g) to be tested in the stimulant addiction trials and the Cmax and AUC should be proportional. At 5 g/day, Cmax if dosed BID is predicted to be ~85 µg/mL; AUC is predicted to be ~ 366.9 µg*h/mL

6.2 TABLE OF STUDY ASSESSMENTS

Table 3. Schedule of Assessments

	Screening Days −28 to −3	Day −2	Day −1	Day 1	Days 2 to 3	Day 4	Days 5 to 6	Day 7	Days 8 to 9	Day 10	Day 11	End of Study Day 12
Informed consent	X											
Medical history	X	X										
Confinement[a]		X	X	X	X	X	X	X	X	X	X	
Laboratory profile[b]	X	X										X
Urine toxicology	X	X										
Electrocardiogram[c]	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[d]	X	X										X
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[f]	X	X										X
Vigabatrin dosing[g]				X		X		X		X		
Moxifloxacin dosing[h]				X		X		X		X		
Placebo dosing[i]				X		X		X		X		
Pharmacokinetic blood collection[j]				X	X	X	X	X	X	X	X	X
Adverse event monitoring[k]	X	X	X	X	X	X	X	X	X	X	X	X
Previous/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Discharge[l]												X

[a] Subjects were confined from Check-in (Day –2) through Day 12 or early withdrawal.
[b] Laboratory profiles were obtained at Screening, Day –2, and Day 12 or early withdrawal.
[c] Standard 12-lead electrocardiograms were collected at Screening, Day –2, Day 12, and at the following time points on Days 1, 4, 7, and 10: before dosing (0 hour), and 0.75, 8, and 24 hours after dosing. Digital electrocardiograms from Holter monitoring were collected at the following time points on Days 1, 4, 7, and 10: before dosing (–1.5, –1.0, –0.5, and 0 hours), and 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 16, and 22 hours after dosing. Baseline ECGs were collected at matching time points on Day –1.
[d] A complete physical examination was performed at Screening, Day –2, and Day 12 or early withdrawal.
[e] Vital sign measurements were collected with the subject in a seated position at Screening, and with the subject in a supine position on Day –2, Day –1, Day 12, and at the following time points on Days 1, 4, 7, and 10: before dosing (0 hour), and 0.75, 8, and 24 hours after dosing.
[f] A serum pregnancy test for female subjects was performed at Screening, Day –2, and Day 12 or early withdrawal.
[g] Vigabatrin was administered on Days 1, 4, 7, and 10 according to the randomization schedule as follows: 3.0 g solution and 1 placebo moxifloxacin tablet (Treatment A); 6.0 g solution and 1 placebo moxifloxacin tablet (Treatment B).

Table 3. Schedule of Assessments (continued)

[h] Moxifloxacin was administered on Days 1, 4, 7, and 10 according to the randomization schedule as follows: 1 overencapsulated 400 mg moxifloxacin tablet and placebo solution (Treatment C).
[i] Placebo was administered on Days 1, 4, 7, and 10 according to the randomization schedule as follows: placebo solution and 1 placebo moxifloxacin tablet (Treatment D).
[j] Blood samples for pharmacokinetic analyses were collected at the following time points on Days 1, 4, 7, 10: before dosing (0 hour), and 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 16, 23, 36, and 48 hours after dosing.
[k] Collection of adverse event data began after the informed consent form was signed.
[l] Subjects were discharged after completion of the study procedures on Day 12 or early withdrawal.

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/s/

Joanne Zhang
1/27/2009 01:02:50 PM
BIOMETRICS

Qianyu Dang
1/27/2009 01:10:53 PM
BIOMETRICS

Justin C Earp
1/27/2009 02:04:01 PM
BIOPHARMACEUTICS

Christine Garnett
1/27/2009 03:24:31 PM
BIOPHARMACEUTICS

Suchitra Balakrishnan
1/27/2009 05:58:30 PM
MEDICAL OFFICER

Norman Stockbridge
1/28/2009 09:49:59 AM
MEDICAL OFFICER

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA#:	**22006**
Submission Date:	12/28/2007
Brand Name:	Sabril®
Generic Name:	Vigabatrin
Formulation:	Powder for solution
Strength:	500mg powder
Sponsor:	OVATION Pharmaceuticals
Reviewer:	John Duan, Ph.D.
Submission Type:	NDA for infantile spasms

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

The original NDA 22-006 for Sabril® (vigabatrin) for Oral Solution was submitted on October 17, 2006 for the treatment of Infantile Spasms (IS) in infants from birth to 2 years. The Division issued a Refusal to File letter on November 9, 2006. Subsequent submissions were considered incomplete responses. The current resubmission is in response to the April 3, 2007 incomplete response letter.

This NDA is closely related to NDA 20-427, which has a long history including a series of resubmissions. The original NDA 20-427 for vigabatrin tablets was submitted on April 29, 1994 for the treatment of partial complex seizures. Eventually, a non approval letter was issued on October 26, 1998 due to the reports of visual field defects (VFD) associated with vigabatrin therapy. This review summarizes the studies previously reviewed, evaluates the newly submitted studies and focuses on the issues identified.

1.1 Recommendation

NDA 22-006 is acceptable from a clinical pharmacology standpoint, provided the labeling changes are incorporated in the final label. The Phase 4 commitment should be conveyed to the sponsor.

The following comments should be conveyed to the medical division.

Comments to the medical division

1. Study showed that the powder formulation is bioequivalent to the tablet formulation.

2. Pharmacokinetics in infants:

    - The results of the pharmacokinetic study conducted in infants (5 month - 2 years, n=6) and children (4 - 14 years, n=6) showed differences in the pharmacokinetics of the two enantiomers after a single dose of 50mg/kg. The difference is in the same trend as that in adult pharmacokinetic studies.
    - Multiple doses of 50 mg/kg/day given as bid for 5 days did not show significant accumulation based on pre-dose levels.
    - The differences of the pharmacokinetic parameters of vigabatrin between infants (5 month - 2 years, n=6) and children (4 - 14 years, n=6) can be described as a power model with the power with respect to body weight around 0.75 as shown in the following formula.

$$CL = 0.449 \times WT^{0.7585}$$

    - The above formula over predicts the clearance of adults by about 60% (11.26 L/h predicted vs. observed clearance value of 7 L/h), implying the difference in pharmacokinetics in children compared to adults.

- The pharmacokinetic data for children ages birth to 5 months and 2 to 4 years are not available. Pharmacokinetics may be different in the infants < 5 months due to development of the renal function. Additional PK data in infants < 5 months should be considered if it is clinically desirable to obtain exposure information in the age group. Missing data in the age group of 2-4 years is not only related to pharmacokinetics, but would also apply to effectiveness and safety in this age group. Additional data necessary in this age group should be based on clinical use in this age range.

3. Primarily from a safety perspective and based on the pharmacokinetic difference between different groups of children and between children and adults, the proposed starting dose (50mg/kg/day) and maximum dose (150mg/kg/day) for pediatrics would generate higher exposure in heavier children. Also, the exposure would be higher than that for the proposed starting dose (1g/day) and maximum dose (3g/day) in adults. Although a dose reduction is suggested by this reviewer (see Table below) in order to obtain comparable exposure among children with different body weights, and also to obtain exposure comparable to adults; the question of how this would translate to effectiveness can not be answered because of the lack of the knowledge of a dose response relationship in the IS patient population. Also the need to obtain comparable exposure to adults for effectiveness can not be justified as the disease state is different in the two populations (seizures in adults and IS in infants). Therefore, based on the PK differences among children with different body weights and between children and adults, dose reductions are suggested only for safety reasons. The medical division should take this into consideration along with the effectiveness and safety data in infants in order to assess the need for dose reduction in this population, although additional effectiveness assessments may need to be considered to determine the adequacy of these suggested doses.

Body weight (kg)	Starting Dose (mg/day)		Maximum Dose (mg/day)	
	Reviewer	Applicant	Reviewer	Applicant
1	50	50	150	150
2	100	100	300	300
3	150	150	450	450
4	200	200	600	600
5	200	250	600	750
6	250	300	750	900
7	250	350	750	1050
8	300	400	900	1200
9	300	450	900	1350
10	350	500	1050	1500
11	350	550	1050	1650
12	400	600	1200	1800
13	400	650	1200	1950
14	450	700	1350	2100
15	450	750	1350	2250

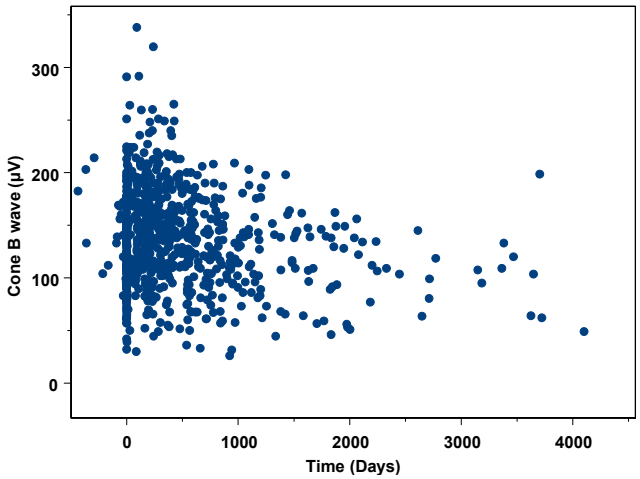
4. Dosing recommendation in renally impaired infants:

A renal impairment study in adults with mild, moderate and severe impairment suggested dose reductions of 25%, 50%, and 75%, respectively, in these populations. Adequate labeling/monitoring should be considered for infants with varying degrees of renal impairment (if any), while the renal function is being matured in infants up to 2 years of age.

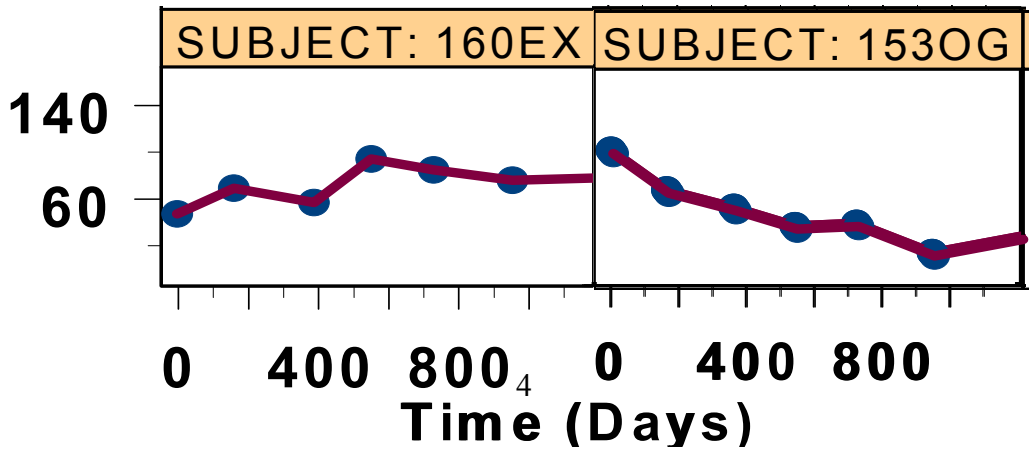
5. Exploratory analysis of VFD data:

   The medical division may consider these observations/exploratory analyses regarding the VFD.

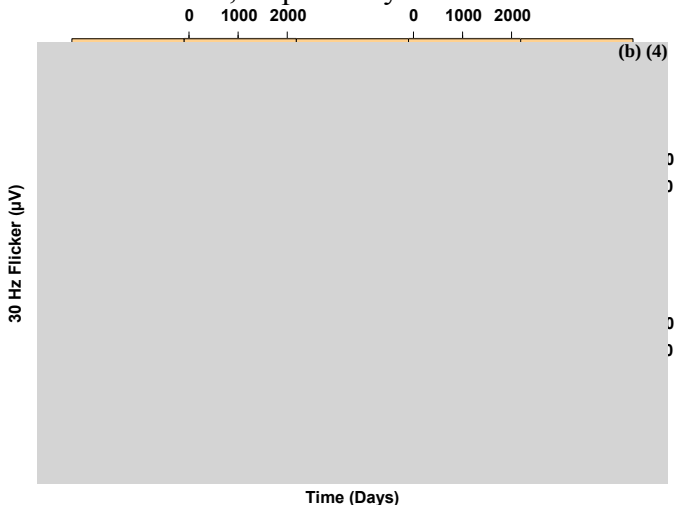
- The claim made by the applicant that visual field defect (VFD) only occurred long time after the initiation of vigabatrin dosing is misleading. It discounted the disease progression process of VFD and may result in missing the early warning signs of the worst forthcoming.
- The time courses of the ERG measurements (cone b-wave and 30 Hz flicker) show general trend for declining along with the time after dosing of vigabatrin as shown in the following figure (for cone b-wave), indicating the development of VFD may be an evolving process.



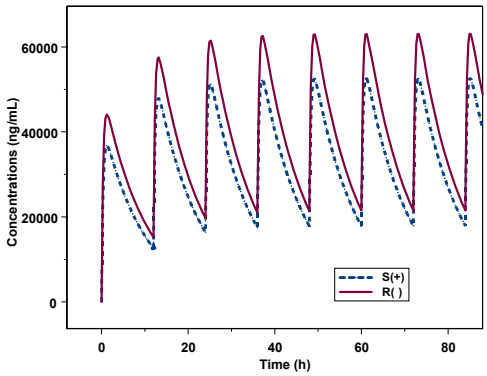
- Considering the subjects with more than 3 time points of ERG measurements, it is recognized that the declines had different slopes among the subjects. In a general consideration, the subjects can be divided into two groups according to the shapes of the time course of ERG. In one group, the 30 Hz flicker or cone b-wave showed a decline trend (as displayed in the right panel of the following figure for 30 Hz flicker) while in the other group, the measurements kept relatively constant (the left panel in the following figure).



- If as reported, 30 Hz flicker and cone b-wave have a close relationship with VFD, these measurements may reflect the VFD evolving process when monitored frequently enough. While the diagnosis of VFD using visual field measurement is a none-or-all process and difficult to pick the early warning signs, ERG may provide a more quantitative signal of the disease progression at relatively early time points.
- Based on limited data, it seems that the initial trends determined the general directions for future ERG measurements. Based on this hypothesis, ERG data from 88 patients in Toronto study (children) who had at least four measurements were analyzed. First three measurements were used to predict the general trend. Following figure overlaps the predicted trend lines (red lines) with the actual measurements (blue line with empty circles, which may not be seen due to overlaps). The shaded areas are the age corrected normal range with low and high boundaries representing the lower and upper limits of 95% confidence intervals of normal values of 30 Hz flicker, respectively.



- Although more data and analyses are needed, measurements of ERG at early time points should be treated as signals for the direction of further development of VFD. From conservative point of view, qualitatively speaking, a warning sign is signaled if the slope goes to negative. Further investigation should establish quantitative criteria.
- Vigabattin is a mixture of enantiomers. Vigabatrin exists as a 50/50 racemic mixture of two enantiomers; the S(+) isomer is pharmacologically active while the R(-) enantiomer is inactive. However, the difference of toxicity profiles between these two isomers is not clear. Although no data allow us to differentiate the contribution of different enantiomers to VFD and other adverse events, it is speculated that the inactive enantiomer may contribute to the adverse event with its higher concentrations (shown in the following figure) considering that dose is a significant predictor for VFD.



- Although VFD was found in considerable portion of the patients, some subjects were not affected although they had high exposure to vigabatrin. Given the evidence suggesting an idiosyncratic drug response, a literature search for the role of genetic variation was conducted. Two relevant studies have been found in this regard. One study (Hisama FM, Mattson RH, Lee HH, Felice K, Petroff OAC. GABA and the ornithine (delta)-aminotransferase gene in vigabatrin-associated visual field defects. Seizure 2001;10(7):505-7) identified a common intronic polymorphism although no clinically significant mutation was detected. Another study (Kinirons P, Cavalleri GL, Singh R, Shahwan A, Acheson JF, Wood NW, Goldstein DB, Sisodiya SM, Doherty CP, Delanty N. A pharmacogenetic exploration of vigabatrin-induced visual field constriction. Epilepsy Res 2006 Aug;70(2-3):144-52) found that the degree of visual field constriction correlated with three SNPs and one haplotype in a cohort of 73 patients. However the authors were unable to replicate these findings in a second independent cohort consisting of 58 patients, suggesting the initial results were possibly false positives, or variants of weak effect. Further investigation in this regard is warranted.

1.2 Phase 4 commitments

The following Phase 4 commitment should be conveyed to the applicant:

1. The applicant should evaluate the pharmacokinetics of vigabatrin in infants (birth to 5 months).
2. The applicant should evaluate the pharmacokinetics of vigabatrin in children (2 to 4 years), depending on clinical use in this age group.

1.3 Summary of important clinical pharmacology findings

Vigabatrin is an irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the catabolism of the inhibitory neurotransmitter gamma aminobutyric acid (GABA) in the brain. The mechanism of action of vigabatrin is attributed to irreversible enzyme inhibition of GABA-T, and consequent increased levels of the inhibitory neurotransmitter, GABA.

The original NDA for Sabril® (vigabatrin) for Oral Solution was submitted on October 17, 2006 for the treatment of Infantile Spasms (IS). The Division issued a Refusal to File letter on November 9, 2006. Subsequent submissions were considered incomplete responses. The major concerns include visual field defects (VFD) associated with vigabatrin therapy and the Agency requested information on the nature and reversibility of this side effect in adult and pediatric patients.

The current resubmission is in response to the April 3, 2007 incomplete response letter, in which the applicant was requested from clinical pharmacology perspective to provide study #, date, IND/NDA submission#, Series#, date, section/volume # or otherwise full reports for studies that support labeling. In this submission the sponsor has submitted 5 PK studies and 2 Analytical validation reports. Some of the studies in this submission have been submitted earlier with NDA 20-427 (Vigabatrin Tablets), which was submitted in 1994 and reviewed by Dr. Vijay Tammara. In his review of the original NDA, Dr. Vijay Tammara provided a summary of the clinical pharmacology of vigabatrin. Most of the following summary is from Dr. Tammara's review.

I. BIOAVAILABILITY:

A. Relative Bioavailabilitv:

The current submission includes a study showing the powder formulation to be reconstituted with 200 mL of water is bioequivalent with the tablet formulation.

II. PHARMACOKINETICS:

Vigabatrin exists as a 50/50 racemic mixture of two enantiomers; the S(+) isomer is pharmacologically active while the R(-) enantiomer is inactive. The plasma concentration-time profile for the R(-) enantiomer was approximately 1.25 times higher than the S(-) isomer after administration of 0.5 g or 2.0 g vigabatrin. Since the half-life values between enantiomers were similar, the difference in systemic bioavailability may be due to differences in absorption or distribution.

A. Absorption:

Following multiple oral doses of 1.5 g bid in adult epileptic patients, mean (%CV) Cmax was 61 μg/mL (21 %) with a Tmax of about 1.0 hour (34%). The Tmax is about 2.5 hours in infants (5 month-2 years) and 1.3 hours in children (4-14 years) after a single dose of 50mg/kg.

B. Distribution:

Mean (%CV) steady state volume of distribution is 1.1 L/Kg (20%). Equilibrium dialysis study using reconstituted human serum indicated that vigabatrin did not bind to plasma proteins.

C. Metabolism:

Vigabatrin was essentially excreted unchanged in humans as demonstrated by a radiolabeled study. Following a single 1.5 g dose (15 mL of 100 mg/mL oral solution containing 50μCi) of 14C-vigabatrin to 6 healthy male volunteers, it was observed that plasma radioactivity reached mean maximal level of 49 (13%) μg Eq./mL at 0.7 hours, indicating rapid absorption (Study 71754-1-C-027). The percent of radioactivity recovered in the urine after 72 hours was found to be 95% (20%) of the administered dose. Further, it was observed that in urine 82% (28%) of the administered dose was excreted as unchanged vigabatrin. The metabolites (vigabatrin-Iactam and another unidentified metabolite) accounted for less than 5% of the total dose in urine. Neither of these could be measured in plasma.

D. Elimination:

The mean apparent half-life of vigabatrin following administration of 500 mg tablet in adults was found to be 7.5 hours (CV 31%). In children, the half-lives are shorter. The relationship between clearance and body weight in children can be described by the following formula.

$$CL = 0.449 \times WT^{0.7585}$$

This formula over-predicts adult clearance by about 60%, implying the pharmacokinetic differences between adults and children.

III. DOSE PROPORTIONALITY:

Dose proportionality of vigabatrin was assessed from several studies by Dr. Tammara. In a single dose study involving Caucasians, dose-proportionality of vigabatrin at four dose levels (0.5, 1, 2, and 4 g) was evaluated in 23 normal healthy male volunteers (Study 71754-1-C-014). AUC and Cmax of vigabatrin increased proportionally with dose, while half-lives stayed constant at about 7.0 hours across doses. Thus, it can be concluded that vigabatrin displays linear kinetics in the 0.5 - 4 g dose range.

In a multiple dose study in Caucasians dose-proportionality was assessed at 0.5 and 2 g doses administered every 12 hours for 5 days to 24 normal healthy male subjects (Study 71754-1-C-015). Steady state is attained within two days. Accumulation of the drug appears to be modest at multiple dosing (i.e., accumulation: 1.2; theoretical R= 1.5). Based on normalized AUC0-12, Cmax, and Cmin values, vigabatrin displays linear kinetics over the dose range of 0.5 - 2.0 g bid. Further, both the R (-) and S (+) enantiomer displayed linear pharmacokinetics over the dose range of 0.5 - 2.0 g bid. It was observed that the enantiomers do not interconvert.

In another study, dose proportionality at three single dose levels of 1, 2, and 4 g was evaluated in 7 Japanese healthy male subjects (Study JGVG-CL-101 A). The mean AUC and Cmax values for 1, 2, and 4 g doses were found to be proportional. The mean half-

life decreased from 7.6 hours at 1 g dose to 5.5 hours at the 4 g dose (a 30% decrease). This decrease in half-life was accompanied by a 30% decrease in the volume of distribution such that the overall clearance of the drug remained the same.

Population analysis indicated that vigabatrin did not deviate from linearity at 4 - 6 g daily dose.

The two dose proportionality studies above (Caucasian and Japanese) allow for an across race comparison which is presented under the section - Effect of Race.

IV. BIOEQUIVALENCE STUDY

In addition to the study mentioned in section I, the US film-coated vigabatrin tablet (the to-be-marketed formulation for NDA 20427) was tested for equivalency with US uncoated vigabatrin tablet (which was used in clinical and pharmacokinetic studies) in 12 healthy male subjects (Study 71754-1-C- 029). 90% Confidence interval analysis (two one-sided tests procedure) using log transformed data for vigabatrin AUC0-∞ and Cmax indicated that the US film-coated tablets are bioequivalent to the US uncoated tablets; AUC 99 - 105%; Cmax 89 - 104%. Mean Tmax was comparable (0.8 hrs). Variability in the pharmacokinetic parameters was < 20%.

V. MULTIPLE DOSE STUDY-PATIENTS VS. HEALTHY SUBJECTS

A cross study comparison of vigabatrin pharmacokinetics between patients (n = 11; 6M/5F; Study 71754-1-C-018) who received 1.5 g bid for 4 days and healthy subjects who received 2 g bid for 5 days was performed (Study 71754-1-C-015). This involved a 25% normalization of the data obtained in subjects. The demographics of the two populations are comparable. No difference was observed in the mean pharmacokinetic parameters of AUC, Cmax, and CL; Tmax occurred 15 minutes earlier and Cmin was 28% lower in epilepsy patients in comparison to healthy subjects -- (mean Cmins 4.4 vs 6.1 pg/mL; CVs for both population about 25%). There was no difference in the excretion of vigabatrin in these two populations as indicated by similar CLtotal, CLr, and percent of vigabatrin recovered in the urine.

VI. FOOD EFFECT STUDY

The influence of food on the bioavailability of vigabatrin 500 mg US uncoated tablets was studied in 24 healthy male volunteers in a single dose, crossover study (Study 71754-1-C-017). Each treatment was separated by a one week washout period. Subjects received 2 x 500 mg tablets after an overnight fast or 2 x 500 mg tablets along with a standardized calorie-rich breakfast (2 slices of toasted white bread with butter, 2 eggs fried in butter, 2 slices of bacoa, 2 ounces of hash-brown potatoes, 8 ounces of whole milk). It was observed that in the presence of a calorie-rich breakfast, mean Cmax of vigabatrin decreased 33% and mean tmax increased two-fold (fasted: 1 hr; fed: 2 hrs). Food increased the variability of these parameters. There was no change in AUC. Thus, oral

administration of vigabatrin during a meal resulted in a slower rate of absorption compared to its administration in a fasted state.

In the bioequivalence study (Study 71754-1-C-029), it was seen that US film coated tablet (the to-be-marketed formulation for NDA 20427) is bioequivalent to US uncoated tablet. Even though a direct food effect study on film coated tablets was not performed, the conclusions drawn from this food study (involving uncoated tablets), would provide for a reasonable representation of the effect of food on film coated tablets. However, it is not clear what extend of food effect would be on the powder formulation.

VII. SPECIAL POPULATION STUDIES

Effect of Age-elderly:

Pharmacokinetics of vigabatrin in 12 healthy elderly male subjects (mean age: 75.3 ± 6.8 years; mean wt: 77.8 ± 10.6 Kg; Study 71754-1-C-023) and in 24 healthy young subjects (mean age: 27.3 ± 8.2 years; mean wt: 71.6 ± 10.2 Kg; Study 71754-1-C-014) was evaluated in a cross-study single dose (1 g) comparison using tablets formulation. Renal and oral clearance of vigabatrin were 33% and 20% less in elderly subjects in comparison to young subjects.

Population analysis of vigabatrin pharmacokinetics in the patient population indicated that oral clearance of the drug increased with a patient's body weight and decreased with their age.

Caution should be exercised in elderly patients due to their decreased clearance of vigabatrin.

Effect of Age-pediatric:

The results from the study conducted in pediatric patients showed the differences in the pharmacokinetics of the two enantiomers. The difference is in the same trend as that in adult pharmacokinetic studies. The differences between infants (5 month to 2 years) and children (4-14 years) of the pharmacokinetics could be described by a formula $CL = 0.449 \times WT^{0.7585}$. The age-related differences could be accounted for by either a lower bioavailability or a higher renal clearance (on the body weight normalized basis) in younger subjects. The latter is consistent with the normal changes in renal clearance with age. However, the age effect has not been studied systematically. The pharmacokinetics of vigabatrin in children below 5 months and between 2 and 4 years have not been documented. The formula listed above over-predicts the adult clearance by about 60%, implying the pharmacokinetic difference between children and adults.

Effect of Gender:

No gender differences were observed for the pharmacokinetic parameters of vigabatrin in patients (6M/5F; Study 71754-1-C-018). Further, population analysis (Report K-92-0350-

CDS) also indicated that there is no gender difference in the pharmacokinetics of vigabatrin.

Effect of Race:

The applicant did not investigate race differences in the pharmacokinetics of vigabatrin. However, in a cross-study comparison of the pharmacokinetics of vigabatrin in 23 Caucasians (Study 71754-1-C-014) and in 7 Japanese (Study JGVG-CL- 101A) subjects who were administered 1, 2, and 4 g doses of vigabatrin indicated that the AUC, Cmax, and half-life are comparable. As tablets formulation, the mean renal clearance of Caucasians (5.2 L/hr) was about 25% higher than the Japanese (4 .0 L/hr). Inter-subject variability in Caucasians was observed to be ≈ 20%; in Japanese it was ≈ 30%.

Effect of Renal Insufficiency:

Pharmacokinetics of vigabatrin following single dose of 0.75 g oral solution was evaluated in 24 adult subjects with varying degrees of renal function (Study 71754-1-C-016). Dr. Tammara reclassified renal impairment into four groups, instead of three as originally provided by the sponsor; these groups are as follows: normal (creatinine clearance Clcr > 70 mL/min), mild (CLcr from > 50-70 mL/min), moderate (CLcr from> 30-50 mL/min), and severe (CLcr from> 10-30 mL/min). Dialysis patients were not studied.

Mild vs. Normal: Mean AUC∞ increased by 30% and the terminal half-life increased by 55% (8.1 hr vs 12.5 hr) in mildly renally impaired group in comparison to normal group. Inter-subject variability for these pharmacokinetic parameters was observed to be comparable between the two groups. An increase in AUC resulted in a corresponding decrease in clearance of vigabatrin. (Renal clearance was obviously less in this group (40%)).

Moderate vs. Normal: Mean AUC∞ increased by two-fold and the terminal half-life increased by two-fold in moderately renally impaired group in comparison to normal group. (Renal clearance is 3-fold less in this population). Inter-subject variability for these pharmacokinetic parameters was observed to be higher in the moderate group (CV: 35% vs. 15%). Accumulation of vigabatrin can occur in the moderate group and dosage adjustment is recommended. Patients with moderate renal impairment should be started with a lower dose of vigabatrin and monitored for any side effects.

Severe vs Normal: Mean AUC∞ increased by 4.5-fold and the terminal half-life increased by 3.5-fold in severely renally impaired group in comparison to normal group. (Renal clearance is 8-fold less in this population). Accumulation of vigabatrin can occur in the severe group and dosage adjustment is recommended. Patients with severe renal impairment should be started with a lower dose of vigabatrin and monitored for any side effects.

If pediatric patients, who are in renal development stage, have renal malfunction, it may be reasonable to reduce the dose by the same percentage as adults with different degree of renal impairments, if considered clinically relevant.

VIII. DRUG INTERACTION STUDIES

Phenytoin: Data from a number of clinical and pharmacokinetic studies have shown that a vigabatrin-phenytoin interaction exists. Upon administration of 2-3 g vigabatrin to eight stable, patients with epilepsy (six week treatment) taking phenytoin for at least one month, plasma levels of phenytoin decreased 23% (Report S-87-0018-C). An additional study measuring the steady-state pharmacokinetic interaction between vigabatrin and phenytoin in healthy male subjects was performed to characterize this interaction. The results showed that there was a mean trend toward decrease in total phenytoin plasma area under the concentration-time curve, maximum concentration, and trough concentration of approximately 17-23% (Reports K-97-0494-D, Study 0260). The mechanism causing the interaction was previously unknown. The common causes of interaction such as changes in protein binding or alterations of absorption have been ruled out. Recent in vitro studies have demonstrated decreased phenytoin concentrations is likely due to induction of cytochrome P450 2C enzymes in some patients.

Individual changes in phenytoin pharmacokinetics demonstrated varying results that were not always reflected in the mean response. Consequently, plasma phenytoin concentrations of patients on phenytoin therapy should be monitored after adding vigabatrin to the patient's therapeutic regimen. Phenytoin dose adjustment should be considered in those cases in which plasma levels of phenytoin are no longer in the therapeutic range and/or clinical effects of concentration changes are demonstrated.

Plasma vigabatrin trough concentrations were not significantly affected by coadministration with phenytoin.

Clonazepam: The interaction of vigabatrin with clonazeparn was investigated in 12 healthy male volunteers (Study W-91-0056-C). Vigabatrin (or placebo) was administered as 1.5 g bid for two days; to the ongoing treatment on day three a single dose of clonazepam (0.5 mg) was administered. Clonazepam co-administration has no influence on the pharmacokinetics of vigabatrin. In turn, vigabatrin seems to increase the mean Cmax of clonazepam by 30% and decrease the mean Tmax by 45%. AUC values for clonazeparn were not computed because the sponsor mentions that several samples were below the limit of quantification.

Alcohol: The interaction of vigabatrin with alcohol was investigated in 12 healthy male volunteers (Study W-91-0057-C). Vigabatrin (or placebo) was administered as 1.5 g bid for two days; to the ongoing treatment on day three a single dose of ethanol (0.6 g/kg) was administered. The results indicated a slight reduction in Cmax (11 %) and AUC0-12 (5%) of vigabatrin when coadministered with ethanol; Tmax was prolonged by 40 minutes. It was observed that vigabatrin did not alter the pharmacokinetics of ethanol. Overall, it appears that neither drug influences the pharmacokinetics of the other.

IX. POPULATION PHARMACOKINETIC ANALYSIS

Population analysis was performed on vigabatrin pharmacokinetic data obtained in a clinical efficacy study involving 174 adult patients with uncontrolled complex partial seizures (Report K-92-0350-CDS). The clinical study was a double-blind, placebo controlled, randomized, parallel group dose response study.

These patients were already receiving other antiepileptic drugs (AEDs) such as carbamazepine, phenytoin, valproic acid, primidone, and phenobarbital. The patients were randomized to receive placebo (45), 1 g/day vigabatrin (45), 3 g/day vigabatrin (43), and 6 g/day vigabatrin (41) titrated over 6 weeks. The regimen was maintained over the following 12 weeks. Plasma samples were collected periodically during the study for the measurement of vigabatrin and other concomitant AEDs. Pharmacokinetic analysis of plasma concentrations using NONMEM indicated that potential covariates such as race, gender, study site, concomitant AEDs, and creatinine clearance had no influence on the pharmacokinetic parameters of vigabatrin. However, it was observed that oral clearance of vigabatrin increased with a patient's body weight and decreased with their age.

X. PHARMACOKINETIC - PHARMACODYNAMIC ANALYSIS

In random order at weekly intervals, 10 healthy volunteers received single oral doses of either placebo, 1 g, 2 g, 3 g of vigabatrin or 3 mg lorazepam to evaluate cognitive function and attention tests. Relative to a 3 mg dose of lorazepam serving as a control and showing significant deterioration in cognitive function and attention tests, the three different dose levels of vigabatrin showed minimal changes.

XI. DOSE LEVELS OF VIGABATRIN IN CSF AND CSF BIOCHEMISTRY

Vigabatrin was administered in a single-blind design to 6 epileptic patients (S-84-0044-C). For the first 2 weeks, 1 g/day of vigabatrin was added to pre-existing anti-convulsant therapy; this was followed by 2 weeks of treatment with 2 g/day and then by 2 weeks of placebo. Upon completion of the placebo period, patients were placed on a chronic regimen of 1.5 to 2 g/day of vigabatrin depending upon efficacy and tolerance. The daily dose of vigabatrin administered during the three year study period ranged from 1.5 g to 4.5 g. Oral administration of vigabatrin resulted in a linear increase in the suboccipital CSF concentrations of vigabatrin with dose. It should be noted that other concomitant AEDs were also administered to this group of patients.

Eleven patients with drug-refractory partial seizures with a mean frequency of at least 4 seizures/month received a single dose of vigabatrin as an oral solution (50 mg/kg; S-88-0014-C). Further, they were receiving at least one, but not more than two other anti-epileptic drugs. CSF vigabatrin concentrations at 6 and 24 hours represented approximately 10% of the corresponding blood concentrations. This single dose of vigabatrin significantly increased total GABA levels till 120 hours post-dosing. Similarly, HC (homocarnosine) concentrations were increased significantly at 6 hours, but by 120

hours they had decreased to predrug levels and were no longer significantly different. Free GABA and 5-HIAA (hydroxyindole acetic acid) concentrations, on the other hand, were only significantly elevated at 72 and 120 hours; HVA (homovanillic acid) concentrations were significantly different at 72, 120, and 168 hours. Thus, significant increases of long duration in CSF concentrations of total and free GABA, HC, 5-HIAA, and HVA were seen after a single dose of vigabatrin. 5-HIAA and HVA might be related to the elevation of CNS GABA.

2. QUESTION BASED REVIEW

1. What are the clinical effectiveness and safety vigabatrin (VGB) in trials for the treatment of infantile spasms?

The effectiveness of VGB in the treatment of IS is supported in this application by the 3 controlled studies (Studies 1A, W019, and FR03). In the 3 controlled studies, a total of 275 subjects received VGB. These subjects were all younger than 2 years of age (at the time of study enrollment) and of either sex. Starting doses of VGB evaluated in these studies ranged from 18 to 150mg/kg/day and the doses were increased to a maximum dose of 369.5 mg/kg/day in the long-term follow-up periods. All 3 controlled studies assessed the effect of VGB therapy on cessation of spasms, either based on clinical evaluations or on clinical evaluations plus video EEG.

Trial 1A is a high/low-dose comparator study of 221 subjects. The primary efficacy endpoint was the proportion of subjects achieving spasm cessation for 7 consecutive days beginning within the first 14 days of therapy and confirmed via closed-circuit television (CCTV) EEG monitoring within 3 days of the seventh day of spasm freedom. High-dose VGB (target of 100 to 148mg/kg/day) was shown to be more effective in achieving spasm cessation than low-dose VGB (target of 18 to 36mg/kg/day). In the high-dose group, 17/107 (16%) of subjects had complete cessation of spasms compared with 8/114 (7%) of subjects in the low-dose group (p=0.0375).

Study FR03 used an active control (hydrocortisone). The primary efficacy endpoint was the proportion of subjects in each group with a total disappearance of spasms. The study was a multicenter, open-label, randomized, comparative, response-mediated, 2-month cross-over study to compare the efficacy and safety of VGB (150mg/kg/day without titration) and hydrocortisone (15mg/kg/day) as first-line monotherapy in the treatment of infants with newly diagnosed IS. Results showed that 100% of VGB-treated subjects vs. 36% of hydrocortisone-treated subjects achieved spasm control and/or cessation (p=0.001). Subjects could be crossed over to the other treatment group after 1 month in the case of inefficacy or intolerance to the first treatment. None of the subjects who initially received VGB crossed over. Seven of the hydrocortisone treated subjects crossed over to VGB because of intolerance (1) or lack of control (6), and all 7 achieved complete spasm cessation with VGB.

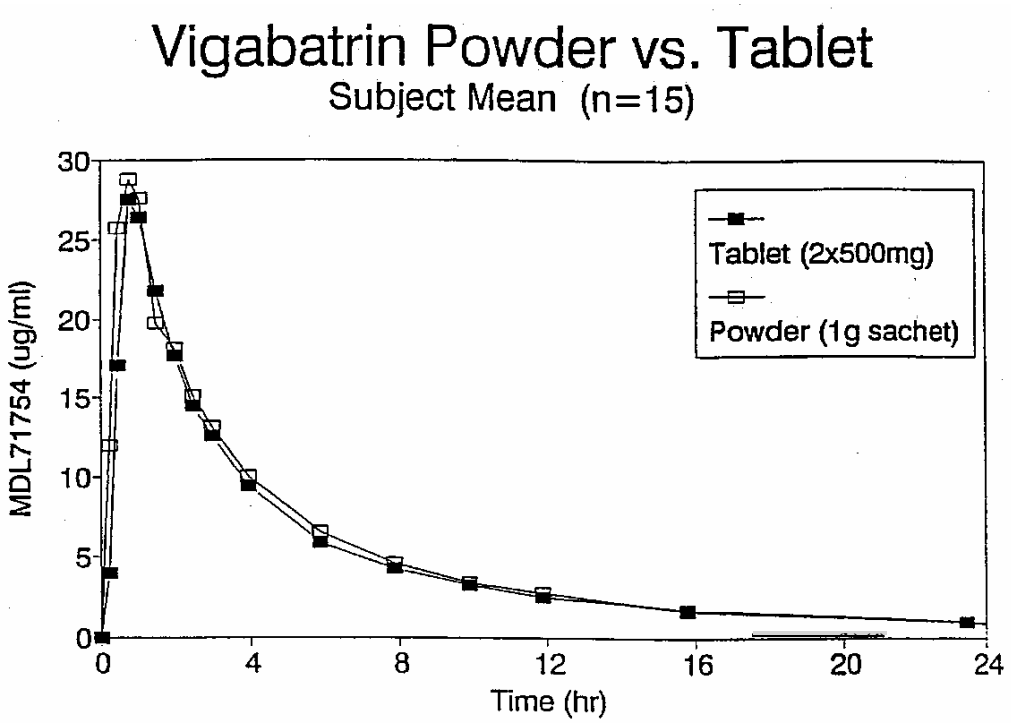
Study W019 used a placebo control and defined the primary efficacy endpoint as the average percent change in spasm frequency over a 2-hour sampling window each day to the final 2 days of the double-blind period. The study consisted of a baseline period of 2 to 3 days, then a 5-day double-blind treatment phase during which subjects were treated with VGB in ascending dose to 150mg/kg/day (if tolerated) or placebo according to predetermined randomization. Subjects were then followed for a period of 6 months, during which all subjects continuing in the study were treated with VGB in open label fashion. The difference in reduction of spasms between VGB and placebo was not statistically significant 54.4% vs 41.5% (p=0.562). The applicant deemed that the

sampling window of 2 hours per day was poorly chosen and the treatment effects could not be properly discerned. When a measure of spasm frequency over 24 hours was used, the percent reduction in spasms in the VGB group was 68.9% compared with 17.0% in the placebo group (p=0.030).

Intramyelinic Edema (IME)/MRI abnormalities and visual field defects (VFD) were the major safety concerns. Vigabatrin related IME was a major preclinical safety finding. IME, manifested as microvacuolization in the brain, has been identified in mice, rats, dogs, and less consistently in monkeys. These findings led to a clinical hold for the CPS development program and 3 advisory committee meetings. VGB causes bilateral, concentric peripheral constriction of the visual field, ranging from mild to severe. Visual field constriction may *begin* immediately in most patients, but not be *detected* for weeks or months until reaching a certain threshold. Most studies support the finding of defect that occurs in approximately 50% of subjects. However, for the roughly 50% of patients that don't develop field defect after a number of years of VGB, some risk of late development of field defect might remain with continued exposure. Improvement of the visual field defect is very rare, and can't be considered likely. To address the VFD safety issues, several studies were conducted including study 4020 (in adults and children), Toronto study and Boston study (both in children). In these studies, visual field perimetry and/or ERG measurements were performed to determine the prevalence, the incidence and clinical course of VFD.

2. Is the powder formulation bioequivalent to the tablet formulation?

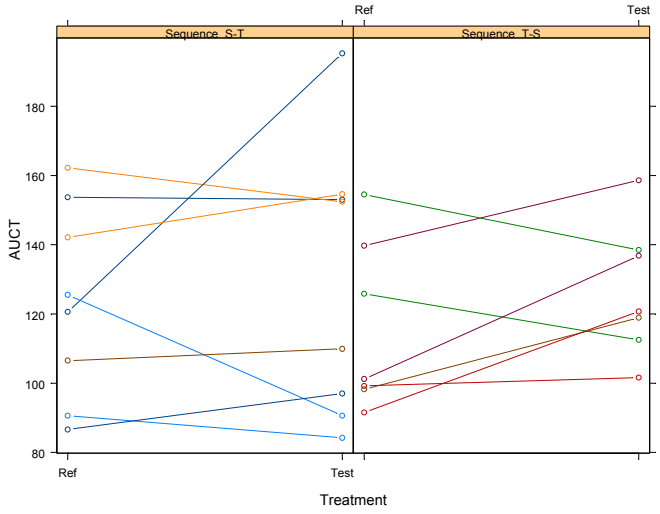
The mean plasma profiles for the tablets formulation and the powder formulation are shown below.

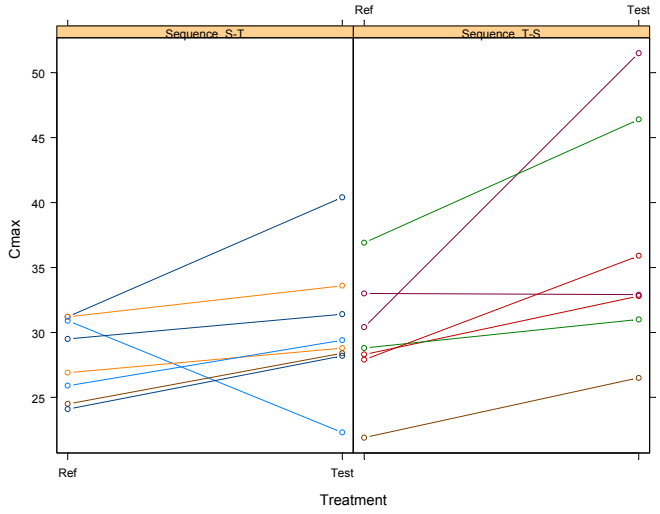


The results of the comparison between the powder and the tablets are summarized in the following table. In the table, the geometric mean ratios for AUC and C_{max} between powder formulation and tablet formulation along with their 90% confidence intervals are listed.

Parameters	Ratio	Upper CI	Lower CI
C_{max}	114.655	124.000	106.015
AUC	106.746	117.163	97.255

Although 90% confidence intervals fall within the bioequivalence range, the AUC and C_{max} for the powder formulation (labeled as Test in the following figures) seem to have a higher trend compared to the tablets (labeled Ref), especially for C_{max} as shown in the following figures. This is understandable due to the fact that solution is generally absorbed faster than the solid dosage forms.

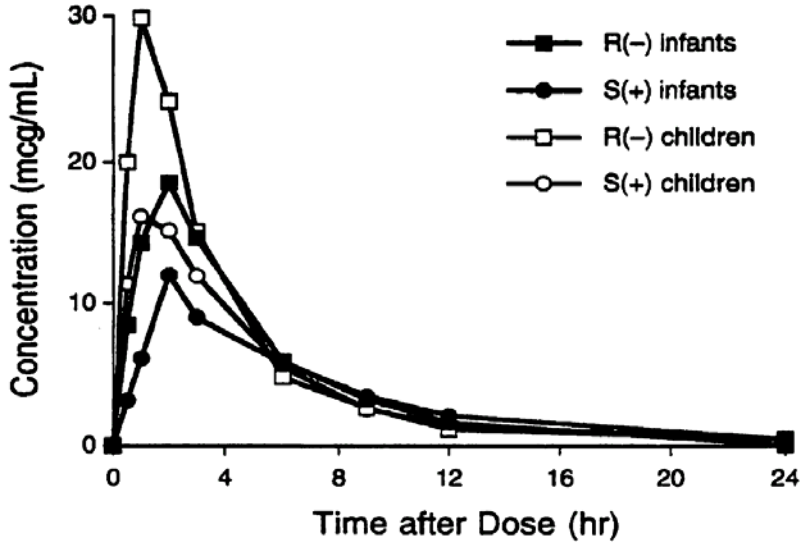




Therefore, the powder formulation can be considered bioequivalent with the tablet formulation.

3. Are the pharmacokinetics of vigabatrin in children and infants comparable? Are the pharamcokinetics comparable to that of the adults? Is the dosing regimen proposed adequate?

Average concentrations in plasma of S(+)-vigabatrin and R(-)-vigabatrin after single oral administration of 50 mg/kg/day of (R,S)-vigabatrin to infant (5 month to 2 years, n=6) and children (4 to 14 years, n=6) patients are shown in the following figure.



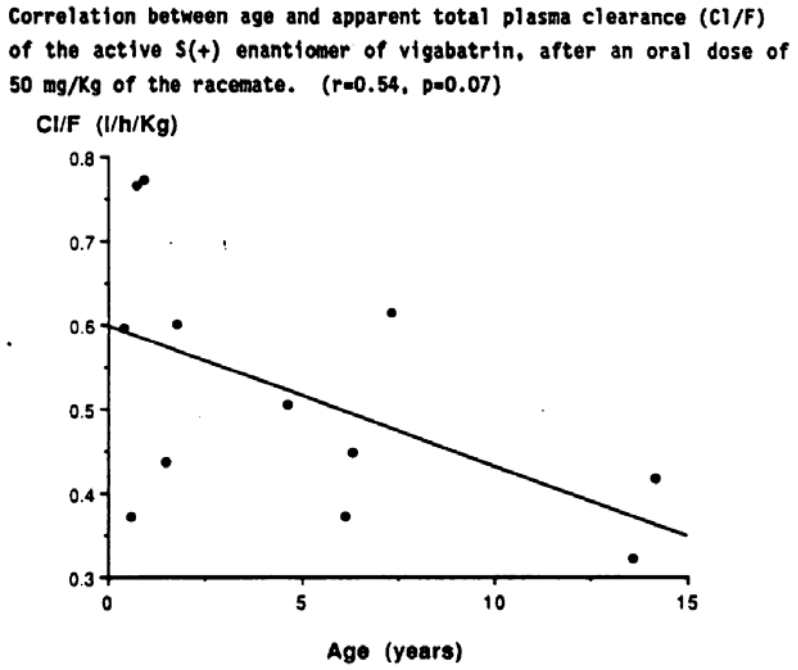
The figure shows that peak plasma concentration and area under the curve were higher for the inactive enantiomer R(-). These differences were significant, the ratio between R(-) and S(+) being of 1.6 to 1.8.

Mean pharmacokinetic parameters and the summary of the descriptive statistics are given in the Table below.

Pharmacokinetic Parameters	Infants		Children	
	S(+)	R(-)	S(+)	R(-)
Tmax (hr)	2.85 ± 1.61	2.35 ± 1.87	1.36 ± 0.96	1.28 ± 0.58
Cmax (mcg/mL)	13.90 ± 4.53	21.00 ± 6.60	23.80 ± 12.20	41.3 ± 13.9
$t_{1/2}$ (hr)	5.65 ± 1.52	2.87 ± 1.03	5.47 ± 1.93	5.68 ± 2.86
$AUC_{0-\infty}$ (mcg/mLxhr)	90.9 ± 27.9	106.00 ± 28.5	117.00 ± 26.00	147.00 ± 34.00
Cl/F (L/hr/kg)	0.591 ± 0.165	0.498 ± 0.110	0.446 ± 0.103	0.355 ± 0.082
Vd/F (L/kg)	4.630 ± 1.120	2.01 ± 0.68	3.480 ± 1.230	2.770 ± 1.190

Area under the concentration-time curves (AUC) for the R(-)-enantiomer were higher than the corresponding AUC for the S(+)-enantiomer. The elimination half-life averaged between 2.87 and 5.68 hr for both enantiomers of vigabatrin in both infants and children. These elimination half-lives were considerably shorter than observed in adults (average at 7.5 hours). Calculated volume of distribution ranged between 2.01 and 4.63 L/kg.

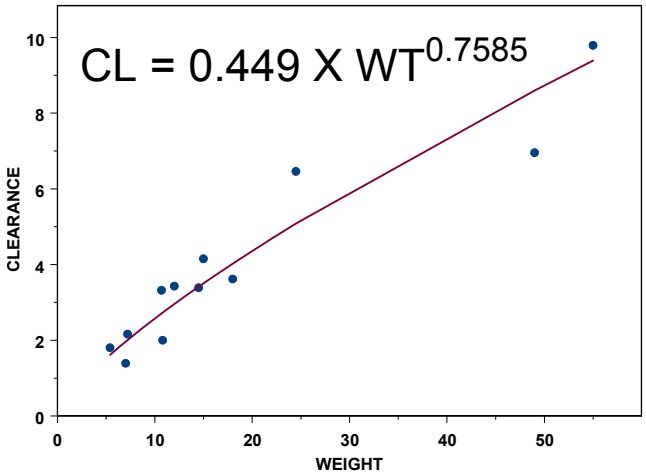
AUC of the active S(+) enantiomer was about 30% lower in infants than in children. There was a non-significant trend for CL/F to decrease with age (r= -0.54, p 0.07). Figure below shows the correlation between age and clearance.



The differences between infants (5 month to 2 years) and children (4-14 years) of the pharmacokinetic parameters of the active S(+)-enantiomer and R(+)-enantiomer indicated smaller AUC implying a faster total plasma clearance (on body weight normalized basis) in infants. The age-related differences could be accounted for by either a lower bioavailability or a higher renal clearance in younger subjects. The latter is consistent with the normal changes in renal clearance with age. This can be further confirmed when the non-normalized clearances are considered. Following table shows the average total clearance (not body weight normalized) in the two pediatric groups.

Species	Group	N	Mean	Std Dev	Minimum	Maximum
S(+)	5 month -2 years	6	5.20	2.11	2.60	8.26
	4 - 14 years	6	12.45	6.66	5.57	22.99
R(-)	5 month -2 years	6	4.31	1.37	2.98	6.34
	4 - 14 years	6	9.70	4.75	4.50	17.05
VGB	5 month -2 years	6	2.35	0.84	1.39	3.43
	4 - 14 years	6	5.73	2.49	3.39	9.79

The relationship between clearance of vigabatrin and body weight can be expressed as a formula of $CL = 0.449 \times WT^{0.7585}$ as shown in the following figure.



Although the figure shows a typical relationship with a power around 0.75, the sample size is small and the age group of 2 – 4 years old is not included. The pharmacokinetic behavior of vigabatrin in children aged between birth to 5 months and 2 to 4 years have not been documented.

If this relationship is used for prediction of the clearance of an adult with body weight of 70 kg, the predicted value would be 11.26 L/h, which is higher than the observed value around 7 L/h (adult clearance value from Dr. Tammara's review). This 60% over-prediction indicates the difference of elimination between adults and pediatrics.

The proposed starting dose for pediatric is 50mg/kg/day. If using the same power of weight in the above formula for doses, the formula Dose = Constant × $(WT)^{0.7585}$ can be used to calculate the doses. If assuming the constant in the above formula is obtained from the dosing regimen of 50mg/kg/day for 1 kg (or 2 kg) infants (Constant is 50 and 60, respectively), then the following table shows the doses should be used for the infants based on their body weights.

Body weight (kg)	Dose with C=50	Dose with C=60
1	50	60.00
2	84.59	101.50
3	115.04	138.05
4	143.10	171.72
5	169.49	203.39
6	194.62	233.55
7	218.76	262.52
8	242.08	290.50
9	264.71	317.65
10	286.73	344.07
11	308.22	369.87
12	329.25	395.10
13	349.86	419.83
14	370.09	444.11
15	389.97	467.97

As shown, the doses calculated are less than proposed, especially for the higher weights. For example, for infants weighted 15 kg, the calculated dose is 389 mg (based on constant=50) or 468 mg (based on constant =60), while the proposed dose is 750 mg.

Note that the above calculation used 50 (or 60) as the constant obtained from the lowest body weights (1 kg and 2 kg). If using the proposed doses, the constant can be calculated for different body weights as shown in the following table.

Body weight (kg)	Dose (50mg/kg)	Constant*	Dose for 70kg**	% higher than 1g
1	50	50	1254.52	25.45
2	100	59.11	1483.12	48.31
3	150	65.19	1635.69	63.57
4	200	69.88	1753.37	75.34
5	250	73.75	1850.45	85.05
6	300	77.07	1933.75	93.38
7	350	79.99	2007.10	100.71
8	400	82.62	2072.87	107.29
9	450	85.00	2132.68	113.27
10	500	87.19	2187.65	118.76
11	550	89.22	2238.58	123.86
12	600	91.12	2286.12	128.61
13	650	92.89	2330.74	133.07
14	700	94.57	2372.83	137.28
15	750	96.16	2412.70	141.27

* Calculated from formula: Dose=constant×$WT^{0.7585}$ using the first two columns.
** Calculated using the above formula with WT=70 and constant value in third column.

If the median of the constant obtained from the above table is used to calculate the dose for a subject with body weight of 70 kg, the result is 2073 mg. Comparing to the proposed adult starting dose 500 mg bid (1g/day), the result is about 100% higher, implying the proposed starting dose for pediatric is higher than the starting dose for adults.

By the similar comparison, the maximum dose proposed for children (150mg/kg/day) is higher than the maximum dose proposed for adults (3g/day).

Based on the proposed starting and maximum doses for adults, from exposure perspective, the following bracketed dosing regimen is recommended.

Body weight (kg)	Starting Dose (mg/day)	Maximum Dose (mg/day)
1	50	150
2	100	300
3	150	450
4	200	600
5	200	600
6	250	750
7	250	750

8	300	900
9	300	900
10	350	1050
11	350	1050
12	400	1200
13	400	1200
14	450	1350
15	450	1350

Although a dose reduction is suggested in order to obtain comparable exposure among children with different body weights, and also to obtain exposures comparable to adults, the question of how this would translate to effectiveness can not be answered because of the lack of the knowledge of a dose response relationship in the IS patient population. Also the need to obtain comparable exposure to adults for effectiveness can not be justified as the disease state is different in the two populations (seizures in adults and IS in infants). Therefore, based on the PK differences among children with different body weights and between children and adults, dose reductions are suggested only for safety reasons. It is stated by the applicant that initiation doses of vigabatrin in clinical studies ranged from 18 to 150mg/kg/day and were increased to a maximum dose of 369.5mg/kg/day in the long-term follow-up periods.

Since vigabatrin is primarily through renal elimination, renal function plays an important role. In pediatric subjects with renal impairment, it may be reasonable to use the similar percentage dose reductions in adult subjects with renal impairment.

Study results also showed the differences in the pharmacokinetics of the two enantiomers. The difference is in the same trend as that in adult pharmacokinetic studies.

4. Is there any drug-drug interaction between vigabatrin and oral contraceptives.

A literature report on drug interactions with oral contraceptives was provided. The study was conducted to determine whether vigabatrin affects in vivo indices of hepatic microsomaI enzyme activity and the pharmacokinetics of steroid oral contraceptives in healthy subjects.

Under double-blind conditions, 13 female healthy volunteers received, in random order and with a washout interval of ≥4 weeks, two oral 4-week treatments with vigabatrin (maintenance dosage, 3,000 mg dai1y) and placebo, respectively. The clearance and half-life of antipyrine (a broad marker of drug oxidation capacity), the urinary excretion of 6-p-hydroxycortisol (a selective marker of cytochrome CYP3A-mediated oxidation), and the activity of serum y-glutamyltransferase (a nonspecific index of microsomal enzyme activity) were determined after 3 weeks of each treatment. The single-dose kinetics of a combined oral contraceptive containing 30 µg ethinyl estradiol and 150 µg levonorgestrel were also determined after 3 weeks of treatment by specific radioimmunologic assays. The results showed that vigabatrin treatment had no influence on antipyrine clearance (28 ±5.6 vs. 30 ± 4.5 mL/h/kg on placebo), antipyrine half-life (15.5 ± 3.5 vs. 14.1 ± 2.1 h), urinary 6-p-hydroxycortisol excretion (488 ± 164 vs. 470 ± 228 nmol/day), 6-p-

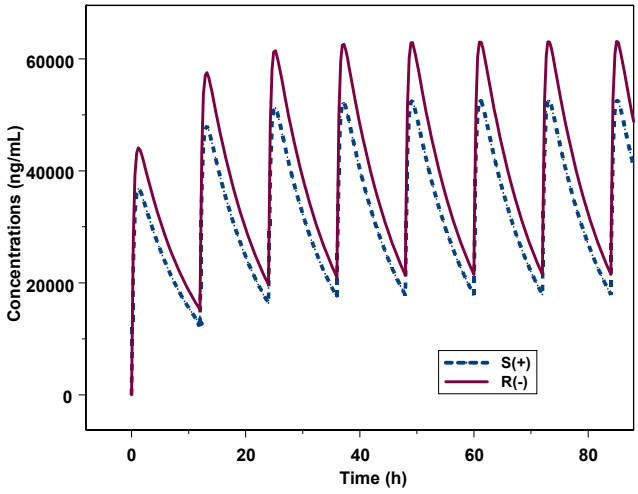
hydroxycortisol-to-cortisol concentration ratio (6.8 ± 3.1 vs. 6.1 ± 3.1) and serum γ-glutamyltransferase activity (12 ± 3 vs. 11 ± 3 IU/L). No difference in pharmacokinetic parameters between vigabatrin and placebo sessions were found for ethinyl estradiol (half-life, 12.5 ± 3.2 vs. 13.9 ± 3.2 h; AUC, 874 ± 301 vs. 939 ± 272 ng/L/h) and levonorgestrel (half-life, 17.7 ± 5.2 vs. 23.1 ± 9.8 h; AUC, 27.5 ± 9.6 vs. 30.0 ± 12.0 µg/L/h). Two subjects, however, showed a 50 and a 39% reduction in ethinyl estradiol AUC during VGB treatment.

The authors concluded that at therapeutic dosages, VGB did not modify in vivo indices of hepatic microsornal enzyme activity and did not interfere significantly with the CYP3A-mediated metabolism of ethinyl estradiol and levonorgestrel. Based on these data, vigabatrin is unlikely to affect consistently the efficacy of steroid oral contraceptives or interact pharmacokinetically with drugs that are eliminated mainly by oxidative pathways, particularly those involving cytochrome CYP3A.

5. Is there any possible effect of inactive enantiomer on the occurrence of adverse events?

Vigabatrin exists as a 50/50 racemic mixture of two enantiomers; the S(+) isomer is pharmacologically active while the R(-) enantiomer is inactive. Further, the plasma concentrations of inactive S(+) isomer is higher than that of the active S(+) isomer. Therefore, in order for the active isomer to reach the effective exposure, the inactive isomer would have a higher exposure as shown in the following figure from a set of simulated data (the simulation used multiple doses of 2 g of vigabatrin bid to reach steady state).

The simulation assumes no difference between the half-lives of S(+) and R(-) isomers based on the report from the applicant. However, in reality, if the clearance of R(-) isomer is slower, its half-life tends to be longer. If that is the case, the accumulation of the inactive R(-) isomer would be higher, resulting even higher exposure. In either case, the unnecessary higher exposure of the inactive isomer is of concern given the high rate of serious adverse events based on the following considerations.



- The enantiomers have different effectiveness profiles: S(+) is active while R(-) is not. However, the adverse event profiles between these two isomers are not clear. There is a possibility that the inactive R(-) isomer makes greater contribution to adverse events such as visual field defects (VFD). This is a speculation at this time since no confirmatory evidence is available.

- Even if the two isomers have equal contribution to VFD or other adverse events, the exposure of inactive isomer is not necessary.

Although the possibility that the inactive R(-) isomer has little contribution for VFD or other adverse events can not be excluded, it is worth investigating in this regard given the high rate of serious adverse events.

6. Is there any dose response regarding adverse event: VFD

1) Dose response for perimetry data

In order to examine any possible relationship between the dose and the abnormality of the visual field, data from study 4020 (in adults and children 8 years or older) were analyzed.

Study 4020 was a Phase 3 clinical trial to determine the prevalence of the VFD in refractory partial epilepsy treated with antiepileptic drugs, which was conducted at 46 clinical sites in France, South Korea, Italy, Spain and Australia. The first subject was enrolled on March 15, 1999 and the last subject was enrolled on April 28, 2003. All subjects completed the study by June 16, 2006. Primary study objectives included the determination of the prevalence of the VFD among subjects treated with AEDs and with vigabatrin in particular. Secondary objectives included determination of the incidence, clinical course and impact of the VFD on daily living.

In order to qualify for participation in Study 4020, subjects were required to be at least 8 years of age with a history of refractory partial epilepsy for a minimum of 1 year. Three groups of subjects were included as follows:

1. Subjects who were taking VGB at the time of study entry and had been taking it for at least 6 months prior to entry (Group I)
2. Subjects who had taken VGB for at least 6 months in the past but who discontinued VGB at least 6 months prior to entry (Group II)
3. Subjects who had no prior VGB treatment (Group III)

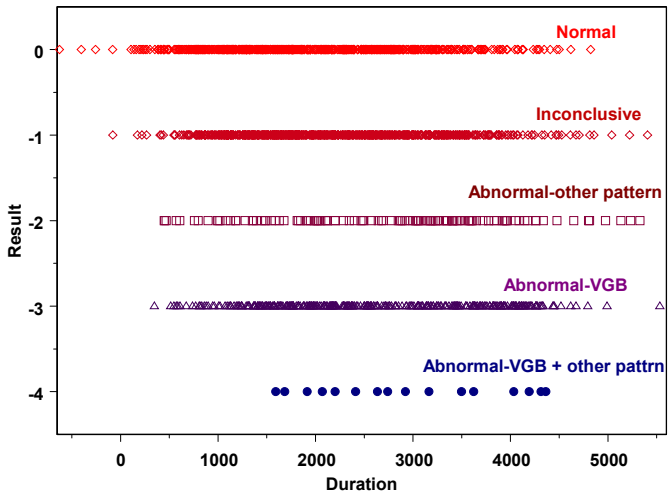
Perimetry examination was the principal measurement tool for evaluation of visual fields during the study. The findings upon perimetry exam were classified into categories ranging from normal to abnormal. To systematize and analyze perimetry data, copies of all reports were sent to a visual field expert (b) (4) who conducted an independent and blinded review of each subject case.

A total of 735 subjects were in the final locked database. Among these subjects, only 427 had both dosing and perimetry information, 219 in Group I, 205 in Group II and 3 in Group III.

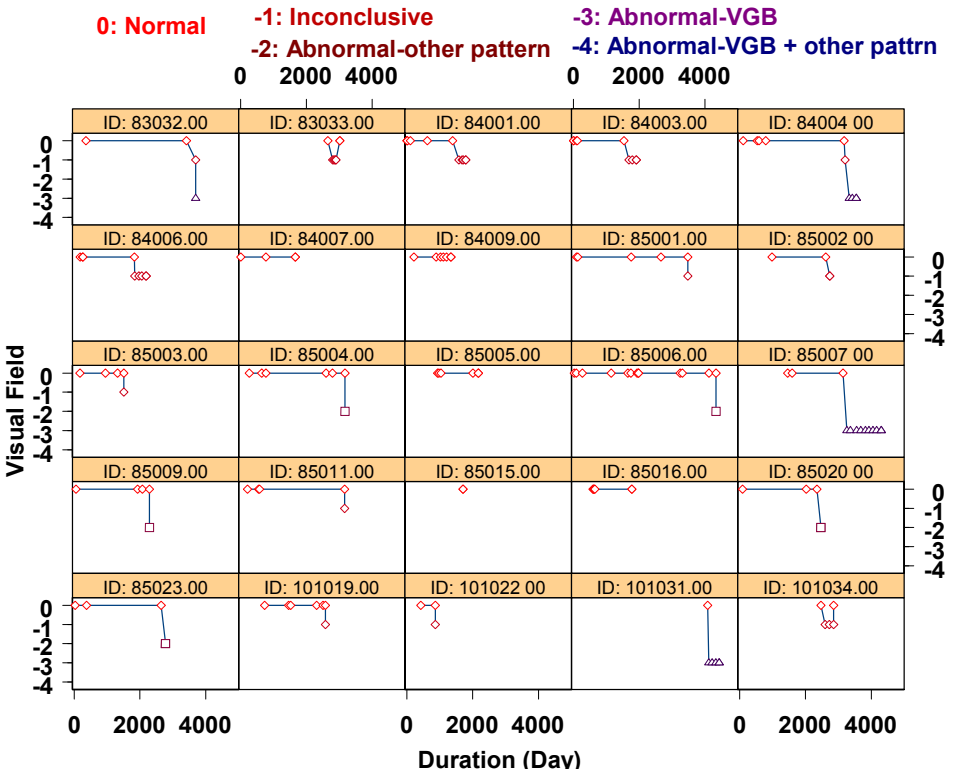
Since the subjects had taken different doses at different times, the investigation started with a time to event analysis for the covariate with time dependent repeated measurements. The subjects with both dose information and measurement of perimetry are selected for analysis. The visual field examination results were classified as Normal, Inconclusive, Abnormal for other patterns, Abnormal for vigabatrin pattern, and Abnormal for mixed patterns (other patterns plus vigabatrin pattern). Following table shows the results when dose, dose duration, age and gender were used as predictors.

Variables	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
Duration	1	-5.5492E-6	4.76701E-7	135.5112	<.0001	1.000
Dose	1	0.0008827	0.0000969	82.9970	<.0001	1.001
Age	1	0.00832	0.00391	4.5157	0.0336	1.008
Sex	1	-0.56839	0.12479	20.7468	<.0001	0.566

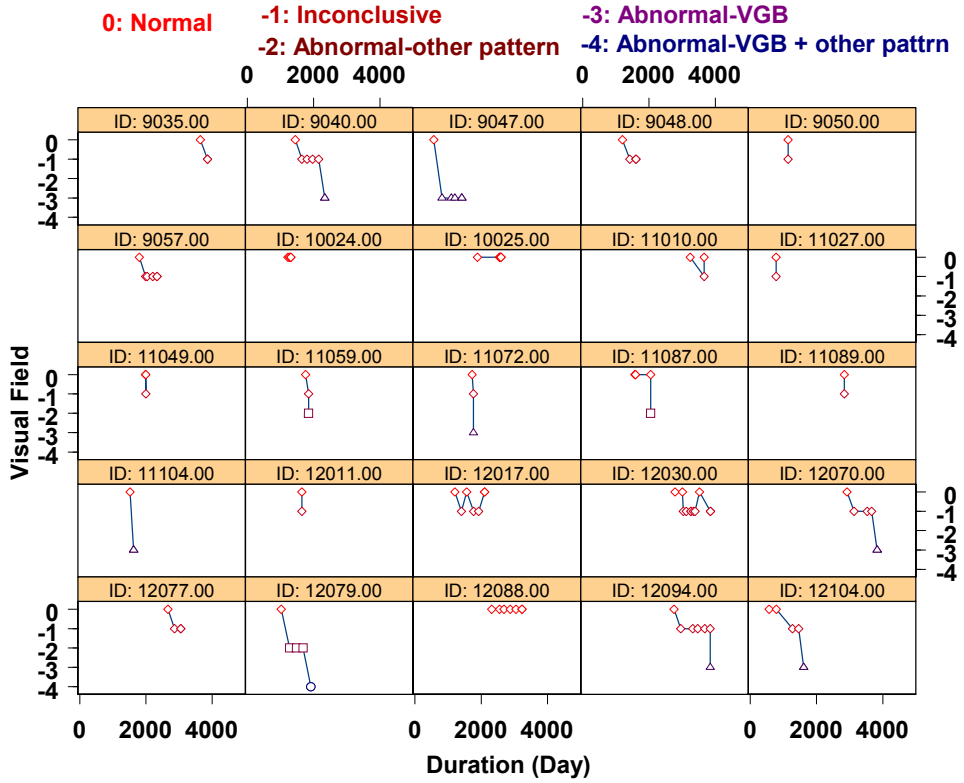
The results indicate that higher dose would increase the VFD risk. In addition, gender and age are significant predictors for VFD risk. Female gender and younger age have less risk. Although the dose duration is a significant predictor, the coefficient is very small suggesting that the effect is not detected in this analysis. However, when the perimetry data was plotted longitudinally, it seems that more abnormalities occurred at later time points as shown in the following figure.



The plots for individual patient give the same trend as shown in the following figure.



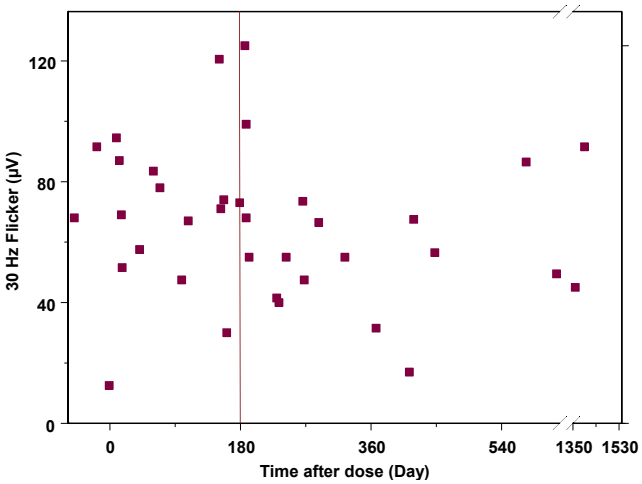
On the other hand, VFD in some patients appeared early as shown in the following figure.



It is noticeable from these figures that the visual field worsening seems a sudden incident. However, considering the judgment for abnormality is a zero-or-one decision process and the examinations were not frequent enough, the above figures may not reflect the development process of VFD. In this regard, ERG measurement is more objective and quantitative. Therefore, the studies with ERG data, such as Boston study and Toronto study were examined.

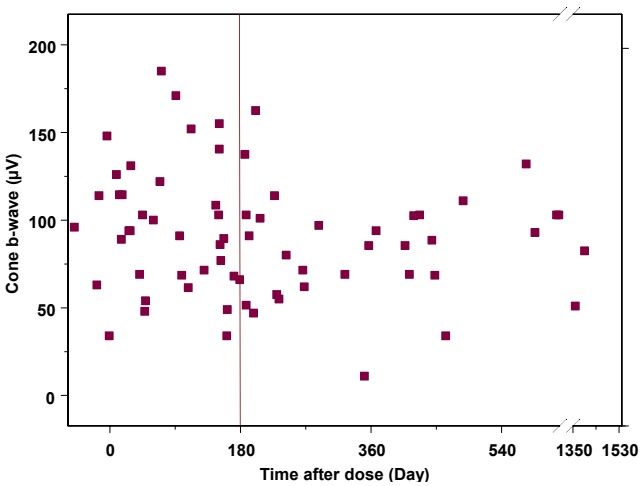
2) Time courses of ERG data in Boston study, Toronto study, and Study R003

Boston study included 49 subjects (all children), of whom 47 had one or more ERG evaluations occurring between September 10, 1998 and July 29, 2005. The following figure shows the 30 Hz flicker average of the right and left eyes of the patients after dosing.



The applicant's analysis compared the mean 30 Hz flicker amplitude for those who were tested less than or at 6 months after the first VGB dose [77.6 μV (± 24.5μV)] to that for subjects tested more than 6 months after the first dose of VGB [54.7 μV (±20.4μV)]. However, as shown in the figure, the decreasing trend starts within 6 months (a vertical line shows the time of 6 month).

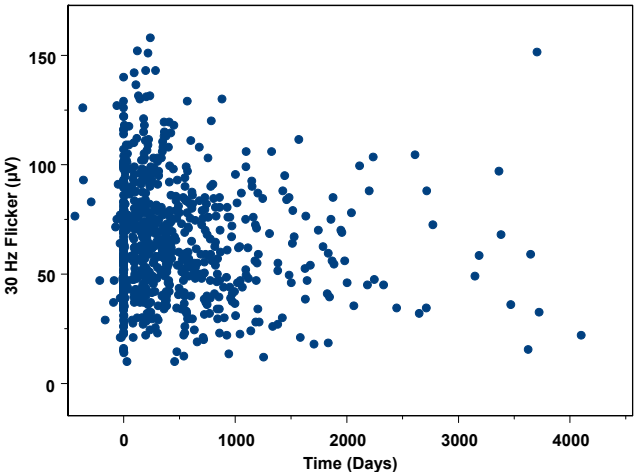
Similar trend was observed for the cone b-wave amplitude as shown in the following figure.



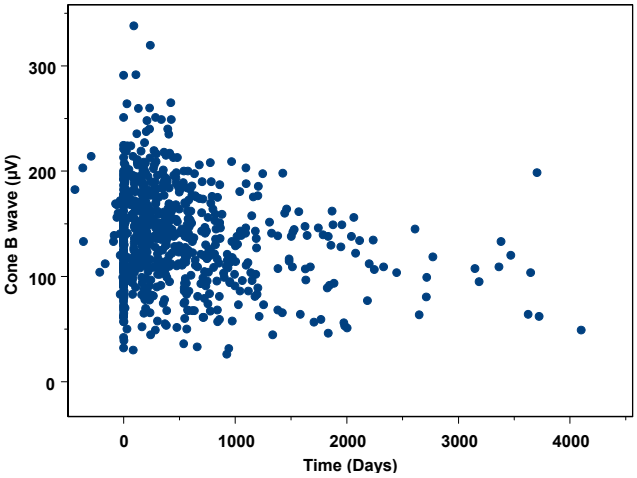
Looking at the individual level, it seems that the cone b-wave of some patients kept consistent while others decrease significantly as shown in the following figures.

(b) (4)

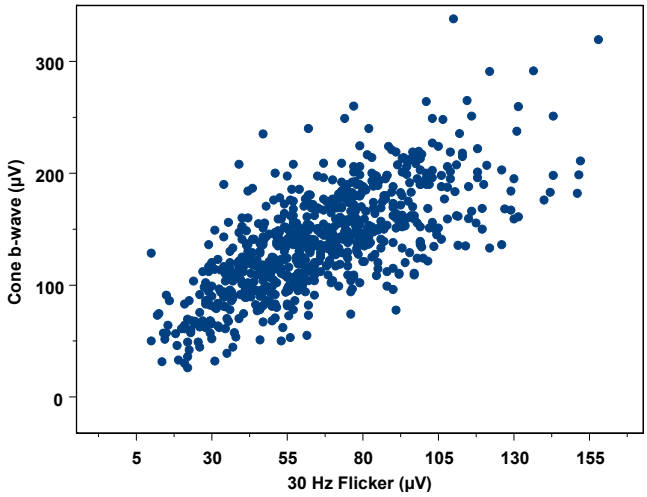
The above observation can be confirmed by a bigger study. The Toronto study included 246 pediatric patients. In this study, the 30 Hz flicker measured at different time points also has the trend to go lower after vigabatrin dosing as shown in the following figure.



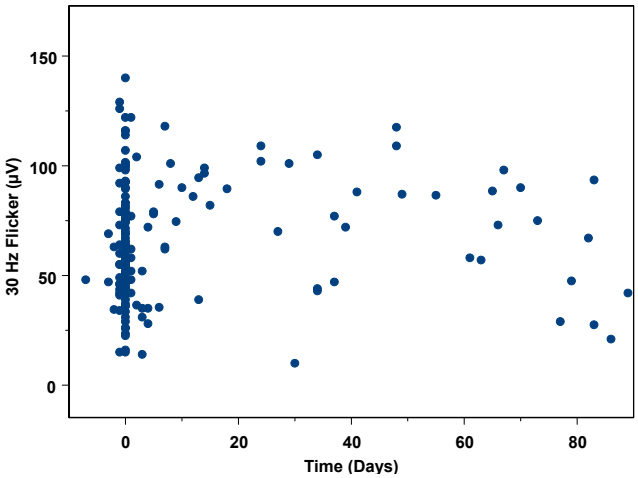
Similarly, Cone b-wave follows the same trend as shown in the following figure.



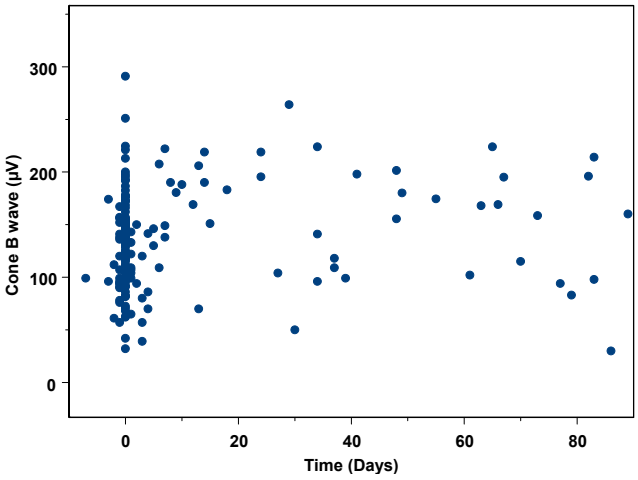
Actually, these two parameters are correlated each other as indicated in the following figure.



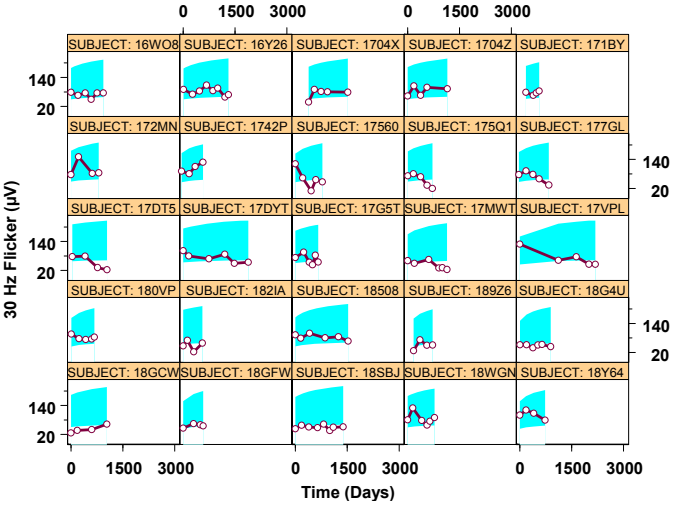
One question is of concern: could the trend be observed earlier given the fact that the parameter decreased along with the time? The data of 30 Hz flicker for the first 90 days after dosing are shown in the following figure.



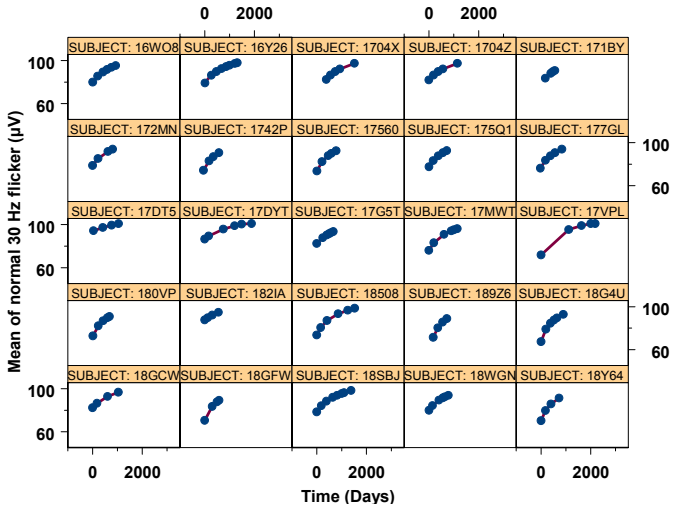
Following figure shows the trend for Cone b-wave for the 90 days after dosing.



As seen above, the trend (up to 90 days) is not as obvious as the long term (up to 4000 days) figure as shown above. It might be due to two reasons. One is that fewer samples were collected before 90 days. Another is that the patients might have different responses after vigabatrin dosing and they could be divided into two groups: a sensitive group and a resistant group as shown in the following figures. The resistant group might mask the trend the other group followed. In the following figure, the shaded areas are the age corrected normal range of 30 Hz flicker amplitude with the lower and upper bound representing the lower and upper 95% confidence limits. The lines with empty circles are the results of the 30 Hz flicker measurements.



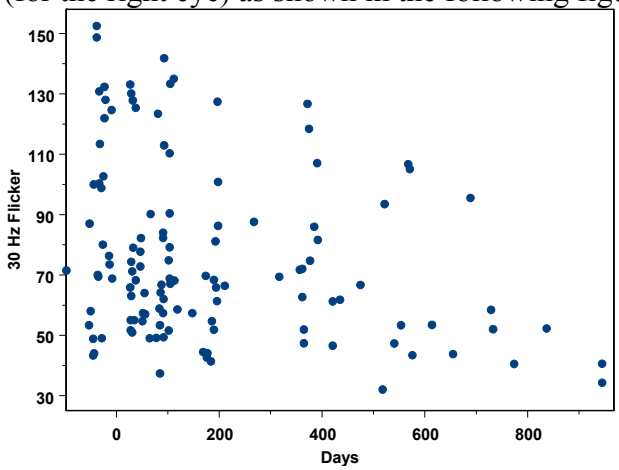
It can be seen that the age corrected normal ranges increase along with ages. The mean age corrected normal values are shown in the following figure.



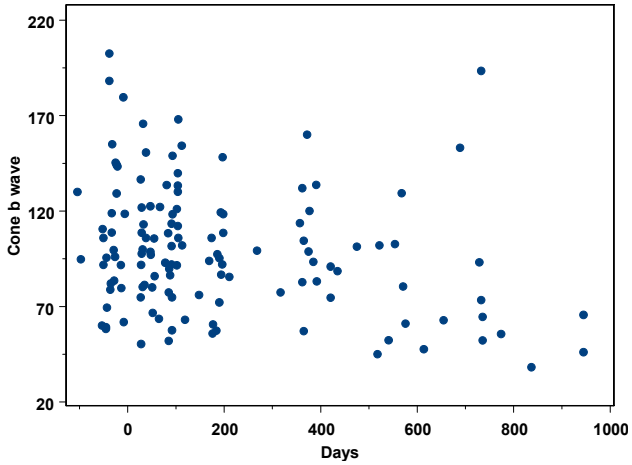
Therefore, if the visual field of the children in the study were not affected by vigabatrin, their 30 Hz flicker measurements should have increased along with time in the same fashion as the normal mean of the parameter. However, due to the effects of vigabatrin, fewer subjects had increased measurements and most of them had the down trend.

Several of them passed the lower limits of the normal ranges. Also, it seems that the longitudinal trends are in the linear fashion.

The observations were further supported by the 25 subjects in study R003, who had ERG measurements. The population, predominately white, consisted of 11 males and 14 females presenting with an average age of 40.3 (± 11.9) years and weight 79.6 (± 23) kg, respectively. The only child who participated was 10 years of age and the adult subjects ranged from 23 to 58 years of age. The mean body mass index (BMI) was 28.3 (± 7.48) kg/m^2 and the two predominant eye colors were hazel or blue (28% and 24% of subjects, respectively). Over half of the subjects (54%) had never smoked, 29% had been previous smokers, and 17% were current smokers. Similar trend was observed for 30 Hz flicker (for the right eye) as shown in the following figure.



Similarly, the cone b-wave plot (for the right eye) is shown below.



The individual plot for 30 Hz flicker (for the right eye) is shown below.

Following figure is the individual plot for cone b-wave.

Based on the above limited data, it appears that the initial trend determined the general trend. To investigate this hypothesis, Toronto study was further examined. There were a total of 246 subjects with ERG data. The total number of measurements was different among the subjects. Following table shows the distribution of the total number of measurements.

Measurement count	Frequency	Percent	Cumulative Frequency	Cumulative Percent
10	2	0.81	2	0.81
9	1	0.41	3	1.22
8	4	1.63	7	2.84
7	5	2.03	12	4.88
6	16	6.50	28	11.38
5	23	9.35	51	20.73
4	37	15.04	88	35.77
3	49	19.92	137	55.69
2	44	17.89	181	73.57
1	65	26.42	246	100.00

As can be seen, there were 88 subjects (35.77%) who had 4 or more 30 Hz flicker measurements. For these 88 subjects, the first three observations were used for a regression analysis. The regression parameters obtained from this analysis served for two purposes: to predict the values of the fourth measurement and to compare the match of the predicted trend with the actual measurements.

The figure below shows the general agreements between the predicted trend (red line) and the actual measurements (blue line with empty circles; in some cases they may overlap with the red lines).

Table below summarizes the statistics for the prediction of the fourth measurement. The Residue is defined as the difference between the prediction and actual measurements (Residue = prediction-actual). RLD is the ratio between Residue and the actual measurements (RLD = Residue/Actual measure).

	N	Mean	Std Dev	Minimum	Maximum
Residue	88	0.44111	37.88260	(b) (4)	
RLD	88	0.15688	1.076223		

Although the mean residue is small (0.44), the standard deviation is large (37.88), spanning a big range from minimum of (b) (4) to maximum of (b) (4). Similarly, the relative deviation has a mean of 15%, ranging from (b) (4)

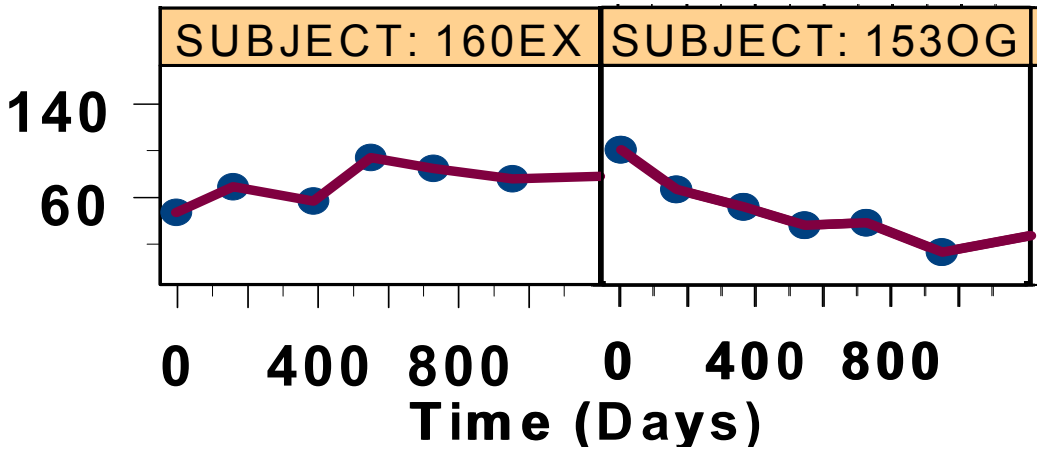
This analysis has following limitations.

- Limited data are available and sample size is small.
- The first three measurements spanned a wide time range. For a more conclusive analysis, the times for first three points should be fixed.
- Although the time course looks linear, it may be more complicated than it looks like based on the following considerations.

- ¬ The whole process may be the combination of several, at least two processes: the natural increase of the parameter along with the age; and the reduction (or no considerable change) by vigabatrin.
- ¬ Some adjustment may be needed, because a linear model is heavily dependent on the accuracy of the data. When more data are available, various covariates should be considered.

From the observations and analysis of the three studies, following points can be inferred.

1. The time courses of the ERG measurements (cone b-wave and 30 Hz flicker) show general trend for declining along with the time after dosing of vigabatrin.
2. Considering the subjects with more than 3 time points, the subjects can be divided into two groups according to the shape of the time course of ERG measurements. In one group, the 30 Hz flicker or cone b-wave showed a decline trend (as shown in the right panel of the following figure for 30 Hz flicker) while in the other group, the measurements kept relatively constant (the left panel in the following figure).



3. If as reported, 30 Hz flicker and cone b-wave have a close relationship with VFD, these measurements may reflect the VFD development process when monitored frequently enough. While the diagnosis of VFD is a none-or-all process and difficult to pick the early warning signs, ERG can give a quantitative signal about disease progression. The applicant's claim that the VFD only happened long time after vigabatrin administration discounted this dynamic process and may miss the early sign for worsening process.
4. Based on limited data, it seems that the initial trend determined the general trend for ERG measurements. Although more data and analyses are needed, initial measurement of ERG should be treated as a signal of the direction of further development of VFD. From conservative point of view, qualitatively speaking, a warning sign is signaled if the slope goes to negative. Further investigation should establish quantitative criteria.

3) Pharmacogenomic consideration

According to the above observation, given the evidence suggesting an idiosyncratic drug response, the role of genetic variation is suspected. A literature search was conducted accordingly. Two relevant studies were found.

One study (Hisama FM, Mattson RH, Lee HH, Felice K, Petroff OAC. GABA and the ornithine (delta)-aminotransferase gene in vigabatrin-associated visual field defects. Seizure 2001;10(7):505-7) identified a common intronic polymorphism although no clinically significant mutation was detected.

Another study (Kinirons P, Cavalleri GL, Singh R, Shahwan A, Acheson JF, Wood NW, Goldstein DB, Sisodiya SM, Doherty CP, Delanty N. A pharmacogenetic exploration of vigabatrin-induced visual field constriction. Epilepsy Res 2006 Aug;70(2-3):144-52) found that the degree of visual field constriction correlated with three SNPs and one haplotype in a cohort of 73 patients. However the authors were unable to replicate these findings in a second independent cohort consisting of 58 patients, suggesting the initial results were possibly false positives, or variants of weak effect.

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4.2. Individual study synopsis

1. Pharmacokinetics of vigabatrin in children and infants (097-332.5, Report W-900001-C)

Title: Pharmacokinetics of the Enantiomers of Vigabatrin in Infants and Children of the Racemate.

Objectives:

1) to determine the pharmacokinetics of the R(-) and S(+) enantiomers after a single 50 mg/kg oral dose of racemic vigabatrin in 6 infants and 6 children.
2) to determine the pharmacokinetics of the enantiomers in the infants and children after multiple oral doses of 50 mg/kg of racemic vigabatrin not exceeding 1.5 g in older children.

Clinical site and investigator:

The study was conducted at the (b) (4)

Subjects:

The subjects were comprised of 2 groups: 1) 6 infants (5 months - 2 years, 5 male, 1 female) and 2) 6 children (4 - 14 years, 4 male and 2 female).

Study design:

Two groups of patients (6 infants and 6 children) were recruited in an open study of the efficacy and safety of vigabatrin in children with refractory epilepsy. All of the patients were treated with between 1 to 3 other antiepileptic drugs. These drugs were kept constant throughout the pharmacokinetic study. Vigabatrin was administered as a single, oral dose of 50 mg/kg added to the already established therapeutic regimen. Twenty-four hours after the single dose, treatment with racemic vigabatrin was continued as 50 mg/kg twice a day. The single and multiple doses did not exceed 1.5 g in older children. The study report did not specify if the patients were confined to the study site, had controlled diet and water intake, had clinical laboratory evaluations, or had given informed consent by a guardian.

Venous blood samples (500 pL) were drawn before the first dose and at 0.5, 1, 2, 3, 6, 9, 12 and 24 hours after the dose. Additional samples were drawn before and 1 hr after the morning dose for 5 days during chronic treatment. Concentrations of the enantiomers of racemic vigabatrin were measured by a GC/MS method.

Pharmacokinetic parameters were calculated using non-compartmental techniques. For each enantiomer R(-) and S(+), time to peak (Tmax), maximum concentration (Cmax),

area under the concentration-time curve (AUC), half-life (t1/2), apparent total plasma clearance (CL/F) and apparent volume of distribution were calculated.

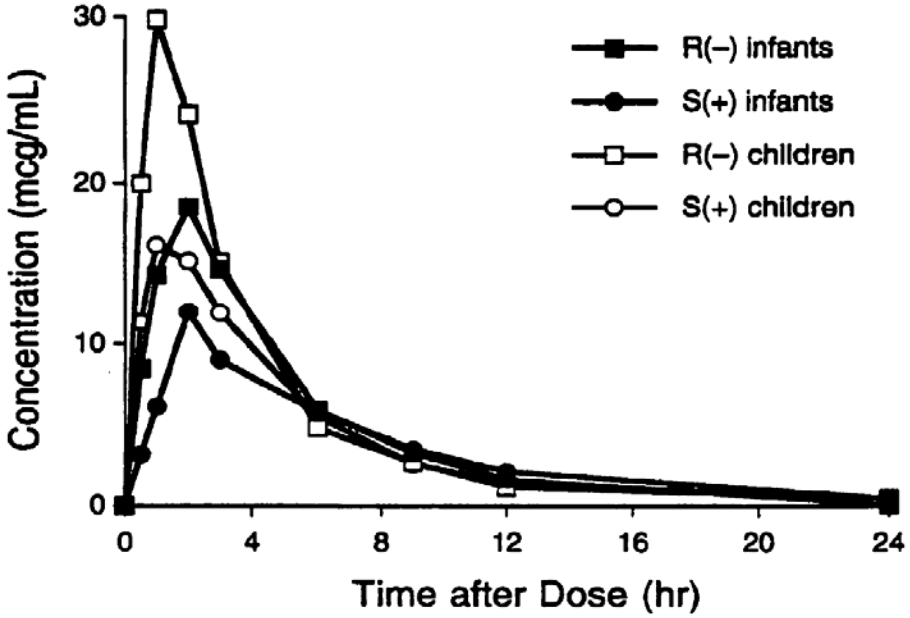
One-way analysis of variance for paired values (the two enantiomers) was used to compare the pharmacokinetic parameters in the two groups of patient. When interaction was significant an analysis of variance for paired values was used to compare Tmax between enantiomers in the same children and the median test to compare Tmax between groups. A two-way analysis of variance for paired values was used to compare the values of Cmin and C1h over 5 days for each enantiomer. The relationship between the different kinetic parameters and age was investigated by linear regression.

Results

The calibration curve for the assay of vigabatrin was linear from 5 to 50 µg/mL. The reproducibility was 5.3% (n = 10) and 4.1% (n = l0) for R(-) and S(+) vigabatrin, respectively, at 5 µg/mL.

Six infants and 6 children entered and completed the study. All of the patients were concurrently treated with between 1 to 3 other antiepileptic drugs including carbamazepine (8 patients), clobazam (4), phenytoin (3), phenobarbital (2) and valproate (2). The drugs were kept constant throughout the pharmacokinetic study.

Average concentrations in plasma of S(+)-vigabatrin and R(-)-vigabatrin after oral administration of 50 mg/kg of (R,S)-vigabatzin to infant and child patients are shown below.



The figures shows that peak plasma concentration and area under the curve were higher for the inactive enantiomer R(-). These differences were significant, the ratio between R(-) and S(+) being of 1.6 to 1.8.

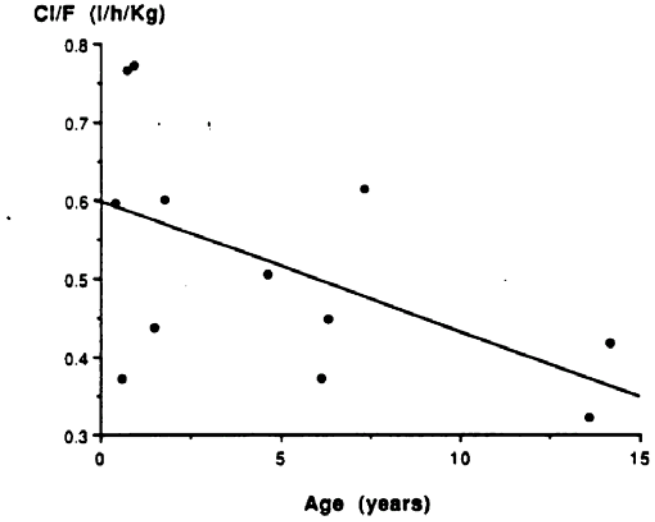
Mean pharmacokinetic parameters and the summary of the descriptive statistics are given in the Table below.

Pharmacokinetic Parameters	Infants		Children	
	S(+)	R(-)	S(+)	R(-)
Tmax (hr)	2.85 ± 1.61	2.35 ± 1.87	1.36 ± 0.96	1.28 ± 0.58
Cmax (mcg/mL)	13.90 ± 4.53	21.00 ± 6.60	23.80 ± 12.20	41.3 ± 13.9
$t_{1/2}$ (hr)	5.65 ± 1.52	2.87 ± 1.03	5.47 ± 1.93	5.68 ± 2.86
$AUC_{0-\infty}$ (mcg/mLxhr)	90.9 ± 27.9	106.00 ± 28.5	117.00 ± 26.00	147.00 ± 34.00
Cl/F (L/hr/kg)	0.591 ± 0.165	0.498 ± 0.110	0.446 ± 0.103	0.355 ± 0.082
Vd/F (L/kg)	4.630 ± 1.120	2.01 ± 0.68	3.480 ± 1.230	2.770 ± 1.190

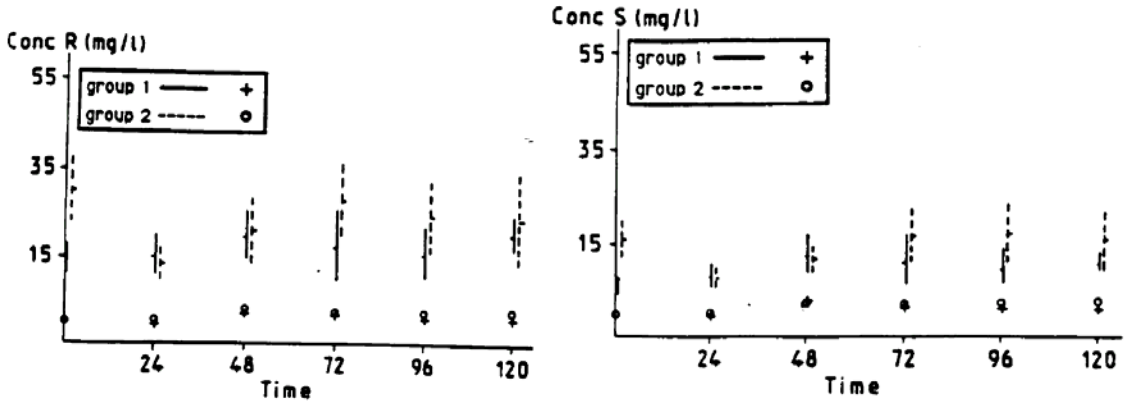
Area under the concentration-time curves (AUC) for the R(-)-enantiomer were higher than the corresponding AUC for the S(+)-enantiomer. The elimination half-life averaged between 2.87 and 5.68 hr for both enantiomers of vigabatrin in both infants and children. These elimination half-lives were considerably shorter than observed in adults. Calculated volume of distribution ranged between 2.01 and 4.63 L/kg.

AUC of the active S(+) enantiomer was significantly lower in infants than in children. The apparent total plasma clearance (CL/F, body weight normalized) was significantly higher in infants. There was a non-significant trend for CL/F to decrease with age (r= -0.54, p 0.07) (Figure below). There were no differences in the apparent volume of distribution and half life between children and infants. The following figure shows the correlation between age and clearance.

Correlation between age and apparent total plasma clearance (Cl/F) of the active S(+) enantiomer of vigabatrin, after an oral dose of 50 mg/Kg of the racemate. (r=0.54, p=0.07)



The following table and figure show the plasma concentrations measured before (Cmin) and one hour after (Clh) the morning doses during repeated oral doses of 50 mg/kg morning and evening (Values at day 1, measured 24 h after 50 mg/kg are not included in the table). The left panel is for the R-enantiomer and right for S-enantiomer.



	GROUP I - Infants (n=5)		GROUP II - Children (n=6)	
	active S(+)	inactive R(-)	active S(+)	inactive R(-)
	mean (range)			
Cmin				
day 2	3.8 (b) (4)	2.9 (b) (4)	2.6 (b) (4)	3.0 (b) (4)
day 3	2.7	2.6	2.4	2.3
day 4	2.0	1.5	2.5	2.3
day 5	2.1	1.5	2.9	2.5
inter-day variation	NS	NS	NS	NS
Clh				
day 2	13.6 (b) (4)	20.7 (b) (4)	11.8 (b) (4)	21.0 (b) (4)
day 3	13.2	20.3	16.8	28.0
day 4	10.3	16.1	17.4	24.6
day 5	11.5	20.9	16.0	24.0
inter-day variation	NS	NS	NS	NS

Comments

1. For ethical reasons, the study was performed not in normal volunteers, but in children who were enrolled in a clinical trial of the efficacy and safety of vigabatrin in refractory epilepsy. All of these children were receiving other antiepileptic drugs. However, it is unlikely that this could have interfered with the results due to the following considerations.
   - Adult pharmacokinetic studies have shown similar results in volunteers and in patients with concomitant administration of other AEDs.
   - Vigabatrin is not bound to plasma proteins and largely excreted unchanged, making it unlikely that other drugs could alter its pharmacokinetics.

2. The results showed the differences in the pharmacokinetics of the two enantiomers. The difference is in the same trend as that in adult pharmacokinetic studies.
3. There were differences between infants and children as regards the pharmacokinetic parameters of the active S(+)-enantiomer and inactive R(+)-enantiomer. There were smaller AUC implying a faster total plasma clearance in infants.
4. The age-related differences could be accounted for by either a lower bioavailability or a higher renal clearance in younger subjects. The latter is consistent with the normal changes in renal clearance with age. It has been shown in adults and elderly patients that the plasma pharmacokinetics of vigabatrin are largely influenced by renal clearance.
5. Compared to adult population, this study showed considerable shorter half-lives for infants and children (2.8-5.6 hours compared to 7.5 hours in adults). However, this age effect has not been studied systematically for all age groups. Children aged between 2 and 4 years have not been studied for pharmacokinetics.
6. The study report did not specify whether the patients were confined to the study site, had controlled diet and water intake, had clinical laboratory evaluations, or had given informed consent by a guardian.

2. Vigabatrin relative bioavailability - powder (1g Sachet) versus tablet (2 × 500mg) (Protocol VIG/AUS/91/1)

Title: A bioequivalence study comparing the rate and extent of release of Vigabatrin from Sabril tablets 500mg and Sabril sachets 1g.

Objectives: To demonstrate the bioavailability of vigabatrin powder, presented as a 1g sachet, relative to two 500mg vigabatrin tablets.

Clinical site and investigator: The clinical study was performed during October and November 1991 at [redacted] (b) (4). The Principal Investigator was [redacted] (b) (4) and the Clinical Investigator was [redacted] (b) (4). The study was clinically monitored for the sponsor by D Feeney of Marion Merrell Dow Pharmaceuticals (Australia) PTY Ltd.

Subjects: Sixteen male subjects were recruited of whom fifteen completed both arms of the study.

Study design: This was a randomized, single dose, cross-over, volunteer clinical study with a one week washout period between doses.

Blood samples were taken 12 hours prior to dosing, immediately before dosing and at time intervals of 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0 and 36.0 hours post-dose. These samples were analyzed for plasma levels of vigahatrin using a validated method involving pre-column derivation and HPLC.

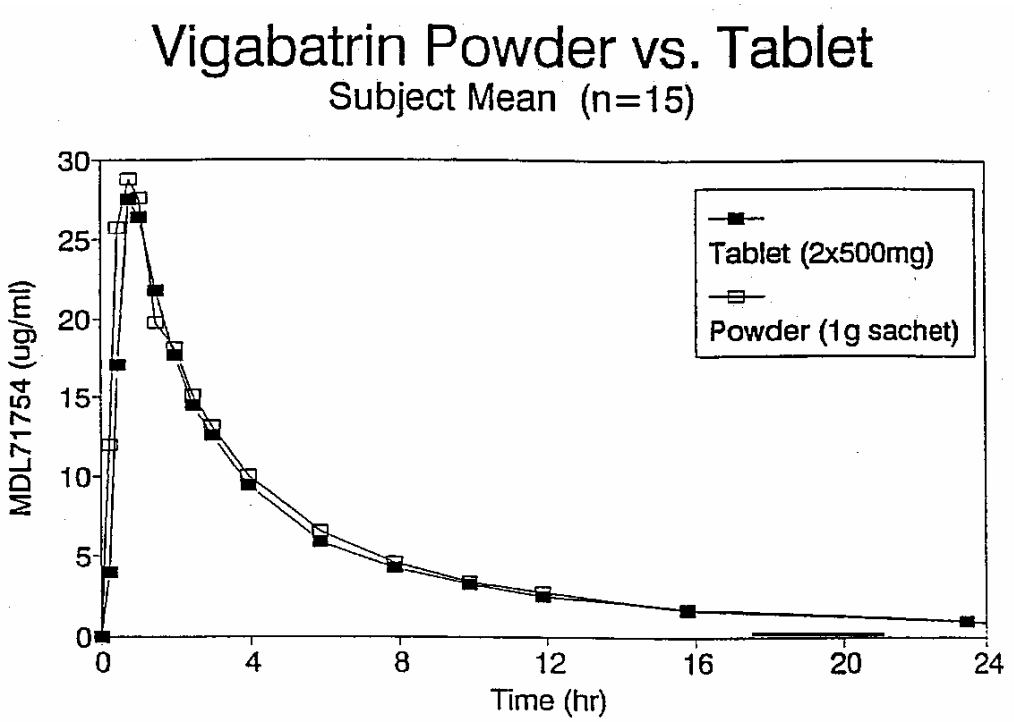
Results:

Eight calibration standards were run over the concentration range 5 to 100 µg/mL (5, 10, 15, 20, 25, 50, 75 and 100). Each of these was analyzed twice in each analytical run.

A summary of the regression analysis and back calculated standard results are given. The mean inter-batch reproducibility of the vigabatrin calibration data varied from 99.9% (CV 9.9%) at nominal 5.0 µg/mL to 101% (CV 4.9%) at nominal 100 µg/mL. The mean correlation coefficient (r) was 0.998 (CV 0.12%) over the 35 runs.

The results for the low, medium and high qua1ity control test samples are summarized. None of the 70 quality contro1 sample sets analyzed exhibited a result which deviated from the nominal concentration by more than 20%. The mean inter-batch precision for vigabatzin taken from the low, medium and high quality control test samples was 6.0% at l6.8 µg/mL, 6.1% at 50.5 µg/mL and. 5.9% at 84.1 µg/mL, with accuracy of 95.7%, 95.4% and 95.8%, respectively.

The mean plasma profiles are shown below for both formulations.



The following table shows the parameter estimates for each formulation and the comparison between them. The ratios and 90% confidence intervals are shown.

Formulation Comparison - Mean Results, Ratios and 90% Confidence Intervals

Parameter (n=15)		Vigabatrin 2 x 500 mg Tablet	Vigabatrin 1000 mg Powder	Ratio	90% CI
AUC(0-24)	µg/ml.hr	119.9	128.3	1.07	0.97 - 1.17
Cmax	µg/ml	28.8	33.3	1.15	1.06 - 1.24
Tmax	hr	0.85	0.66	0.72	0.59 - 0.88

Comments:

1. The results from this study demonstrate that the powder is equivalent to the tablet in extent of bioavailability. The rate of absorption of solution is faster than the tablets.
2. The reviewer's calculation is the same as in the study report. The reviewer's results are show below.

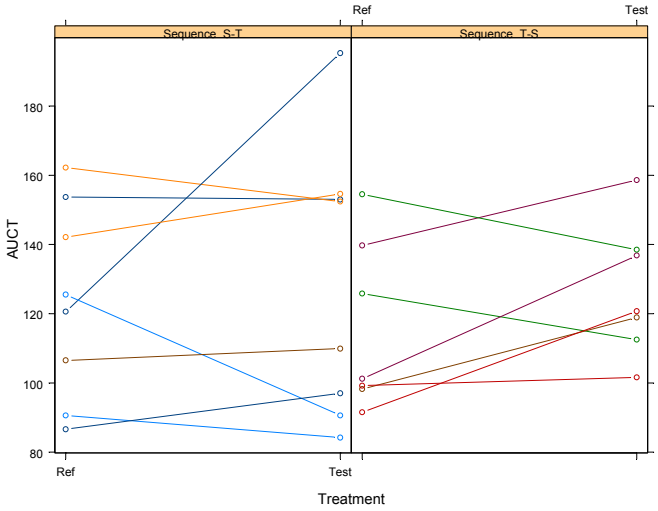
Study Design: The study is a 2-treatment, 2-period, 2-sequence crossover study in 15 subjects as shown in the following table.

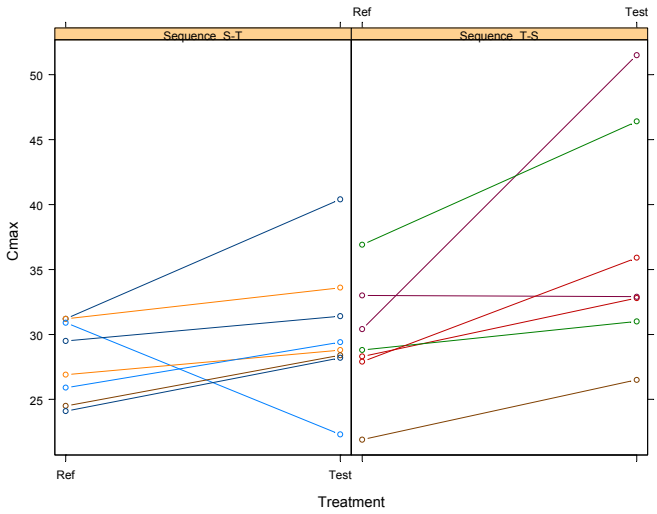
Class	Levels
Subject	15
Sequence	2
Period	2
Treatment	2

Results: The sample size, arithmetic mean, CV, median and range values for each parameter and their log transformed values are shown in the following table. In the table, AUCt, Cmax, Tmax, refer to AUC to last time point, Cmax, Tmax, respectively; LAUCT, LCMAX, are log transformed AUCt, Cmax, values, respectively. TestN and RefN are the sample sizes for the test product and reference product, respectively.

	Reference					Test				
Parameter	N	Mean	CV%	Median	Range	N	Mean	CV%	Median	Range
AUCT	15	119.86	21.48	120.60	75.60	15	128.31	23.99	120.70	111.10
CMAX	15	28.76	13.26	28.80	15.00	15	33.30	23.01	31.40	29.20
LAUCT	15	4.76	4.50	4.79	0.63	15	4.83	4.95	4.79	0.84
LCMAX	15	3.35	3.99	3.36	0.52	15	3.48	6.17	3.45	0.84
Tmax	15	0.85	14.58	0.78	0.31	15	0.66	37.80	0.73	0.82

The AUC to last time point, Cmax, for each subject are plotted against the treatment, respectively, as shown in the following figures.





The following table shows the geometric means of AUC to last time point, Cmax, TestGeoMean and RefGeoMean refer to the geometric means of each parameter for test product and reference product, respectively.

Parameter	TestN	RefN	TestGeoMean	RefGeoMean
AUCT	15	15	117.32	124.94
CMAX	15	15	28.52	32.56

The fit statistics of the ANOVA analysis is summarized in the following table. The R-Square (RSquare) measures how much variation in the log transformed parameter can be accounted for by the model. The larger the value, the better the model's fit. The Coefficient of variation (CV) describes the amount of variation of the log transformed parameter in the population. DepMean is the mean of the parameter (log transformed). RootMSE estimates the standard deviation of the parameter (log transformed) and equals the square root of the Mean Square for Error.

Parameters	RSquare	CV	RootMSE	DepMean
LCMAX	0.815	3.538	0.121	3.417
LAUCT	0.818	2.995	0.144	4.796

The results of the comparison between the text product and the reference product are summarized in the following table. In the table, LowerCL, Difference and UpperCL refer to the differences (Test-Ref) of log transformed means and their lower and upper 90% confidence limits, respectively. Ratio, U_LCI, L_LCI are the ratios (Test/Ref) of the geometric means and their lower and upper 90% confidence limits, respectively.

Parameters	LowerCL	Difference	UpperCL	Ratio	U_LCI	L_LCI
LCMAX	0.058	0.137	0.215	114.655	124.000	106.015
LAUCT	-0.028	0.065	0.158	106.746	117.163	97.255

Conclusions: The study results show that the 90% confidence intervals of the ratios of geometric means fall within 80% to 125% limits for AUC (0 to last time point), Cmax, .

3. Vigabatrin relative bioavailability – Liquid vs chewable tablets (Protocol VGPR0259)

The study report for Protocol VGPR 0259, "Vigabatrin Liquid/Vigabatrin Chewable Tablet Bioavailability/Bioequivalence in Healthy Adult Male Volunteers." is not provided and only a synopsis is presented in the summary section. Following is a brief summary (The study has been reviewed before).

Title: Vigabatrin Liquid/Vigabatrin Chewable Tablet Bioavailability/Bioequivalence in Healthy Adult Male Volunteers. Analytical Data Report: Determination of Vigabatrin (MDL 71,754) in Human Plasma (Samples) by High Performance Liquid Chromatography, Protocol VGPR0259, ([b) (4] Study Number 6151-154)

Objective: The primary objective is to determine the pivotal bioequivalence of the 500 mg chewable tablet and the liquid saccharin/paraben formulation to the liquid xylitol/benzoate formulation used in some of the pediatric pivotal safety and efficacy clinical trials. The secondary objective is to characterize the bioavailability of the 500 mg chewable tablet, the liquid saccharin/paraben formulation and the liquid xylitol/benzoate formulation relative to the US commercial film-coated 500 mg tablet.

Analytical site and time period: The Bioanalytical Chemistry Department at the [b) (4] has determined levels of vigabatrin (VGB) in human plasma samples. The plasma analyses were started on November 13, 1996, and completed on December 6, 1996.

Study design: The study was a single-dose, open-labeled, fasting, randomized, complete 4-period, cross-over study of fifteen (15) normal volunteers with a one-week washout period between doses. The treatments are listed below.

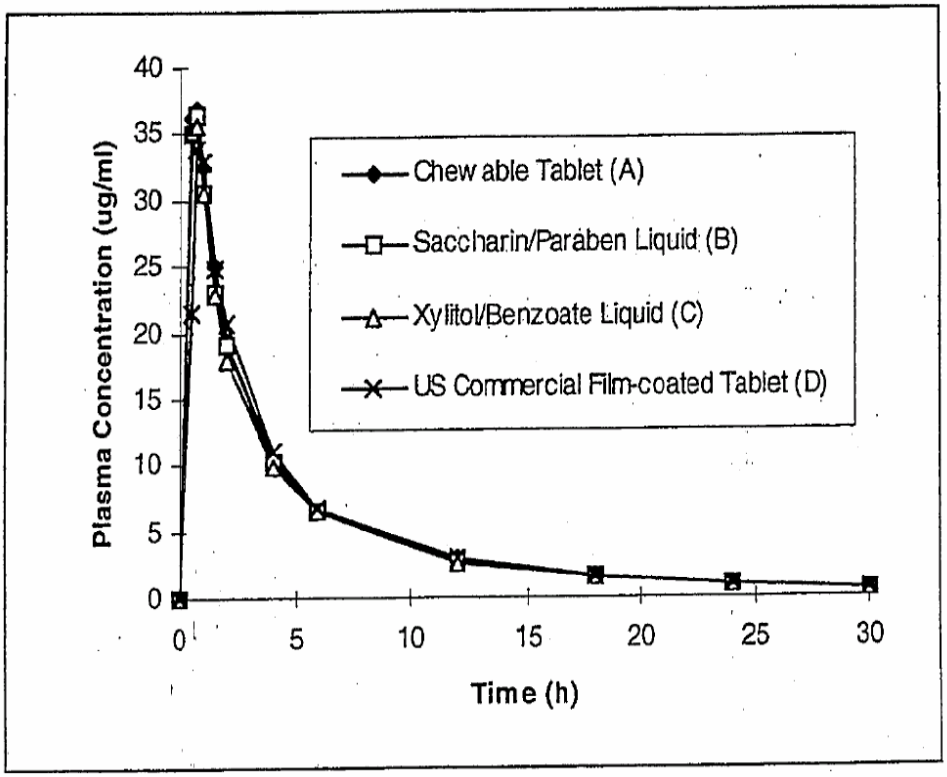
- Treatment A: 2 x 500mg vigabatrin chewable tablets (Batch Number Not Available)
- Treatment B: 10 ml of a 100 mg/ml liquid saccharin/paraben formulation (Batch Number Not Available)
- Treatment C: 10 ml of a 100 mg/ml liquid xylitol/benzoate formulation (Batch Number Not Available)
- Treatment D: 2 x 500 mg vigabatrin US commercial, film-coated tablet (Batch Number Not Available)

Results:
A total of 744 plasma samples were assayed in singlet for vigabatrin in human plasma. The analytical method utilized for these analyses was high-performance liquid chromatography. The following table shows the assay performance.

LOQ (pg/mL)	Range (ng/mL)	QC sample		Calibration	
		Precision (CV%)	Accuracy (%)	Precision (CV%)	Accuracy (%)
0.25	0.250-100	6.5 to 10.6	3.9 to 6.0	3.2 to 5.9	-1.9 to 3.8

The assays are acceptable based on the current standard.

Mean vigabatrin plasma concentration versus time profiles following administration of four vigabatrin formulations to healthy male volunteers are shown in the following figure.



Following table shows the treatment comparisons for key plasma vigabatrin pharmacokinetic parameters including the ratios and their 90% confidence intervals.

Parameter	Treatment	Mean	%CV	Adjusted Mean	Pairwise Comparisons[1]			
					Pair	Ratio (%)	90% CI on Ratio	P Value
AUC (0-∞) (μg°h/mL)	A	160.81	13.54	159.43	A/D	101.48	(97.2, 105.9)	0.570
			13.02	156.17	A/C	104.90	(100.5, 109.5)	0.069
	B	157.44	16.21	151.98	B/D	99.40	(95.2, 103.8)	0.816
			13.62	157.11	B/C	102.76	(98.4, 107.3)	0.294
	C	152.60			C/D	96.73	(92.6, 101.0)	0.206
	D	157.53						
C_{max} (μg/mL)	A	40.22	18.13	39.64	A/D	108.00	(99.6, 117.1)	0.117
					A/C	100.53	(92.7, 109.0)	0.913
	B	38.72	19.95	38.05	B/D	103.66	(95.6, 112.4)	0.458
					B/C	99.49	(89.0, 104.6)	0.461
	C	40.18	22.65	39.43	C/D	107.44	(99.0, 116.6)	0.147
	D	37.65	24.09	36.70				
T_{max} (h)	A	0.66	27.38	0.63	A/D	68.86	(60.5, 78.3)	<0.001
					A/C	104.64	(92.0, 119.0)	0.557
	B	0.67	26.20	0.65	B/D	70.63	(62.1, 80.3)	<0.001
					B/C	107.32	(94.4, 122.1)	0.361
	C	0.62	20.94	0.61	C/D	65.81	(57.8, 75.0)	<0.001
	D	0.95	26.69	0.92				

[1] Based on LS means from ANOVA of log transformed data.

Treatment A: 1000 mg (2x500 mg chewable tablet) vigabatrin given as a single oral dose to fasted subjects.

Treatment B: 1000 mg (10 mL of a 100 mg/mL liquid saccharin/paraben formulation) vigabatrin given as a single oral dose to fasted subjects.

Treatment C: 1000 mg (10 mL of a 100 mg/mL liquid xylitol/benzoate formulation) vigabatrin given as a single oral dose to fasted subjects.

Treatment D: 1000 mg (2x500 mg, US commercial, film-coated tablet) vigabatrin given as a single oral dose to fasted subjects.

Comments:

1. Although the table and figures show that 90% confidence intervals of the ratios among different formulations are within the 80 to 125% range, the detailed study report and the data have not been provided. Therefore, the bioequivalence among the formulations tested could not be confirmed. However, vigabatrin seems to be a BCS class I drug with high solubility and permeability (the percent of radioactivity recovered in the urine after 72 hours was found to be 95% (20%) of the administered dose). The bioequivalence among the different formulations has less concern.

4. Vigabatrin relative bioavailability and food effect study (Protocol 71754-1-C-017)

Title: A definitive study evaluating the relative bioavailability and the effect of food on the bioavailability of vigabatrin following 1.0 g, single doses (The study has been reviewed before).

Objectives: To evaluate the bioequivalence of the US and European vigabatrin uncoated tablet, the effect of a high fat meal on the bioavailability of vigabatrin tablets and to define the relative bioavailability of vigabatrin tablets compared to a solution.

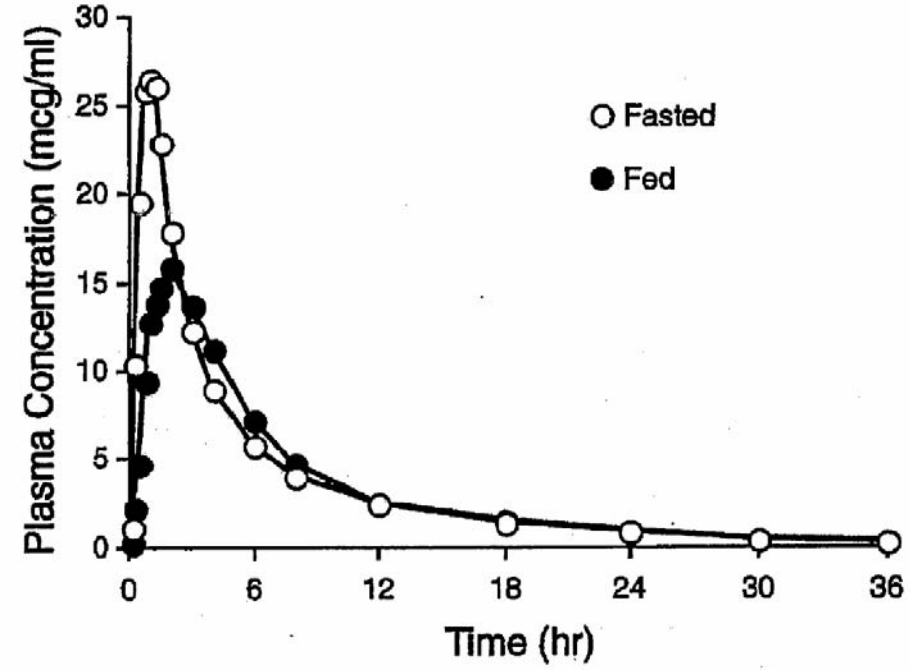
Subjects: Twenty-four male healthy volunteers were recruited in the study.

Study design: The study was an open, randomized balanced, four period, crossover study with one week washout between treatments with twenty-four (24) normal male volunteers. The treatments are listed below.

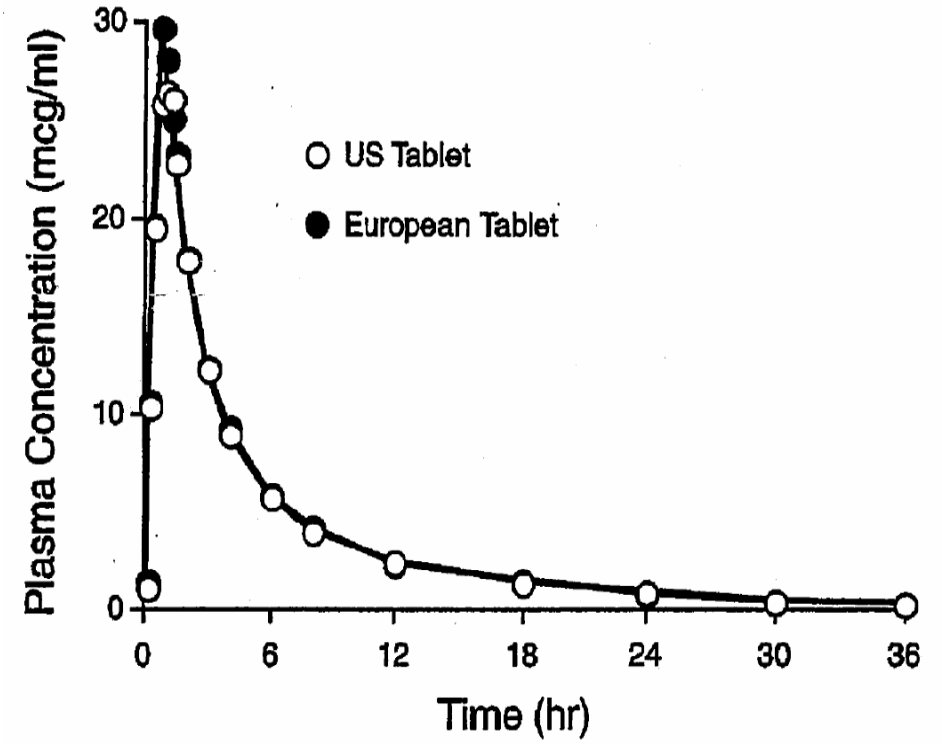
- Treatment A: 2 x 500 mg US tablets in fasted subjects (Batch Number C46848)
- Treatment B: 2 x 500 mg European tablets in fasted subjects (Batch Number 8001)
- Treatment C: 2 x 500 mg US tablets in fed subjects (Batch Number C46848)
- Treatment D: 10 ml of 100 mg/ml oral solution in fasted subjects (Batch Number WN900220)

Results:

The following figure shows the plasma concentration of vigabatrin after administration of 1.0 gram to fed and fasted subjects (n=24).



The following figure shows the mean plasma concentration-time profile of VGB following single dose administrations of US and European tablets.



The following table shows the summary of vigabatrin pharmacokinetic parameters (N=24) in the study evaluating the relative bioavailability and the effect of food on the bioavailability of vigabatrin following 1.0 gram single doses. The ratios of the parameters and their 90% confidence intervals are presented.

	Treatment (Mean ± S.D.)				Crossover ANOVA			
Pharmacokinetic Parameter	**US Fast**	**Euro Fast**	**US Fed**	**Soln Fast**	**Comparison**	**Ratio**	**90% C.I.**	**p-value**
AUC to Infinity [(µg/mL)*hr]	127.1 ± 18.3	129.0 ± 19.0	116.6 ± 14.8	120.9 ± 15.9	Euro Fast/US Fast US Fed/US Fast US Fast/Soln Fast	101.6% 91.8% 105.1%	(99.2%, 103.9%) (89.4%, 94.1%) (102.7%, 107.6%)	0.274 <0.001 0.001
C_{max} (µg/mL)	31.2 ± 6.2	33.2 ± 9.2	20.9 ± 6.7	33.9 ± 5.8	Euro Fast/US Fast US Fed/US Fast US Fast/Soln Fast	106.6% 67.0% 92.0%	(96.4%, 116.8%) (56.9%, 77.2%) (82.7%, 101.4%)	0.282 <0.001 0.161
T_{max} (hr)	1.00 ± 0.29	0.98 ± 0.28	2.14 ± 1.02	0.61 ± 0.25	Euro Fast/US Fast US Fed/US Fast US Fast/Soln Fast	97.9% 213.5% 163.6%	(70.3%, 125.5%) (185.9%, 241.1%) (118.5%, 208.8%)	0.900 <0.001 0.022
Half-Life (hr)	7.15 ± 1.15	7.05 ± 1.17	9.15 ± 4.63	7.07 ± 1.55	Euro Fast/US Fast US Fed/US Fast US Fast/Soln Fast	98.5% 127.9% 101.8%	(82.1%, 15.0%) (111.4%, 144.4%) (85.0%, 118.6%)	0.883 0.006 0.859
Renal clearance (mL/min)	95.0 ± 28.2	92.2 ± 20.5	99.9 ± 26.3	96.2 ± 21.0	Euro Fast/US Fast US Fed/US Fast US Fast/Soln Fast	97.0% 105.1% 98.8%	(85.9%, 108.0%) (94.1%, 116.1%) (87.9%, 109.7%)	0.649 0.444 0.854
Recovery in Urine (%)	69.8 ± 20.4	69.1 ± 12.5	68.2 ± 17.1	65.9 ± 16.1	Euro Fast/US Fast US Fed/US Fast US Fast/Soln Fast	99.0% 97.7% 105.9%	(89.9%, 109.0%) (87.6%, 107.7%) (95.3%, 116.5%)	0.870 0.699 0.359

Comments: This study was reviewed previously by Dr. Tammara and he accepted the bioequivalence between US tablets and European tablets. He also indicated the food effect detected should be stated in the labeling.

5. Vigabatrin bioequivalence study (Protocol 71754-C-029)

Title: A Definitive Study Evaluating the Bioequivalence of Vigabatrin Administered as Uncoated Tablets, Film-Coated Tablets and Oral Solution (The study has been reviewed before).

Objectives: To provide a definitive evaluation of the bioequivalence between uncoated tablets, film-coated tablets and an oral solution of vigabatrin using twelve (12) normal healthy male volunteers.

Subjects: Twelve male healthy volunteers were recruited in the study.

Study design: This was a single-dose, open labeled, fasting, randomized, balanced, three-period, complete cross-over study with a one week washout period between treatments, which are listed below.

- Treatment A: Two uncoated vigabatrin 500mg tablets (Batch Number C49844)
- Treatment B: Two film-coated vigabatrin 500mg tablets (Batch Number C49982)
- Treatment C: 10 ml of 100 mg/ml vigabatrin oral solution (Batch Number C49695)

Results: The following table shows the treatment comparisons for key pharmacokinetic parameters after administrations of coated, uncoated tablets and oral solution.

Dep Var	Pair	Mean Diff	SE of Diff	90% LCL	90% UCL	Ratio	90% LCL on Ratio	90% UCL on Ratio
AUCI	A-C	-0.00788	0.0171638	-0.04	0.02	0.99	0.96	1.02
	B-C	0.01083	0.0171638	-0.02	0.04	1.01	0.98	1.04
	B-A	0.01871	0.0171638	-0.01	0.05	1.02	0.99	1.05
C_{max}	A-C	-0.07800	0.0440772	-0.15	0.00	0.92	0.86	1.00
	B-C	-0.11057	0.0440772	-0.19	-0.03	0.90	0.83	0.97
	B-A	-0.03257	0.0440772	-0.11	0.04	0.97	0.90	1.04
T_{max}	A-C	0.43386	0.0863221	0.28	0.58	1.54	1.33	1.79
	B-C	0.47635	0.0863221	0.33	0.63	1.61	1.39	1.87
	B-A	0.04249	0.0863221	-0.11	0.19	1.04	0.90	1.21

Treatment A: Two uncoated vigabatrin 500mg tablets (Batch C49844)
Treatment B: Two film-coated vigabatrin 500mg tablets (Batch C49982)
Treatment C: 10 ml of 100 mg/ml vigabatrin oral solution (Batch C49695)

Comments: This study was reviewed previously by Dr. Tammara and he accepted the bioequivalence between the film coated tablets, uncoated tablets and the oral solution.

4.3 Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

GENERAL INFORMATION ABOUT THE SUBMISSION

	Information		Information
NDA Number	N22-006	**Brand Name**	NA
OCP Division (I, II, III)	DCP-I	**Generic Name**	Vigabatrin
Medical Division	HFD-120	**Drug Class**	Antiepileptic: inhibitor of GABA transaminase
OCP Reviewer	John Duan	**Indication(s)**	Monotherapy for infantile spasms
OCPB Team Leader	Veneeta Tandon	**Dosage Form**	500 mg powder for solution (with water, juice or sprinkled on food)
		Dosing Regimen	Infantile Spasms (birth to 2 years): Initiate therapy at 50 mg/kg/day twice daily increasing total daily dose per instructions to a maximum of 150 mg/kg/day Dose adjustment recommended in renally impaired patients
Date of Submission	12/30/07	**Route of Administration**	Oral
Estimated Due Date of OCP Review	5/12/08	**Sponsor**	Ovation
PDUFA Due Date	6/30/08	**Priority Classification**	Priority
Division Due Date	5/26/08		

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			

Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	2		Two analytical reports using HP-mass selective detector have been submitted for evaluation of vigabatrin in plasma and urine.
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	X	1 new		Study 332.5 : PK in infants and children
geriatrics:				
Renal impairment:				
Hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				

alternate formulation as reference:	X	3 (2 new + 1 reviewed)		1) Study AUS 911: Relative BE between powder (1 g) and tablet : to review 2) Study 029: Relative BE between Uncoated tablets, Film coated tablets and oral solution: reviewed 3) Study 0259: Relative BE between chewable tablets, film coated tablets, 2 kinds of solution: to reviewed For the third study, study report is not provided, but bioanalytical report only has been provided
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1 already reviewed		Study C017: previously reviewed with N20-427 Study with tablets under fed and fasted conditions, also had a solution arm under fasted condition
Dissolution:				
(IVIVC):				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References		**5 submitted 3 to review+ 2 assay validation**		
Total Number of Studies				

Filability and QBR comments				
	"X" if yes	*Comments*		
Application filable?	*X*	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm?		See below for comments		
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date	John Duan			
Secondary reviewer Signature and Date	Veneeta Tandon			

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

/s/

John Duan
7/30/2008 02:04:36 PM
BIOPHARMACEUTICS

Veneeta Tandon
7/30/2008 02:42:41 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
7/30/2008 06:01:15 PM
BIOPHARMACEUTICS
Phase 4 commitments