CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-427

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 [redacted] 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. b(4)

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 ± 2°C). 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 [redacted] The sponsor submitted the thorough QT study report OV-1033 for vigabatrin, including electronic datasets and waveforms to the ECG warehouse.

b(4)

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 [redacted] are 0.5, 1.5, and 2.5 g bid. To support continued [redacted] 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). b(4)

"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 [redacted] to a centralized ECG core laboratory [redacted] 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. b(4)

The ECGs were interpreted by Cardiologists at [redacted] 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. b(4)

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, QTcI 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 QTcI 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.

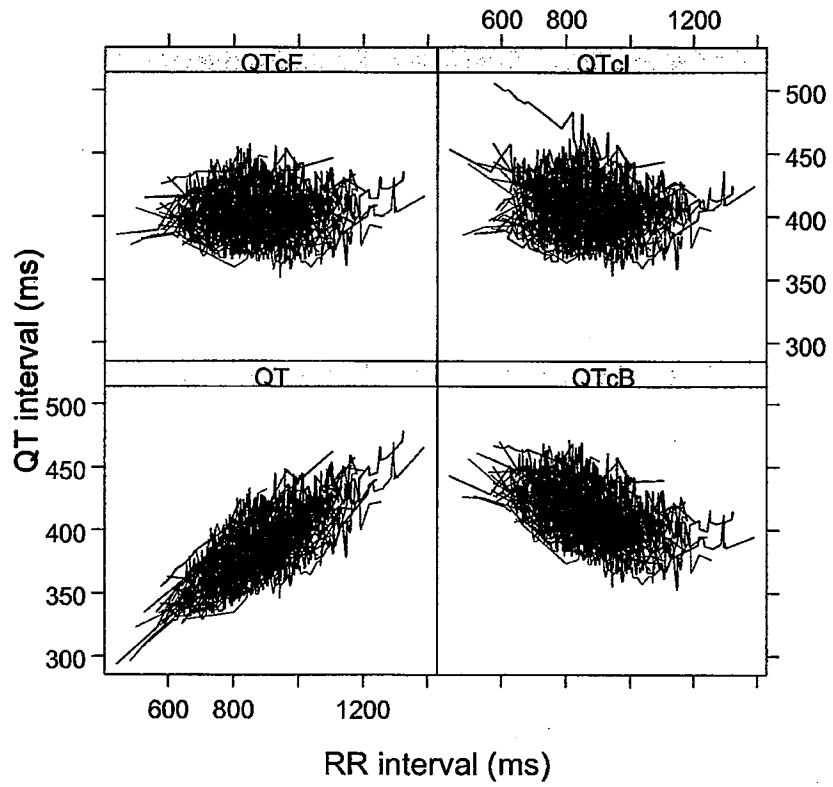
Reviewer's Analysis: A plot of ΔΔQTc vs. drug concentrations is presented in ***Figure 4****.*

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

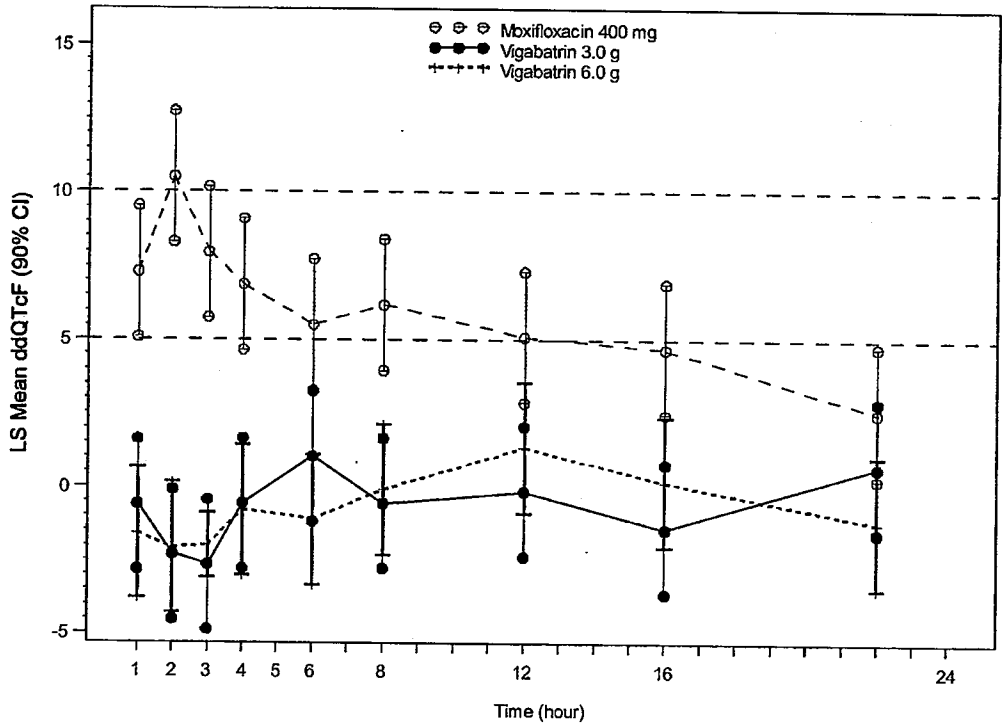
	Moxifloxacin		Placebo		ΔΔQTcF		
Time/(hr)	Mean	Std Err.	Mean	Std Err.	Diff LS Mean	Unadjusted 90% CI	Adjusted 90% CI
1	2.5	1.1	-4.8	1.1	7.3	(5.1, 9.5)	(4.2, 10.2)
2	8.1	1.1	-2.4	1.1	10.5	(8.3, 12.8)	(7.4, 13.3)
3	9.2	1.1	1.2	1.1	8.0	(5.8, 10.2)	(4.8, 10.8)
4	7.9	1.1	1.1	1.1	6.9	(4.7, 9.1)	(3.8, 9.7)

*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											
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											

b(4)

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.

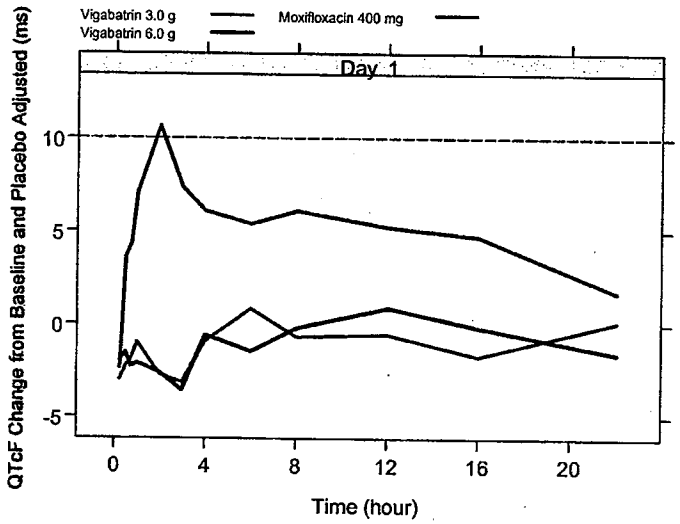
Table 18: Analysis Results of ΔΔQRS by Treatment Group

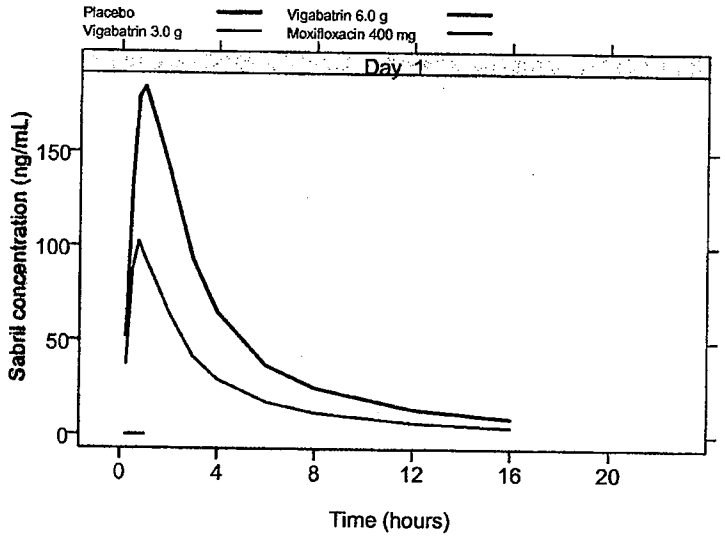
	Vigabatrin 3.0 g		Vigabatrin 6.0 g	
Time/(hr)	LS Mean	90% CI	LS Mean	90% CI
0.25	-0.2	(-0.9, 0.5)	-0.2	(-0.9, 0.5)
0.5	-0.5	(-1.1, 0.2)	-0.9	(-1.5, -0.2)
0.75	-0.9	(-1.6, -0.2)	-1.2	(-1.9, -0.5)
1	-0.2	(-0.9, 0.4)	-0.8	(-1.5, -0.1)
2	-0.7	(-1.3, 0.0)	-0.2	(-0.9, 0.5)
3	-0.2	(-0.9, 0.5)	-0.6	(-1.3, 0.1)
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).

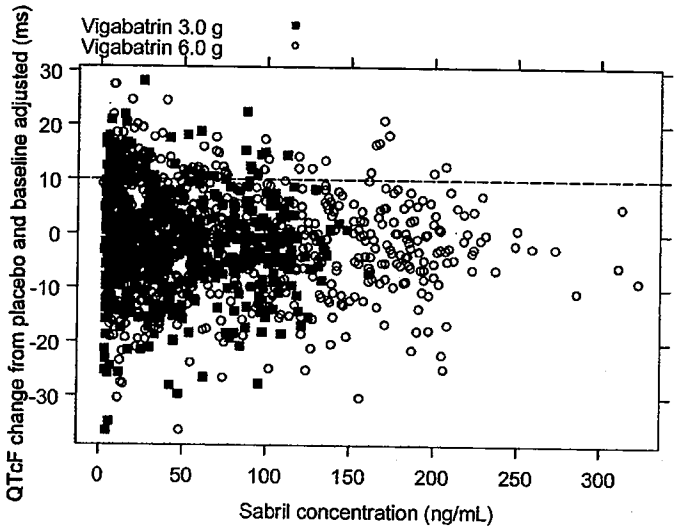




5.3.2 Sabril Concentration-QTcF Analysis

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:	[redacted]
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

b(4)

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

b(4)

Table 1: Highlights of Clinical Pharmacology	
Description	**Result**
Therapeutic Dose	The maximum dose to be used in the [redacted] 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 ($AUC_{0-\tau, ss}$/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#:	**20427**
Submission Date:	12/28/2007
Brand Name:	Sabril®
Generic Name:	Vigabatrin
Formulation:	Tablets
Strength:	500mg
Sponsor:	OVATION Pharmaceuticals
Reviewer:	John Duan, Ph.D.
Submission Type:	Response to Not Approvable Letter

TABLE OF CONTENTS

1. EXECUCTIVE SUMMARY

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 original NDA for Sabril (vigabatrin) tablets was submitted on April 29, 1994 by Aventis, Inc. for the adjunctive treatment of complex partial seizures (CPS). After initially issuing an Approvable Letter on November 26, 1997, the Agency eventually issued a Not Approvable Letter to Aventis on October 27, 1998 due to reports of visual field defects associated with vigabatrin therapy that surfaced during post-marketing experience in Europe. Subsequent submissions were considered incomplete responses.

The current resubmission is in response to the April 3, 2007 incomplete response letter. Considering this NDA has a long history including a series of resubmissions, this review summarizes the studies previously reviewed, evaluates the newly submitted studies and focuses on the issues identified.

1.1 Recommendation

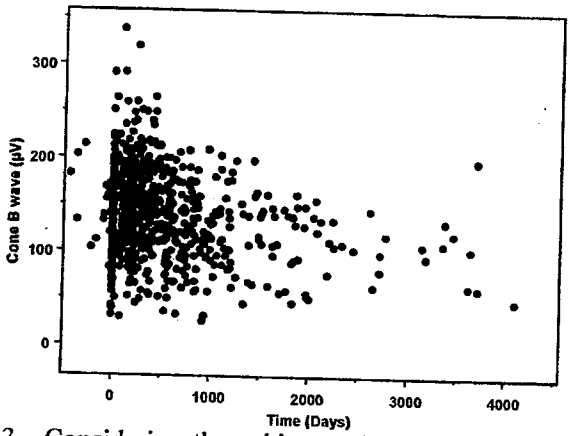
NDA 20-427 is acceptable from a clinical pharmacology standpoint, provided the labeling changes are made. The Phase 4 commitment should be conveyed to the sponsor.

The following comments should be conveyed to the medical division.

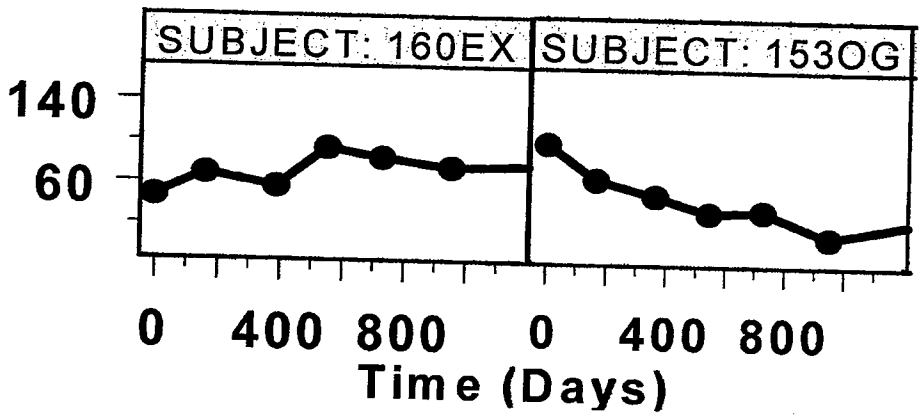
Comments to the medical division

The following comments are made based on the exploratory analysis of visual field defect (VFD).

1. The claim made by the applicant that 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.
2. 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.

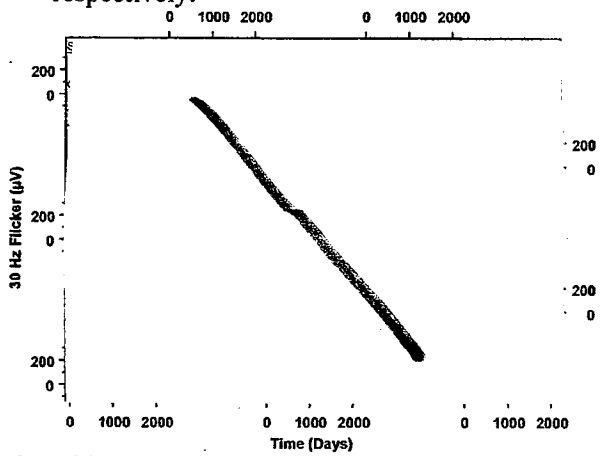


3. Considering the subjects with more than 3 time points of ERG measurements, it is recognized that the declines had different slopes among the subjects. In a general consideration, the subjects can be divided into two groups according to the shapes of the time course of ERG. In one group, the 30 Hz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



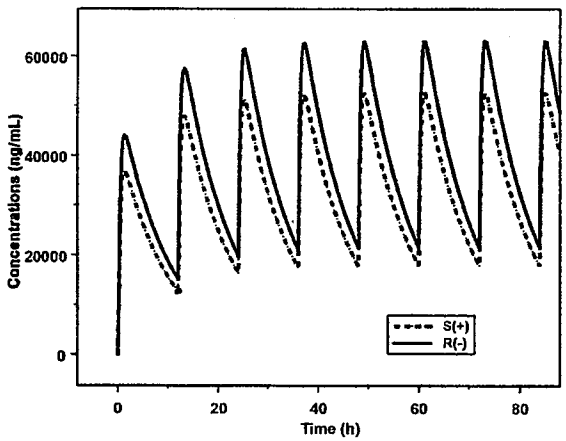
4. If as reported, 30 Hz flicker and cone b-wave have a close relationship with VFD, these measurements may reflect the VFD evolving process when monitored frequently enough. While the diagnosis of VFD using visual field measurement is a none-or-all process and difficult to pick the early warning signs, ERG may provide a more quantitative signal of the disease progression at relatively early time points.
5. 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 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.



b(4)

6. 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.
7. 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 likely 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.



8. 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, the role of genetic variation is suspected.

A literature search has been conducted accordingly. 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 commitment

If this drug gets approved, the following Phase IV commitments should be conveyed to the applicant:

1. The applicant should conduct in vitro studies to evaluate the ability of vigarbatrin to induce CYP1A2 and CYP3A4 using the method described in FDA Guidance for Industry: Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labeling.

2. If the applicant is going to pursue the indication in children, the pharmacokinetic study in the age group 2-4 years should be conducted.

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 tablets was submitted on April 29, 1994 for the treatment of complex partial seizures (CPS). After several review cycles, the Agency issued a not approvable letter eventually. 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 applicant has submitted one drug interaction study and one in vitro study reports. The majority studies submitted earlier were 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 mean (%CV) relative bioavailability of vigabatrin was about 101% (17%) for vigabatrin 500 mg film coated tablets in comparison to an oral solution.

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 epileptic patients, mean (%CV) Cmax was 61 µg/mL (21 %) with a Tmax of about 1.0 hour (34%).

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-lactam 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.

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

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 bacon, 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.

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 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 although the indication is proposed for adults only. 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 is reasonable to reduce the dose by the same percentage as adults with different degree of renal impairments.

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.

John Duan, Ph.D.
Reviewer
Division of Clinical Pharmacology 1

Date

Veneeta Tandon, Ph.D.
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Date

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HFD-860 Mehul Mehta, Ramana Uppoor, Veneeta Tandon, John Duan

2. QUESTION BASED REVIEW

1. What is the relevant pharmacokinetic behavior of vigabatrin in adult subjects?

The original NDA application was submitted on April 29, 1994 reviewed by Dr. Vijay Tammara. Following are the relevant information extracted from Dr. Tammara's summary of the clinical pharmacology of vigabatrin.

1. Vigabatrin exists as a 50/50 racemic mixture of two enantiomers; the S(+) isomer is pharmacologically active while the R(-) enantiomer is inactive.
2. 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.
3. Accumulation of the drug appears to be modest at multiple dosing (i.e., accumulation: 1.2; theoretical R= 1.5).
4. There was a 36% decrease in renal clearance of vigabatrin in the elderly population when compared to young males (0.77 vs. 1.21 mL/min/kg).
5. 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. 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). 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. 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.
6. 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.

2. What is the drug interaction potential and what is the mechanism?

In this submission the applicant has submitted one drug interaction study and one in vitro study report.

A drug interaction study between vigabatrin and phenytoin showed that vigabatrin reduced total and free phenytoin concentration in general, which is consistent with the study previously submitted.

Data from a number of clinical and pharmacokinetic studies have shown that a vigabatrin-phenytoin interaction exists. 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.

On the other hand, the plasma vigabatrin trough concentrations were not significantly affected by coadministration with phenytoin.

Despite the documented decrease in phenytoin serum concentrations with concomitant vigabatrin administration, the mechanism of this interaction remained unclear. Investigation into potential mechanisms presented in the literature revealed that plasma protein binding of phenytoin was not altered by vigabatrin therapy, nor was the clearance and half-life of antipyrine or the urinary ratio of phenytoin metabolites.

The in vitro studies submitted utilized primary cultures of human hepatocytes to evaluate the potential of vigabatrin to induce liver microsomal cytochrome P450 (CYP450) enzymes. Due to the variability and low induction potential of CYP2C enzyme activity in vitro, more sensitive quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) assays were performed with VGB to assess the changes in mRNA expression levels, and hence induction of CYP2Cs, the enzymes responsible for phenytoin metabolism. In these studies, VGB treatment resulted in a concentration-related induction of CYP2C9 mRNA expression in two of three primary donor hepatocyte VGB-treated cultures. Similarly, one of three primary donor hepatocyte VGB-treated cultures displayed an increase in CYP2C19 mRNA expression. These results provide evidence for the mechanism of decreased phenytoin concentrations reported clinically in some patients.

In addition, a literature report on drug interactions with oral contraceptives was provided. This study was conducted to determine whether vigabatrin affects in vivo indices of hepatic microsomal 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 daily) 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.

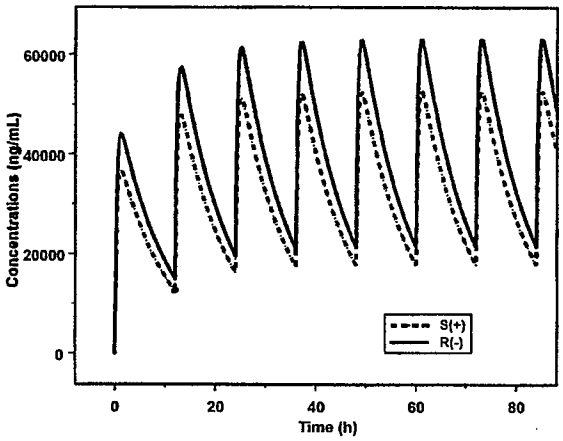
The results showed that vigabatrin treatment had no influence on antipyrine clearance (28 ±5.6 vs. 30 ± 4.5 mL/h/kg on placebo), antipyrine half-life (15.5 ± 3.5 vs. 14.1 ± 2.1 h), urinary 6-p-hydroxycortisol excretion (488 ± 164 vs. 470 ± 228 nmol/day), 6-p-hydroxycortisol-to-cortisol concentration 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 microsomal 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.

3. 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).

- 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.

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

1) Dose response for perimetry data

In order to examine the relationship between the dose and the abnormality of the visual field, data from study 4020 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 VGB 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)

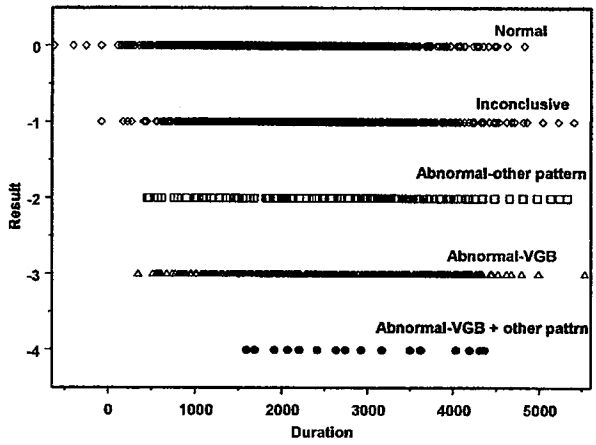
Perimetry examination was the principal measurement tool for evaluation of visual fields during the study. The findings upon perimetry exam were classified into categories ranging from normal to abnormal. To systematize and analyze perimetry data, copies of all reports were sent to a visual field expert (Dr. Wild) 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.

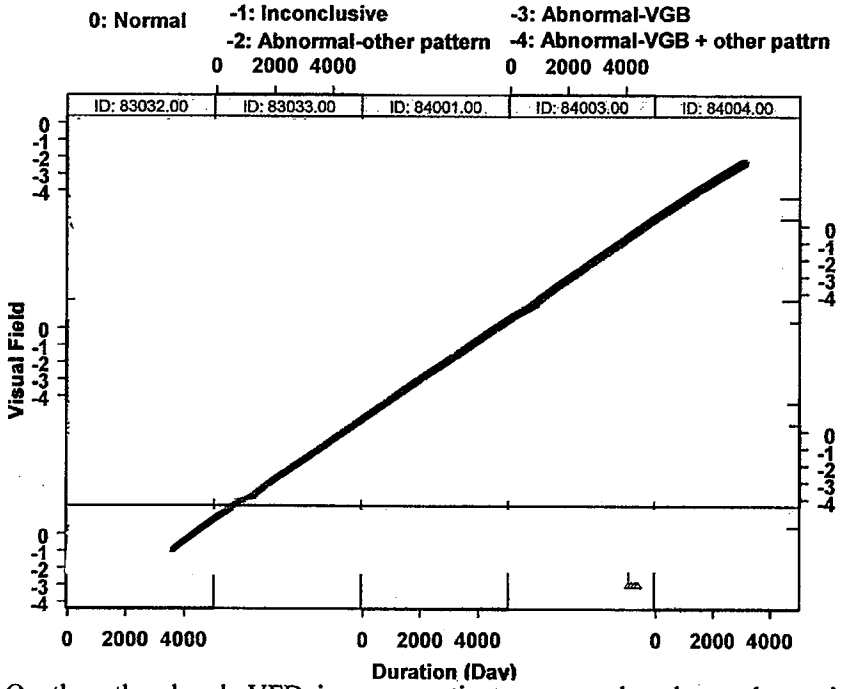
Since the subjects had taken different doses at different times, the investigation started with a time to event analysis for the covariate with time dependent repeated measurements. The subjects with both dose information and measurement of perimetry are selected for analysis. The visual field examination 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.

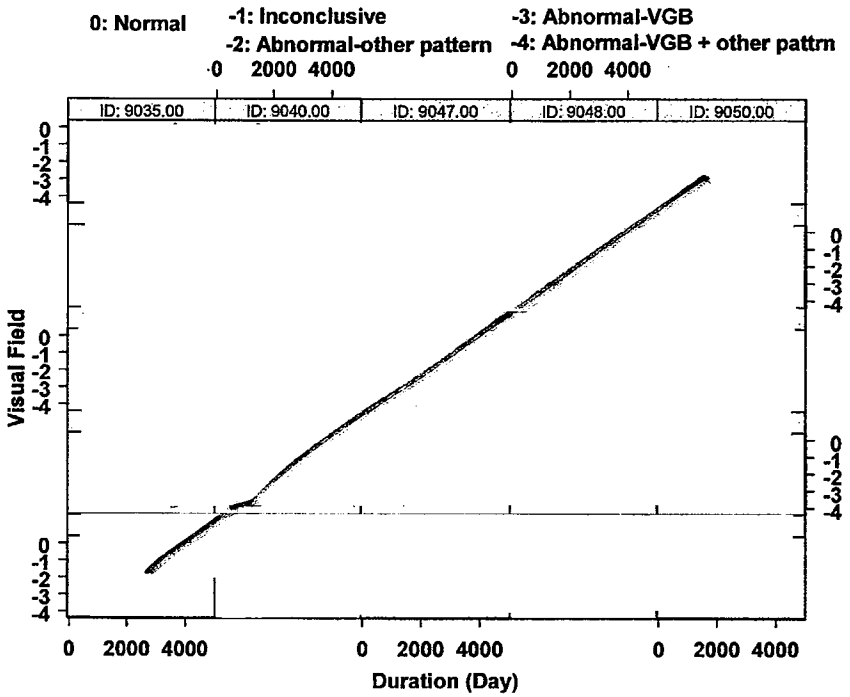


The plots for individual patient give the same trend as shown in the following figure.



b(4)

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



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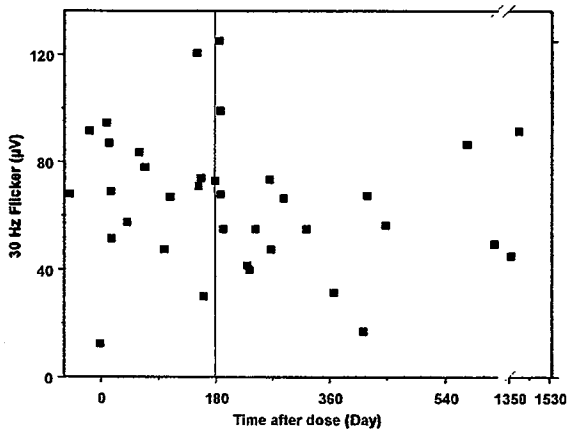
It is noticeable from these figures that the visual field worsening seems a sudden incident. However, considering the judgment for abnormality is a zero-or-one decision process and the examinations were not frequent enough, the above figures may not reflect the development process of VFD. In this regard,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

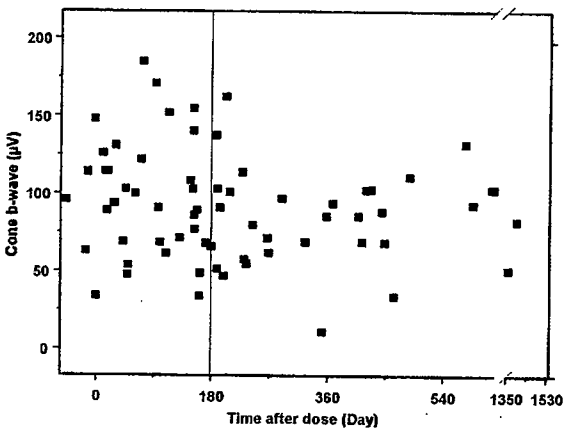
2) Time courses of ERG data in Boston stud, Toronto study, and Study R003

Boston study included 49 subjects, 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.

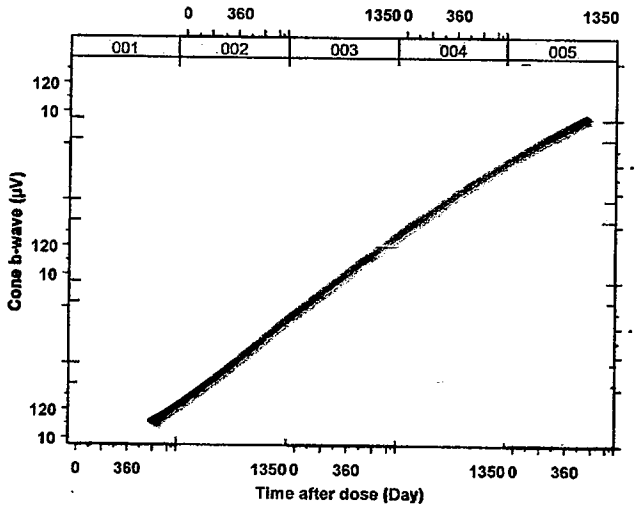


The applicant's analysis compared the mean 30 Hz flicker amplitude for those who were tested less than or at 6 months after the first VGB dose [77.6 μV (± 24.5μV)] to that for subjects tested more than 6 months after the first dose of VGB [54.7 μV (±20.4μV)]. However, as shown in the figure, the decreasing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



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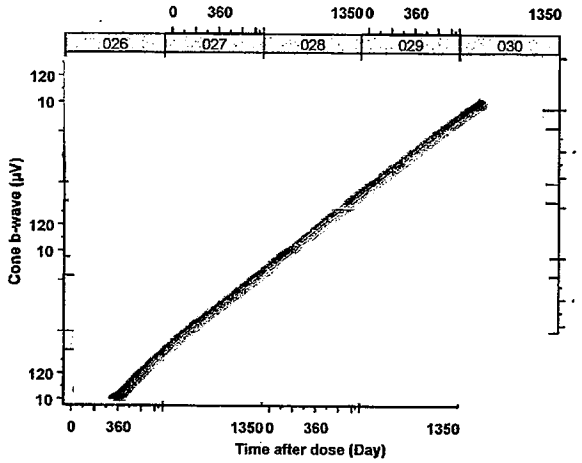
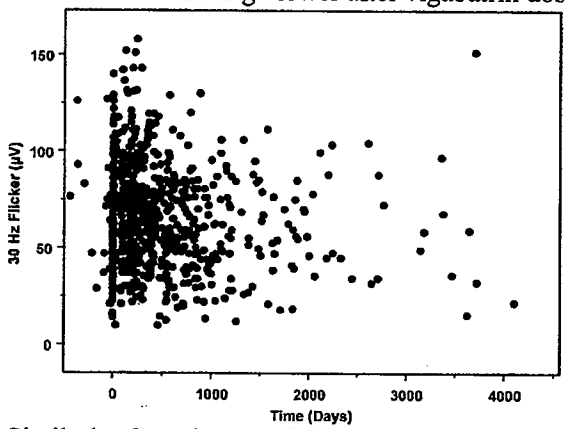
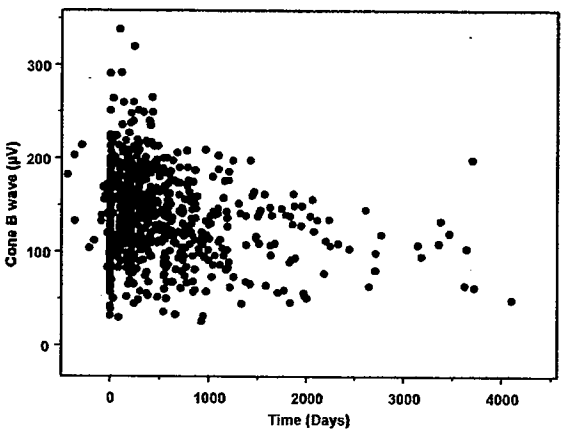


b(4)

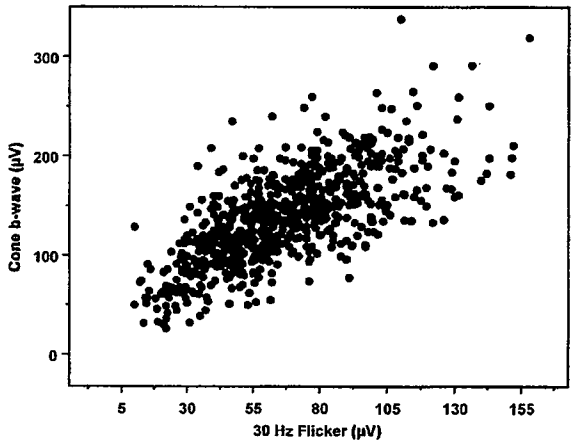
The above observation can be confirmed by a bigger study. The Toronto study included 246 pediatric patients. In this study, the 30 Hz flicker measured at different time points also has the trend to go lower after vigabatrin dosing as shown in the following figure.



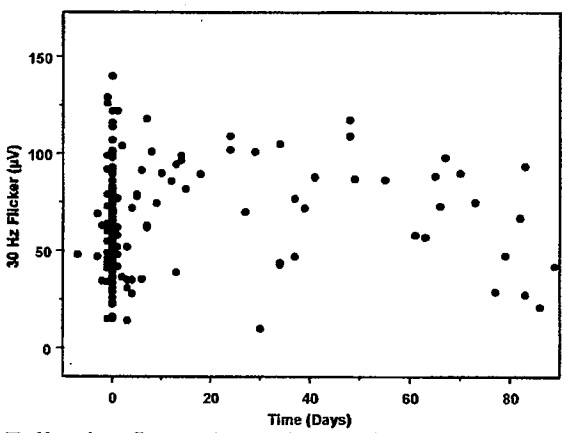
Similarly, Cone b-wave follows the same trend as shown in the following figure.



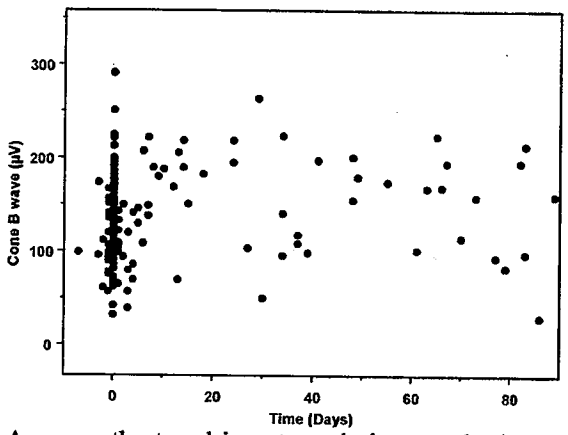
Actually, these two parameters are correlated each other as indicated in the following figure.



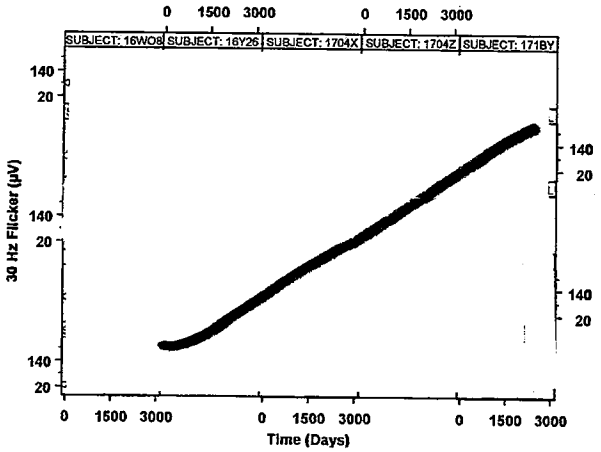
One question is of concern: could the trend be observed earlier given the fact that the parameter decreased along with the time? The data of 30 Hz flicker for the first 90 days after dosing are shown in the following figure.



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

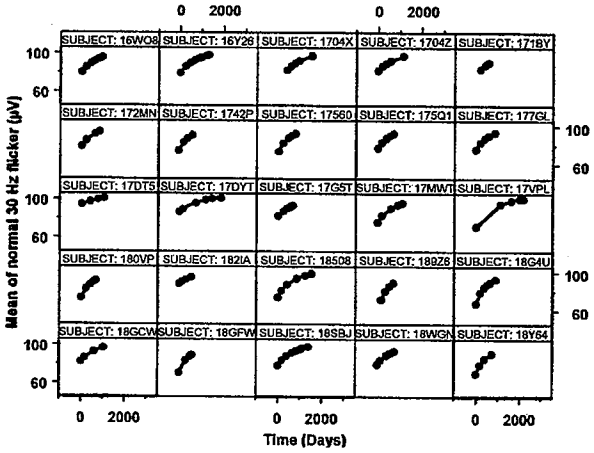


As seen, the trend is not as obvious as the long term figure as shown above. It might be due to two reasons. One is that fewer samples were collected before 90 days. Another is that the patients might have different responses after vigabatrin dosing and they could be divided into two groups: a sensitive 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.



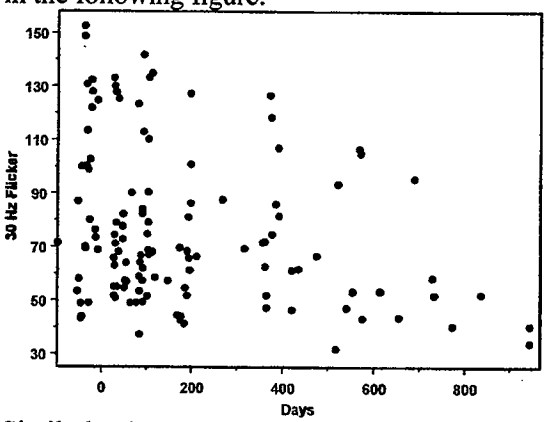
b(4)

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.

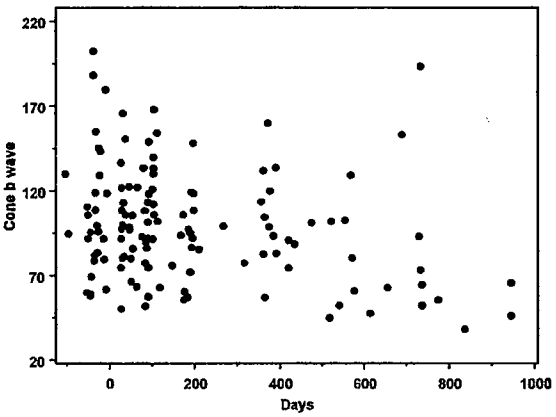


Therefore, if the visual field of the kids in the study were not affected by vigabatrin, their 30 Hz flicker measurements should have increased along with time in the same fashion as the normal mean of the parameter. However, due to the effects of vigabatrin, fewer subjects had increased measurements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

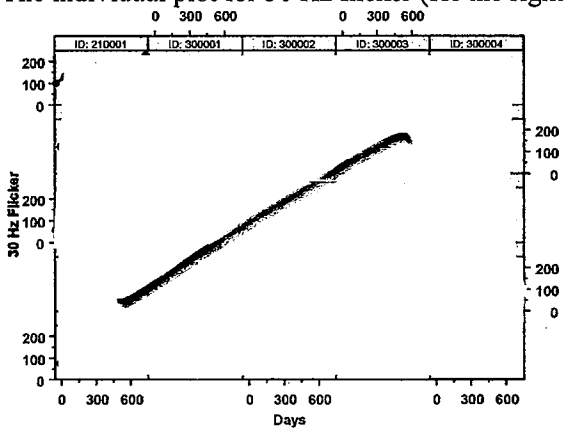
The observations were further supported by the 25 subjects in study R003, who had ERG measurements. Similar trend was observed for 30 Hz flicker (for the right eye) as shown in the following figure.



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.



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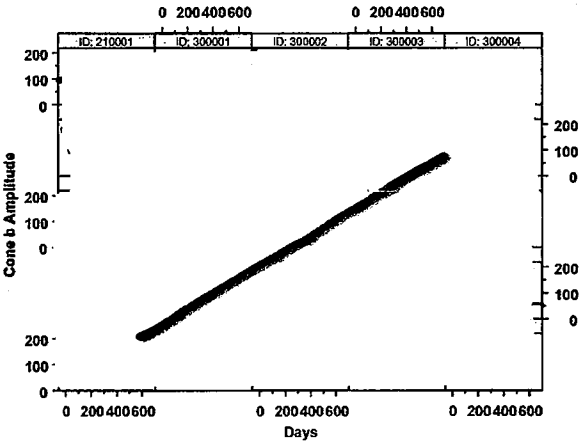
Following figure is the individual plot for cone b-wave.



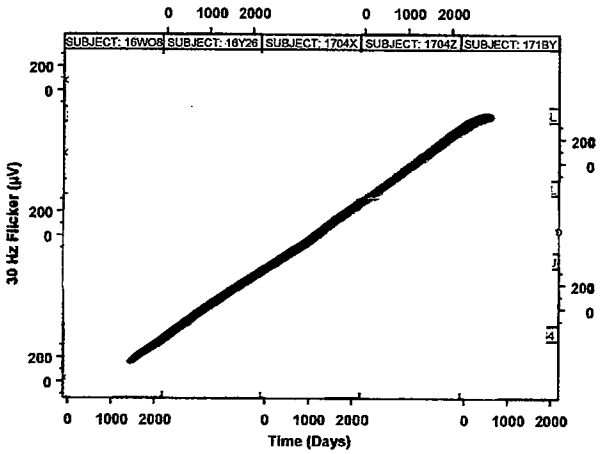
b(4)

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
1	65	26.42	65	26.42
2	44	17.89	109	44.31
3	49	19.92	158	64.23
4	37	15.04	195	79.27
5	23	9.35	218	88.62
6	16	6.50	234	95.12
7	5	2.03	239	97.15
8	4	1.63	243	98.78
9	1	0.41	244	99.19
10	2	0.81	246	100.00

As can be seen, there were 88 subjects (36.77%) 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).



b(4)

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	-115.0152	157.29235
RLD	88	0.15688	1.076223	-1.428597	8.2785449

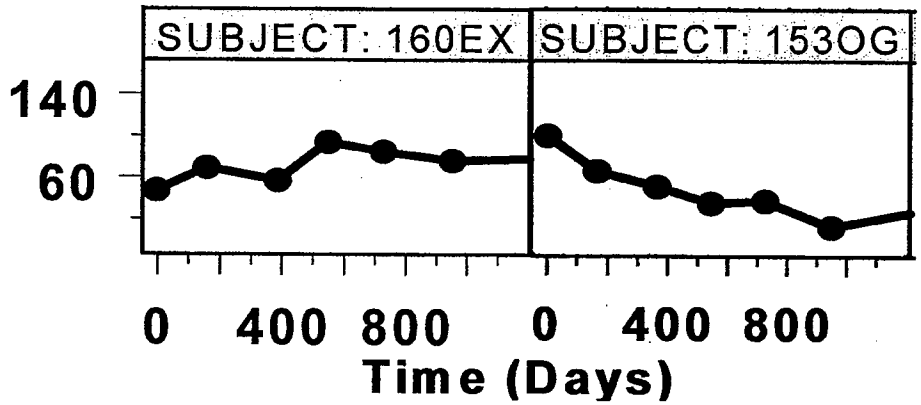
Although the mean residue is small (0.44), the standard deviation is large (37.88), spanning a big range from minimum of -115 to maximum of 157. Similarly, the relative deviation has a mean of 15%, ranging from -142% to 828%.

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 has been conducted accordingly. 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.

36 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 16

4.2 APPENDIX II. Individual Study synopsis

1. Drug interaction study (Protocol VGPR0260 [071754PR0260] Study VGST1849 [071754ST1849], Report K-97-0494-D)

Note: this study is located in submission dated 10-10-2006

Title: The steady-state pharmacokinetic Interaction between vigabatrin and phenytoin in healthy male subjects.

Objectives:

Primary objectives

- To characterize the pharmacokinetics of phenytoin following three weeks of co-administration of phenytoin and vigabatrin.
- To monitor the trough plasma concentrations of vigabatrin during co-administration of phenytoin and vigabatrin.

Secondary objective

- To investigate the time dependence of the interaction by comparing data after 3 weeks of phenytoin/vigabatrin co-administration with data after 6 weeks of co-administration using a subset of the total data.

b(4)

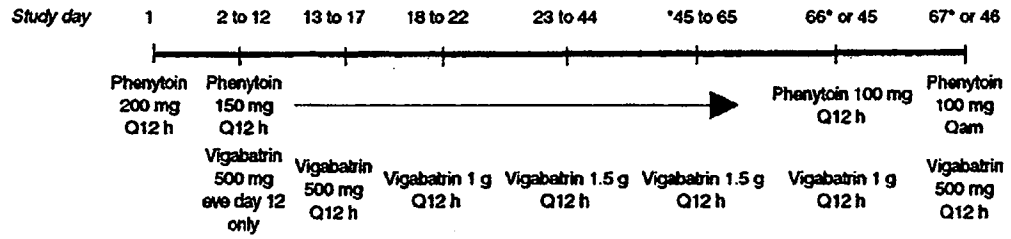
Subjects: The study was conducted in 15 healthy male subjects.

Study design: The trial was a single-center, open-label, single treatment design comparing phenytoin pharmacokinetics prior to and after co-administration with vigabatrin. The following table summarizes the phenytoin and vigabatrin dosing schedules.

Study day(s)	*Phenytoin dosing schedule*	*Vigabatrin dosing schedule*
day 1	phenytoin 200 mg Q12 h	none
day 2 to morning of day 12	phenytoin 150 mg Q12 h	none
evening of day 12	phenytoin 150 mg	vigabatrin 500 mg
days 13 to 17	phenytoin 150 mg Q12 h	vigabatrin 500 mg Q12 h
days 18 to 22	phenytoin 150 mg Q12 h	vigabatrin 1 g Q12 h
day 23 to day 65* or 44**	phenytoin 150 mg Q12 h	vigabatrin 1.5 g Q12 h
day 66* or 45**	phenytoin 100 mg Q12 h	vigabatrin 1 g Q12 h
day 67* or 46**	phenytoin 100 mg QAM	vigabatrin 500 mg Q12 h

*(subjects 0001-0005)
**(subjects 0006-0015)

A schematic of this dosing regimen is as follows.



Plasma concentrations of phenytoin, the 5pHPPH metabolite of phenytoin, and free phenytoin were measured serially for 12 hours after the morning dose on days 12, 44, and 65 (subjects 0001-0005 only) and trough concentrations were measured approximately weekly. Vigabatria plasma trough concentrations were measured on days 21-23, 42-44, and 63-65. Concentrations of phenytoin, total 5pHPPH, and unconjugated 5pHPPH were measured in urine over the 12 hour dosing interval on days 12, 44 and 65. Adverse events, electrocardiograms, clinical laboratories and physical examinations were monitored for safety evaluations.

Comparisons between earlier and later day plasma and urine parameters were evaluated with an analysis of the natural log transformed data. An analysis of variance, with terms for subject and day, was done for each parameter from which 90% confidence intervals for the ratio of days were obtained. Trough concentrations were evaluated with an analysis of the natural log transformed data. An analysis of variance, with terms for subject and day, was done within each week from which 90% confidence intervals for the ratio of days were obtained.

Results

The accuracy and precision statistics of the plasma methods across study sample analyses can be found in the following summary tables.

Summary of method performance across sample analyses, batch-to-batch statistics, from plasma bioanalytical data reports for protocol VGPR0260

Analyte	*Samples*	*Accuracy (1)*	*Precision (2)*
Vigabatrin	QC Samples	94.4 to 101.1%	5.2 to 7.7%
Vigabatrin	Calibration Standards	95.7 to 102.9%	0.5 to 4.3%
free Phenytoin	QC Samples	0.0 to 7.5%	4.3 to 5.9%
free Phenytoin	Calibration Standards	-2.6 to 2.0%	4.9 to 10.0%
Phenytoin	QC Samples	-9.4 to 4.0%	2.4 to 5.4%
Phenytoin	Calibration Standards	-2.0 to 5.0%	3.1 to 12.0%
5-pHPPH	QC Samples	-13.1 to -2.2%	3.7 to 14.2%
5-pHPPH	Calibration Standards	-2.5 to 4.0%	3.6 to 10.0%

Vigabatrin: K-97-0363-D; free phenytoin, phenytoin and 5-pHPPH: K-97-0467-D

(1) Accuracy, expressed as % recovery, relative to theory for vigabatrin or expressed as % error, relative to theory for all other analytes

(2) Precision, expressed as % coefficient of variation

Summary of method performance across sample analyses, batch-to-batch statistics, from urine bioanalytical data reports for protocol VGPR0260

Analyte	*Samples*	*Accuracy (1)*	*Precision (2)*
Phenytoin	QC Samples	-7.3 to 0.00%	7.9 to 8.8%
Phenytoin	Calibration Standards	-10 to 3.0%	2.7 to 11.1%
5pHPPH	QC Samples	-10.7 to -2.0%	4.9 to 13.5%
5pHPPH	Calibration Standards	-10 to 3.5%	1.6 to 7.8%
"Total" 5pHPPH	QC Samples	-12.0 to -6.5%	3.0 to 6.0%
"Total" 5pHPPH	Calibration Standards	-10 to 3.0%	2.9 to 8.9%

(1) Accuracy expressed as % error relative to theory

(2) Precision expressed as % coefficient of variation

The following table summarizes the total phenytoin plasma pharmacokinetic parameters and comparisons between phenytoin administered alone to steady-state, day 12, versus after 3 weeks of co-administration with vigabatrin, day 44.

	*Pairwise Comparisons**						
Parameter (units)	*Ratio 44/12 (%)*	*90% CI on Ratio*	*P-Value*	*Day*	*Mean (Range)*	*%CV*	*Adjusted Mean**
$AUC(0\text{-}12\ h)_{ss}$	87.19	(65.4,116.3)	0.406	12	114.75	29.05	110.32
(h•µg/mL)	-	-	-	44	110.46	68.94	96.18
$Cl_{po,ss}$	114.70	(86.0,153.0)	0.406	12	23.59	29.89	22.66
(mL/min)	-	-	-	44	30.44	46.24	25.99
$C_{max,ss}$	82.96	(67.6,101.9)	0.130	12	10.94 (6.12-15.50)	27.79	10.52
(µg/mL)	-	-	-	44	10.01 (4.87-25.60)	66.89	8.73
$C_{min,ss}$	77.55	(60.3, 99.8)	0.098	12	8.97 (5.06-13.00)	29.04	8.61
(µg/mL)	-	-	-	44	7.63 (3.01-18.50)	65.15	6.68
$T_{max,ss}$	109.72	(69.3,173.8)	0.720	12	3.41	86.72	2.45
(h)	-	-	-	44	3.70	65.03	2.69

12: day 12, phenytoin 150 mg Q12 h prior to vigabatrin coadministration
44: day 44, phenytoin 150 mg and vigabatrin 1.5 g Q12 h after 3 weeks of steady-state coadministration

* Log transformed results of the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% CI.

The average total phenytoin area under the curve, maximum concentrations, and minimum concentrations are decreased by approximately 17-23% with a corresponding increase in apparent oral clearance when phenytoin was coadministered with vigabatrin although the magnitude of the change was not statistically significant. These results are similar to that previously reported in epilepsy patients with an average decrease of approximately 15-20% in phenytoin concentrations.

There was a decrease in free phenytoin parameters of approximately 11-12% as shown in the following table.

	Pairwise comparisons*						
Parameter (unit)	Ratio 44/12 (%)	90% CI on Ratio	P-Value	Day	Mean	%CV	Adjusted Mean*
$AUC(0\text{-}12\ h)_{,ss}$	89.83	(72.4,111.4)	0.385	12	16.93	32.46	16.01
(h*ng/mL)	-	-	-	44	16.21	67.92	14.38
$Cl_{po,ss}$	111.32	(89.8,138.1)	0.385	12	167.42	44.10	156.22
(mL/min)	-	-	-	44	207.21	46.08	173.89
$C_{max,ss}$	89.59	(72.7,110.3)	0.359	12	1.50	31.82	1.43
(µg/mL)	-	-	-	44	1.42	64.91	1.28
$C_{min,ss}$	88.96	(70.3,112.5)	0.385	12	1.35	34.49	1.27
(µg/mL)	-	-	-	44	1.29	73.19	1.13
$T_{max,ss}$	1018.6	(154.2, 6730)	0.051	12	0.55	95.74	0.04
(h)	-	-	-	44	2.00	176.38	0.44
Ratio	-	-	-	12	0.15	26.94	-
	-	-	-	44	0.15	8.74	-

12: day 12, phenytoin 150 mg Q12 h prior to vigabatrin coadministration
44: day 44, phenytoin 150 mg and vigabatrin 1.5 g Q12 h after 3 weeks of steady-state coadministration

* Log transformed results of the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% CI.

There was a decrease in the 5pHPPH metabolite plasma parameters of approximately 20-25% as shown in the following table.

	Pairwise comparisons*						
Parameter (unit)	Ratio 44/12 (%)	90% CI	P-Value	Day	Mean	%CV	Adjusted Mean*
$AUC(0\text{-}12\ h)_{,ss}$	72.14	(47.8,108.8)	0.158	12	2.32	15.14	2.30
(h*µg/mL)	-	-	-	44	1.71	24.96	1.66
$C_{max,ss}$	80.59	(42.6,152.3)	0.483	12	0.22	15.73	0.22
(µg/mL)	-	-	-	44	0.19	37.55	0.18
$C_{min,ss}$	75.17	(58.3, 97.0)	0.078	12	0.19	18.73	0.19
(µg/mL)	-	-	-	44	0.14	15.56	0.14
$T_{max,ss}$	8.89	(0.1, 851.1)	0.300	12	4.13	84.20	2.63
(h)	-	-	-	44	1.25	100.66	0.23

12: day 12, phenytoin 150 mg Q12 h prior to vigabatrin coadministration
44: day 44, phenytoin 150 mg and vigabatrin 1.5 g Q12 h after 3 weeks of steady-state coadministration

* Log transformed results of the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% CI.

Urinary excretion showed trends toward an average decrease in urinary excretion of total phenytoin with renal clearance decreasing by 13%. The amount excreted in urine for total, conjugated or unconjugated 5pHPPH was unchanged on average, however, the renal clearance of total 5pHPPH was increased. There was no significant difference in phenytoin pharmacokinetics after 3 weeks as compared to 6 weeks of phenytoin and vigabatrin coadministration. individual changes in phenytoin pharmacokinetics demonstrated varying results that were not always reflected by the mean. Although the majority of subjects showed a decrease in total phenytoin maximum concentrations (5 subjects > 30%) during vigabatrin coadministration, two subjects had a percent increase in maximum concentration from baseline of 16 and 97%.

The pharmacokinetic parameters describing total phenytoin urine excretion are as follows.

	*Pairwise comparisons**						
Parameter (unit)	*Ratio 44/12 (%)*	*90% CI*	*P-value*	*Day*	*Mean*	*%CV*	*Adjusted mean**
A_e	55.94	(31.4, 99.5)	0.098	12	1407.33	69.70	1397.88
(µg)	-	-	-	44	1182.71	89.99	781.94
Renal clearance	86.81	(60.1,125.4)	0.499	12	0.22	68.76	0.18
(mL/min)	-	-	-	44	0.19	63.32	0.16
% of dose excreted	-	-	-	12	0.94	69.70	-
(%)	-	-	-	44	0.79	89.99	-

12: day 12, phenytoin 150 mg Q12 h prior to vigabatrin coadministration
44: day 44, phenytoin 150 mg and vigabatrin 1.5 g Q12 h after 3 weeks of steady-state coadministration

* Log transformed results of the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% CI.

The following summarizes the comparisons by day and descriptive statistics for the 5pHPPH metabolite in the urine. It should be noted that total 5pHPPH was detectable in the urine of the predose sample far 8 of the 15 subjects. These values are being investigated further by the bioanalytical site. The concentrations were very low and close to the limit of quantitation with amount excreted in urine ranging from 27 to 267 µg compared to 30888 to 121031 µg after phenytoin dosing.

Parameter units*	Pairwise comparisons: Ratio 44/12 (%)	90% CI	P-value	Day	Mean	%CV	Adjusted mean*
Amount of total 5pHPPH excreted in urine	105.00	(72.7,151.7)	0.815	12	82098.22	35.04	74528.91
µg	-	-	-	44	93006.24	30.79	78256.37
% dose excreted in urine for total (conjugated +	-	-	-	12	31.36	35.06	-
unconjugated) 5pHPPH %	-	-	-	44	35.50	30.81	-
Amount of unconjugated 5pHPPH excreted in urine	99.19	(68.3,144.1)	0.969	12	1143.79	56.45	1043.00
µg	-	-	-	44	1149.74	50.79	1034.59
% dose excreted in urine for unconjugated 5pHPPH	-	-	-	12	0.72	56.45	-
%	-	-	-	44	0.72	50.79	-
Amount of conjugated 5pHPPH excreted in urine	105.09	(72.7,151.9)	0.812	12	80954.43	35.00	73386.27
µg	-	-	-	44	91856.50	30.78	77124.61
% dose excreted in urine for conjugated 5pHPPH	-	-	-	12	30.65	35.00	-
%	-	-	-	44	34.77	30.78	-

12: day 12, phenytoin 150 mg Q12 h prior to vigabatrin coadministration
44: day 44, phenytoin 150 mg and vigabatrin 1.5 g Q12 h after 3 weeks of steady-state coadministration

* Log transformed results of the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% CI.

Plasma vigabatrin trough concentrations were not significantly affected by co-administration with phenytoin as shown in the following table.

Pair	Pairwise comparisons*: Ratio	90% CI	P-value	Treatment	Mean	%CV	Adjusted mean*
day 42-44/ day 21-23	90.35	(84.1, 97.1)	0.027	day 21-23	6.52	17.53	6.39
day 63-65/ day 21-23	87.85	(78.7, 98.1)	0.057	day 42-44	5.90	18.17	5.77
day 63-65/ day 42-44	97.24	(87.1,108.5)	0.659	day 63-65	5.48	23.98	5.61

day 21-23: average of days 21, 22, and 23, at end of vigabatrin titration and start of steady-state coadministration
day 42-44: average of days 42-44, after 3 weeks coadministration
day 63-65: average of days 63-65 after 6 weeks of coadministration

* Log transformed results of the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% CI.

Comments

- The 90% confidence interval showed that vigabatrin reduced total and free phenytoin concentration in general.

- 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.

2. Vigabatrin in-vitro induction study (Study # OVNC9014)

Title: In Vitro Assessment of the Induction Potential of Vigabatrin in Primary Human Hepatocytes.

Objectives: The aim of this in vitro study was to utilize primary cultures of human hepatocytes to evaluate the potential of vigabatrin to induce liver microsomal cytochrome P450 (CYP450) enzymes.

b(4)

Study design: Vigabatrin (50, 500, and 5000 µM; 6.5, 65, 650 µg/mL) and known CYP450 inducers, phenobarbital (PB) and rifampicin (RIF), were incubated in cultures of human hepatocytes from three separate donors for three consecutive days. In situ samples were collected and activities of CYP2B6 and CYP3A4 were determined using selective metabolite markers. Messenger RNA (mRNA) levels for CYP2B6, CYP2C9, CYP2C19 and CYP3A4 were also analyzed using quantitative RT-PCR (TaqMan®-based)

Results: Summaries of the CYP activities and mRNA levels after treatment with Vigabatrin are shown in the tables below. Increases in enzyme activity or mRNA levels = 40% of the respective positive control samples are considered an indication of demonstrable induction.

Table. Summary of CYP Activity as a Percent of Positive Control Induction after Treatment with Vigabatrin

Treatment	% of Positive Control Induction					
	2B6			3A4		
	Hu596	Hu598	Hu8025	Hu596	Hu598	Hu8025
Phenobarbital (1000 µM)	**100**	**100**	**100**	104	80.9	107
Rifampicin (10 µM)	35.1	57.8	18.7	**100**	**100**	**100**
Vigabatrin (50 µM)	0.35	-1.9	0.83	-4.3	-0.58	6.6
Vigabatrin (500 µM)	1.0	-1.9	-0.10	-0.47	0.78	-1.1
Vigabatrin (5000 µM)	1.2	-3.5	1.0	-2.5	-0.88	5.1

Numbers highlighted in **BOLD** denote the isoform-specific prototypical inducer.

Numbers highlighted in **BOLD** and *Italics* indicate ≥40% of positive control induction.

Table. Summary of mRNA Levels as a Percent of Positive Control Induction after Treatment with Vigabatrin

Treatment	% of Positive Control Induction											
	2B6			2C9			2C19			3A4		
	Hu596	Hu598	Hu8025	Hu596	Hu598	Hu8025	Hu596	Hu598	Hu8025	Hu596	Hu598	Hu8025
Phenobarbital (1000 µM)	**100**	**100**	**100**	142	84.0	107	196	27.0	104	124	61.3	91.3
Rifampicin (10 µM)	34.7	80.9	25.9	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
Vigabatrin (50 µM)	0.08	-3.0	2.2	3.8	2.0	37.2	7.2	-86.9	3.7	-2.3	0.44	9.3
Vigabatrin (500 µM)	0.18	-2.8	1.3	15.3	3.6	28.1	0.88	12.9	13.7	-1.4	0.21	2.5
Vigabatrin (5000 µM)	2.5	-3.6	9.6	***91.5***	4.1	***41.3***	***54.3***	33.3	-4.4	2.3	0.99	6.2

Numbers highlighted in **BOLD** denote the isoform-specific prototypical inducer.

Numbers highlighted in **BOLD** and *Italics* indicate ≥40% of positive control induction.

Vigabatrin was examined at 50, 500, and 5000 μM (6.5, 65, 650 μg/mL) concentrations which represent 0.1X, 1X, and 10X the steady-state Cmax of vigabatrin in patients after 1.5 g BID dosing (Cmax value of vigabatrin in these patients was ~ 62 - 75 μg/mL or 480 - 580 μM). This study indicates that there is low potential for drug-drug interactions with vigabatrin due to enzyme induction of CYP2B6 or CYP3A4 at the concentrations examined. While concentration-related increases in CYP2B6 enzyme activity and/or mRNA content were observed, the amount of induction was less than 40% of the adjusted positive control response. Therefore, these lower efficacy induction responses would not be predicted to have the potential for clinical significance at the concentrations examined. The specific activities for CYP2C9 and CYP2C19 were not examined in this study because these isoforms are not highly inducible and produce variable induction in vitro. However, the expression of mRNA for a specific CYP enzyme can be quantified using RT-PCR and provides a more sensitive probe to analyze induction of these CYPs. Induction of CYP2C9 mRNA expression by vigabatrin at 5000 μM (650 μg/mL; 10X the steady-state Cmax) was observed at levels greater than 40% of the adjusted positive control in two of the three human donors analyzed. Furthermore, when the highest concentration of vigabatrin (5000 μM (650 μg/mL); a concentration equal to 10X the steady-state Cmax was tested, induction of CYP2C19 mRNA expression was observed at levels greater than 40% of the adjusted positive control in one of three donors analyzed. The results from this mRNA expression analysis, in comparison to historical data which have shown a correlation between increased mRNA levels and induction of CYP450 activity, suggest that vigabatrin may have the potential for induction of CYP2C9 and/or CYP2C19 in vivo. However, mRNA expression of these isoforms was not induced at the clinically relevant Cmax concentration of vigabatrin and increases in mRNA expression could also be associated with other enzymatic pathways within the liver.

Comments:

1. This study showed that vigabatrin may have induction potential for CYP2C19 and CYP2C9.

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/s/

John Duan
7/30/2008 12:32:22 PM
BIOPHARMACEUTICS

Veneeta Tandon
7/30/2008 02:37:37 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
7/30/2008 05:59:30 PM
BIOPHARMACEUTICS
Signoff for phase 4 commitments

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA (Serial Number):	20427 (amendment)
Sponsor:	Ovation
Drug:	Vigabatrin (SABRIL)
Formulation:	Tablets and Sachet
Proposed Indication:	Complex Partial Seizures and Infantile Spasms
Material Submitted:	NDA Submission Plans
Correspondence Date:	8/15/05
Reviewer:	Sally Usdin Yasuda, MS, PharmD

Background:

Vigabatrin is an irreversible inhibitor of GABA transaminase (GABA-T) that is being developed for treatment of complex partial seizures and infantile spasms. The original NDA for SABRIL, sponsored by Aventis, received a non-approval letter in October 1998 due to concerns regarding visual field defects associated with vigabatrin therapy. Ovation Pharmaceuticals has the rights to the NDA and plans to re-submit NDA 20427 for complex partial seizures and a new NDA for infantile spasms.

Proposed Submission
Ovation intends to cross reference the Pharmacokinetic and Biopharmaceutics information under NDA 20-427 to support the new NDA.

NDA Amendment 20427 for SABRIL (vigabatrin tablets for refractory complex partial seizures in adults) will include a clinical pharmacology study evaluating the interaction between VGB and phenytoin, as well as an in vitro metabolism study of drug-drug interactions using human hepatocytes. The Sponsor does not plan to provide a summary of clinical pharmacology or biopharmaceutics overview as this information was submitted in the original NDA 20427 (4/29/94).

A new NDA for SABRIL will be submitted for infantile spasms. The following will be **included as "Reports of Biopharmaceutic Studies":**

- **71754-1-C-029 – "A Definitive Study Evaluation of the Bioequivalence of** Vigabatrin Administered as Uncoated Tablets, Film-coated Tablets and **Oral Solution".**
- **VIG/AUS/91/1 – "Vigabatrin Relative Bioavailability Powder (1g sachet) versus Tablet (2x500 mg)"**
- **71754/W/AUS/03 – "An Open Randomized Crossover Study of the** Bioavailability of Vigabatrin Tablets and Sachets in Healthy Male **Subjects"**

The following will be included as "Reports of Human Pharmacokinetic (PK) Studies":

- **Prt 097-332.5 – "Pharmacokinetics of the Enantiomers of VGB in Infants and Children".**

The Study Report for the BE Study (Protocol 71754-1-C-029) will be submitted to IND 17213 prior to December 2005 and will be submitted again as part of the CTD in December 2005. This protocol was reviewed by OCPB in the original NDA and will be cross-referenced to the original NDA.

CMC information will be submitted for both NDAs.

Questions from Sponsor

The following questions from the Sponsor were included in the present submission but are not addressed to Clinical Pharmacology.

1. If Ovation submits as proposed in our pre-NDA meeting a safety update in the amended CPS NDA, does this preclude Ovation from having to submit CTD Section 2.5.5 "Overview of Safety" and Section 2.7.4 "Summary of Clinical Safety"?
2. If Ovation submits an ISE and ISS for the new CTD for Infantile Spasms, does this preclude Ovation from having to submit Section 2.7.3 "Summary of Clinical Efficacy" and Section 2.7.4 "Summary of Clinical Safety"?
3. Is submission of a single batch production record for each drug product sufficient?
4. Ovation seeks confirmation that if a draft report of our ongoing juvenile rat toxicology study is submitted in December with the final pieces of the CTD and we submit a final report during the first three months of the CRTD review, the review clock will not be suspended upon submission of the final report.

Conclusions and Recommendations:

From a Clinical Pharmacology/Biopharmaceutics perspective, it would be preferable if the Sponsor would include executive summaries of the pivotal pharmacokinetic/biopharmaceutics studies in the new NDA as discussed with them at the Sponsor meeting of 12/1/04.

Sally Usdin Yasuda, MS, PharmD
Reviewer, Neurology Drug Products Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: Ramana Uppoor, PhD
Team Leader, Neurology Drug Products Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

cc: HFD-120 NDA 20427
CSO/C. Calder
/Biopharm/S. Yasuda
/TL Biopharm/R. Uppoor
HFD-860 /DD DPE1/M. Mehta, N.A.M. Rahman

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/s/

Sally Yasuda
9/15/2005 07:49:26 AM
BIOPHARMACEUTICS

Ramana S. Uppoor
9/15/2005 09:29:45 AM
BIOPHARMACEUTICS

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OCT 8 1998

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NDA 20-427
Vigabatrin (SABRIL™)
500 mg Tablets

Hoechst Marion Roussel Inc.,
10236 Marion Park Drive
Kansas City, MO 64134-0627

Submission Dates:
December 23, 1997
April 24, 1998
May 21, 1998
June 4, 1998

Reviewer: Vijay K. Tammara, Ph.D.

Type of Submission: Response to Approvable Letter

Vigabatrin is a selective and irreversible inhibitor of (-aminobutyric acid transaminase (GABA-T), which is the enzyme responsible for the metabolism of the central nervous system (CNS) inhibitory neurotransmitter (-aminobutyric acid (GABA). Vigabatrin is indicated as add-on therapy for the treatment of complex partial seizures. The mechanism of action is dose-dependent inhibition of GABA-T and consequent increased levels of GABA in the CNS. The starting dose is 1g daily (one 500 mg tablet bid), which may be increased or decreased in 500 mg increments at weekly intervals, depending on clinical response and tolerability. The recommended maintenance dose is 3 g daily (three 500 mg tablets bid); dose can be increased to a maximum of 6 g in patients.

This submission reported the phenytoin-vigabatrin interaction study results (protocol 0260; Attachment 1). The study was conducted in 15 healthy male subjects as a single-center, open-label, single treatment design comparing phenytoin levels prior to and after coadministration with vigabatrin. Following a loading dose of 200 mg phenytoin every 12 hours for one day, subjects were administered 150 mg phenytoin every 12 hours to steady-state (days 2-12). Vigabatrin was then added on the evening of day 12 starting with doses of 500 mg every 12 hours and increased up to 1 g every 12 hours (5 days at each dose). Vigabatrin was then increased to 1.5 mg every 12 hours and was coadministered for 6 weeks (subjects 0001-0005) or 3 weeks (subjects 0006-0015) with phenytoin 150 mg every 12 hours. At the end of the coadministration period, vigabatrin was decreased down to 500 mg every 12 hours over 2 days then discontinued. Phenytoin was titrated down to 100 mg every 12 hours for 3 doses and then discontinued.

Upon review of the results, this reviewer observed that the total phenytoin concentrations decreased by about 15-20%. Further, it was observed that the mean total phenytoin area under the curve, maximum concentration at steady state, and minimum concentration at steady state are decreased by approximately 13-23% with a corresponding increase in apparent oral clearance when phenytoin was coadministered with vigabatrin although the magnitude of the change was not statistically significant. However, a check of individual data demonstrated that although the majority of subjects showed a decrease in total phenytoin concentrations (> 30%) during vigabatrin coadministration, two subjects had shown increase in total phenytoin concentrations by about 16 and 97% from baseline. These results are similar to that previously reported in epilepsy patients with an average decrease of approximately 14-40% in phenytoin concentrations (original NDA review dated March 3, 1995; Attachment 2). While the decrease in mean free fraction of phenytoin parameters is approximately 11-12% and that of 5pHPPH metabolite plasma parameters is

approximately 20-25%.

Urinary excretion showed trends toward an average decrease in urinary excretion of total phenytoin with renal clearance decreasing by 13%. The amount excreted in urine for total, conjugated or unconjugated 5pHPPH was unchanged on an average.

There was no significant difference in phenytoin pharmacokinetics after 3 weeks as compared to 6 weeks of phenytoin and vigabatrin coadministration (Attachment 3).

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

The sponsor also provided changes in labeling for review. However, the Agency is likely to issue a "Non-Approvable" letter as per project Manger Ms. Melina Malandrucco, hence labeling changes are not being reviewed at this time.

COMMENT TO THE MEDICAL REVIEWER:

Based on the above information, the reviewer recommends the following comment to be placed in the labeling under Pharmacokinetics: Drug Interactions section:

"Total phenytoin concentrations decreased by about 15-30% with a corresponding increase in apparent oral clearance when phenytoin was coadministered with vigabatrin. However, two subjects have shown an increase in phenytoin levels by about 16 and 97%, respectively. Therefore, caution should be exercised when coadministering phenytoin with vigabatrin".

RECOMMENDATION:

This submission (NDA 20-427) has been reviewed by the office of Clinical Pharmacology and Biopharmaceutics and has been found to be acceptable. Please, forward this recommendation and the Comment to the Medical Reviewer.

Tammara 10/8/98

Vijay K. Tammara, Ph. D.
Division of Pharmaceutical Evaluation I

RD/FT Initialed by C. Sahajwalla, Ph. D. 10/8/98

CC: NDA 20,427 (Suppl.), HFD-120, HFD-860 (Tammara, Sahajwalla, Mehta), CDR (for Drug Files).

ATTACHMENT 1

STUDY SYNOPSIS

Protocol VGPR0260 [071754PR0260]

Study VGST1849 [071754ST1849]

Title
THE STEADY-STATE PHARMACOKINETIC INTERACTION BETWEEN VIGABATRIN AND PHENYTOIN IN HEALTHY MALE SUBJECTS

Investigator(s), study site(s)

[redacted] b(4)

Phase I

Indication
not applicable

Objectives

Primary objectives
To characterize the pharmacokinetics of phenytoin following three weeks of coadministration of phenytoin and vigabatrin.

To monitor the trough plasma concentrations of vigabatrin during coadministration of phenytoin and vigabatrin.

Secondary objective
To investigate the time dependence of the interaction by comparing data after 3 weeks of phenytoin/vigabatrin coadministration with data after 6 weeks of coadministration using a subset of the total data.

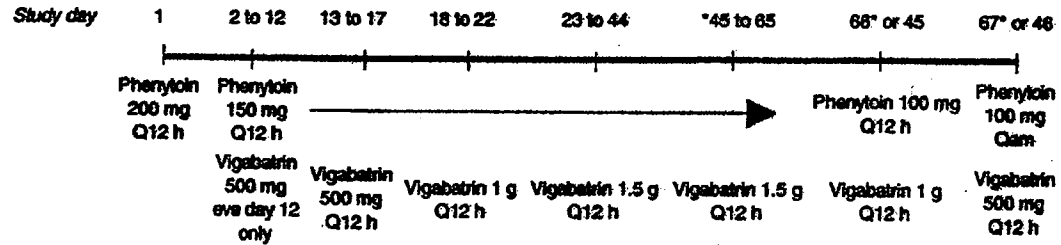
Design

The trial was conducted as a single-center, open-label, single treatment design comparing phenytoin pharmacokinetics prior to and after coadministration with vigabatrin. The following summarizes the phenytoin and vigabatrin dosing schedules.

Study day(s)	*Phenytoin dosing schedule*	*Vigabatrin dosing schedule*
day 1	phenytoin 200 mg Q12 h	none
day 2 to morning of day 12	phenytoin 150 mg Q12 h	none
evening of day 12	phenytoin 150 mg	vigabatrin 500 mg
days 13 to 17	phenytoin 150 mg Q12 h	vigabatrin 500 mg Q12 h
days 18 to 22	phenytoin 150 mg Q12 h	vigabatrin 1 g Q12 h
day 23 to day 65* or 44**	phenytoin 150 mg Q12 h	vigabatrin 1.5 g Q12 h
day 66* or 45**	phenytoin 100 mg Q12 h	vigabatrin 1 g Q12 h
day 67* or 46**	phenytoin 100 mg QAM	vigabatrin 500 mg Q12 h

*(subjects 0001-0005)
**(subjects 0006-0015)

A schematic of this dosing regimen is as follows.



*subjects 0001-0005 only

Population

The study was conducted in 15 healthy male subjects.

Treatments

Drug code:	M071754	RU796
INN:	vigabatrin	phenytoin
Formulation:	500 mg film-coated tablet	50 mg chewable tablet, Dilantin®
Manufacturer:	Hoechst Marion Roussel	Parke-Davis
Lot No.	R55991	01236V
Date of manufacture:	13 Apr 95	-
Expiry date:	30 Apr 98	Feb 98

Pharmacokinetic data

Plasma concentrations of phenytoin, the 5pHPPH metabolite of phenytoin, and free phenytoin were measured serially for 12 hours after the morning dose on days 12, 44, and 65 (subjects 0001-0005 only) and trough concentrations were measured approximately weekly. Vigabatrin plasma trough concentrations were measured on days 21-23, 42-44, and 63-65. Concentrations of phenytoin, total

5pHPPH, and unconjugated 5pHPPH were measured in urine over the 12 hour dosing interval on days 12, 44 and 65.

Safety data
Adverse events, electrocardiograms, clinical laboratories and physical examinations were monitored for safety evaluations.

Study duration and dates
The first set of 5 subjects enrolled in the trial on 7 Aug 96 and completed the trial on 14 Oct 96. The remaining 10 subjects enrolled in the trial on 30 Nov 96 and completed the trial on 16 Jan 97.

Statistical procedures
Comparisons between earlier and later day plasma and urine parameters were evaluated with an analysis of the natural log transformed data. An analysis of variance, with terms for subject and day, was done for each parameter from which 90% confidence intervals for the ratio of days were obtained.

Trough concentrations were evaluated with an analysis of the natural log transformed data. An analysis of variance, with terms for subject and day, was done within each week from which 90% confidence intervals for the ratio of days were obtained.

Interim analysis
Previous data regarding the potential drug-drug interaction between phenytoin and vigabatrin suggested that the interaction may take as long as 6 weeks to come to equilibrium. There was a desire to investigate the interaction for a period shorter than 6 weeks in order to reduce the exposure of these drugs in normal healthy subjects. The study was designed so that the interaction after 3 weeks of coadministration could be compared to the interaction after 6 weeks of coadministration. Criteria were established in an analysis plan prior to availability of the data to determine if the study could be shortened.

Five of the planned 15 subjects were enrolled and 4 of the 5 subjects completed the trial. An interim analysis comparing 3 weeks versus 6 weeks of coadministration was conducted with data from the 4 completed subjects. The prespecified critieria for shortening the study were met and a decision was made to amend the study to end after 3 weeks of coadministration. The protocol amendment of 19 Dec 96 addressed this change.

Results - Study subjects and conduct
Fifteen subjects were enrolled in the trial. Of those 15 subjects, all 15 were exposed to at least one dose of phenytoin and 13 were exposed to at least one dose of vigabatrin. Four subjects prematurely discontinued from the study (2 for personal reasons, 1 discontinued by investigator due to elevated baseline phenytoin concentrations and 1 due to an adverse event) and 1 subject had a dose adjustment due to elevated baseline phenytoin concentrations. The remaining 10 subjects successfully completed the trial.

Results - Pharmacokinetics
Mean phenytoin pharmacokinetic parameters were not statistically significantly altered by coadministration of phenytoin and vigabatrin. There was a mean trend toward decrease in total phenytoin plasma area under the curve, maximum concentration, and trough concentration of approximately 17-23%, decrease in free phenytoin parameters of approximately 11-12%, and decrease in the 5pHPPH metabolite plasma parameters of approximately 20-25%. Urinary excretion

showed trends toward an average decrease in urinary excretion of total phenytoin with renal clearance decreasing by 13%. The amount excreted in urine for total, conjugated or unconjugated 5pHPPH was unchanged on average, however, the renal clearance of total 5pHPPH was increased. There was no significant difference in phenytoin pharmacokinetics after 3 weeks as compared to 6 weeks of phenytoin and vigabatrin coadministration.

Individual changes in phenytoin pharmacokinetics demonstrated varying results that were not always reflected by the mean. Although the majority of subjects showed a decrease in total phenytoin maximum concentrations (5 subjects > 30%) during vigabatrin coadministration, two subjects had a percent increase in maximum concentration from baseline of 16 and 97%.

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

Results - Safety

Phenytoin and vigabatrin were well tolerated in this trial. Minor but expected increase in the hepatic enzyme GGT and decrease in the hepatic enzyme ALT were detected.

Conclusions

- Mean phenytoin pharmacokinetic parameters were not significantly altered by coadministration of phenytoin and vigabatrin. There was no significant difference in phenytoin pharmacokinetics after 3 weeks as compared to 6 weeks of phenytoin and vigabatrin coadministration.
- 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 for approximately 3 weeks 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.
- Phenytoin and vigabatrin were well tolerated when taken in combination. Changes in clinical laboratories are similar to that previously reported when either phenytoin or vigabatrin are taken alone.

7.2.1.3 Phenytoin metabolite, 5pHPPH

The plasma concentration data for the phenytoin 5pHPPH is somewhat limited in that plasma concentrations profiles above the limit of quantitation were only available for 4 of the subjects (subjects VGST1849-0001, 0005, 0011, and 0014). In 3 of the 4 subjects, the plasma 5pHPPH concentrations decreased and in the remaining subject the concentrations were essentially unchanged. *Figure 4, page 90* shows the mean of the 4 subjects with quantifiable concentrations for concentration over time for the 5pHPPH metabolite in plasma and *Table 4, page 11* contains the data which support the figure.

Table 13, page 21 contains the results of the trough analysis which showed steady-state for phenytoin dosed alone and phenytoin when coadministered with vigabatrin had been reached by day 12 and again by day 44, respectively.

The following is a summary of the descriptive statistics and statistical comparisons for the phenytoin metabolite, 5pHPPH, when phenytoin was administered alone, day 12, compared to phenytoin and vigabatrin coadministered for 3 weeks, day 44.

	*Pairwise comparisons**						
Parameter (unit)	*Ratio 44/12 (%)*	*90% CI*	*P-Value*	*Day*	*Mean*	*%CV*	*Adjusted Mean**
$AUC(0\text{-}12\ h)_{,ss}$	72.14	(47.8,108.8)	0.158	12	2.32	15.14	2.30
(h*µg/mL)	-	-	-	44	1.71	24.96	1.66
$C_{max,ss}$	80.59	(42.6,152.3)	0.483	12	0.22	15.73	0.22
(µg/mL)	-	-	-	44	0.19	37.55	0.18
$C_{min,ss}$	75.17	(58.3, 97.0)	0.078	12	0.19	18.73	0.19
(µg/mL)	-	-	-	44	0.14	15.56	0.14
$T_{max,ss}$	8.89	(0.1, 851.1)	0.300	12	4.13	84.20	2.63
(h)	-	-	-	44	1.25	100.66	0.23

12: day 12, phenytoin 150 mg Q12 h prior to vigabatrin coadministration
44: day 44, phenytoin 150 mg and vigabatrin 1.5 g Q12 h after 3 weeks of steady-state coadministration

* Log transformed results of the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% CI.

Supporting data:

A decrease in the plasma 5pHPPH metabolite concentrations was shown by decrease in the area under the curve, maximum concentration and minimum concentration of approximately 20-28%. This percent decrease is of a slightly greater magnitude than the average decrease in plasma total phenytoin. The time to maximum concentration varied greatly with coefficients of variation of 84 and 101%. Consequently, the statistical comparison of this parameter does not give any useful information when comparing phenytoin alone to phenytoin with vigabatrin. The limitations of the

5pHPPH data (i.e. only 4 subjects) should be kept in mind when attempting to interpret the data. Individual pharmacokinetic parameters can be found in *Appendix C.2.2.13 Plasma individual pharmacokinetic parameters for 5pHPPH phenytoin metabolite, page 815.*

7.2.1.4 Vigabatrin

As was discussed in the introduction of this report, previous studies showed no change in vigabatrin plasma concentrations when phenytoin and vigabatrin were coadministered. The data from this study are consistent with previous reports. *Figure 5, page 29* shows the mean and individual trough vigabatrin plasma concentrations by day. *Table 6, page 14* and *Appendix C.2.2.4 Listings of plasma concentration over time for vigabatrin, page 754* contain the data which support the figure, however, concentrations on days 21-23 were dose adjusted from 1.0 g to 1.5 g for presentation in the figure.

Analysis of the trough concentrations indicated that vigabatrin was at steady-state by day 23 at the end of the titration of the vigabatrin dose. The trough concentrations were also at steady-state when comparing days 42 to 44, after 3 weeks of coadministration, and when comparing days 63 to 65, after 6 weeks of coadministration (subjects 0001-0005 only). *Table 13, page 21* contains the results of these analyses.

The trough analysis indicated that it would be acceptable to pool the data within days 21 to 23, days 42 to 44, and days 63 to 65. The trough concentrations were pooled to give an average trough vigabatrin concentration at the start of the coadministration (at the end of titration), after 3 weeks of coadministration and after 6 weeks of coadministration. The following is the descriptive statistics and statistical comparisons between these pooled trough concentrations. The concentrations for day 21-23 were dose adjusted to 1.5 g.

*Pairwise comparisons**

Pair	*Ratio*	*90% CI*	*P-value*	*Treatment*	*Mean*	*%CV*	*Adjusted mean**
day 42-44/ day 21-23	90.35	(84.1, 97.1)	0.027	day 21-23	6.52	17.53	6.39
day 63-65/ day 21-23	87.85	(78.7, 98.1)	0.057	day 42-44	5.90	18.17	5.77
day 63-65/ day 42-44	97.24	(87.1,108.5)	0.659	day 63-65	5.48	23.98	5.61

day 21-23: average of days 21, 22, and 23, at end of vigabatrin titration and start of steady-state coadministration
day 42-44: average of days 42-44, after 3 weeks coadministration
day 63-65: average of days 63-65 after 6 weeks of coadministration
* Log transformed results of the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% CI.

Supporting data:

There was no statistically significant change in trough vigabatrin concentrations after 3 weeks of vigabatrin and phenytoin coadministration. An insignificant decrease of 3% was seen after 6 weeks of coadministration compared to 3 weeks of coadministration.

7.2.2 Urine pharmacokinetics

7.2.2.1 Total phenytoin

The pharmacokinetic parameters describing total phenytoin urine excretion are as follows.

	*Pairwise comparisons**						
Parameter (unit)	*Ratio 44/12 (%)*	*90% CI*	*P-value*	*Day*	*Mean*	*%CV*	*Adjusted mean**
A_e	55.94	(31.4, 99.5)	0.098	12	1407.33	69.70	1397.88
(µg)	-	-	-	44	1182.71	89.99	781.94
Renal clearance	86.81	(60.1,125.4)	0.499	12	0.22	68.76	0.18
(mL/min)	-	-	-	44	0.19	63.32	0.16
% of dose excreted	-	-	-	12	0.94	69.70	-
(%)	-	-	-	44	0.79	89.99	-

12: day 12, phenytoin 150 mg Q12 h prior to vigabatrin coadministration
44: day 44, phenytoin 150 mg and vigabatrin 1.5 g Q12 h after 3 weeks of steady-state coadministration

* Log transformed results of the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% CI.

Supporting data:

The amount of total phenytoin excreted in the urine decreased by 44% when phenytoin was coadministered with vigabatrin, but the decrease was not statistically significant. The amount and % of the phenytoin dose excreted in urine were both more variable when phenytoin was given with vigabatrin such that the coefficient of variation increased from approximately 70% to approximately 90%. The renal clearance of phenytoin decreased by 13%, an insignificant effect. The amount of phenytoin excreted decreased in all but 2 individuals, subjects 0005 and 0012. *Table 14, page 22* shows the change from day 44 compared to day 12 for individuals. Individual pharmacokinetic parameters can be found in *Appendix C.2.2.8 Urine pharmacokinetic parameters for total phenytoin, page 801.*

In comparing the urine excretion back to the plasma phenytoin parameters, there is a anomalous response in that the plasma phenytoin concentrations decrease with a decrease in renal elimination of phenytoin. It should be kept in mind that phenytoin is extensively metabolized and that the renal elimination of parent phenytoin is typically less than 5% of the dose. In this case, less than 1% of the dose was excreted as parent phenytoin.

7.2.2.2 Total, conjugated, and unconjugated phenytoin metabolite, 5pHPPH, in urine

The following summarizes the by day comparisons and descriptive statistics for the 5pHPPH metabolite in the urine. It should be noted that total 5pHPPH was detectable in the urine of the predose sample for 8 of the 15 subjects. These values are being investigated further by the bioanalytical site. The concentrations were very low and close to the limit of quantitation with

amount excreted in urine ranging from 27 to 267 µg compared to 30888 to 121031 µg after phenytoin dosing.

Parameter units*	Pairwise comparisons: Ratio 44/12 (%)	90% CI	P-value	Day	Mean	%CV	Adjusted mean*
Amount of total 5pHPPH excreted in urine	105.00	(72.7,151.7)	0.815	12	82098.22	35.04	74528.91
µg	-	-	-	44	93006.24	30.79	78256.37
% dose excreted in urine for total (conjugated +	-	-	-	12	31.36	35.06	-
Unconjugated) 5pHPPH %	-	-	-	44	35.50	30.81	-
Amount of unconjugated 5pHPPH excreted in urine	99.19	(68.3,144.1)	0.969	12	1143.79	56.45	1043.00
µg	-	-	-	44	1149.74	50.79	1034.59
% dose excreted in urine for unconjugated 5pHPPH	-	-	-	12	0.72	56.45	-
%	-	-	-	44	0.72	50.79	-
Amount of conjugated 5pHPPH excreted in urine	105.09	(72.7,151.9)	0.812	12	80954.43	35.00	73386.27
µg	-	-	-	44	91856.50	30.78	77124.61
% dose excreted in urine for conjugated 5pHPPH	-	-	-	12	30.65	35.00	-
%	-	-	-	44	34.77	30.78	-

12: day 12, phenytoin 150 mg Q12 h prior to vigabatrin coadministration
44: day 44, phenytoin 150 mg and vigabatrin 1.5 g Q12 h after 3 weeks of steady-state coadministration

* Log transformed results of the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% CI.

Supporting data:

There were no statistically significant changes in the mean amount excreted or % of dose excreted in the urine for 5pHPPH either total, conjugated or unconjugated. The 5pHPPH metabolite accounts for approximately 30% of the phenytoin dose and almost all of the 5pHPPH is excreted in urine as the conjugated form with less than 1% excreted unconjugated.

The individual elimination is mixed with 5pHPPH (total, conjugated or unconjugated) urine excretion both increasing and decreasing when vigabatrin is added to therapy compared to phenytoin administered alone. Again, subject 0012 is of note with significantly greater amounts of 5pHPPH in urine when the drugs are coadministered compared to phenytoin administered alone. The renal

clearance of total 5pHPPH could be examined in the 4 subjects for which there were quantifiable concentrations of 5pHPPH in the plasma.