# Clinical Pharmacology Review

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| NDA #: | 20-427 S011/22-006 S012 |
| NDA TYPE: | Priority |
| PRODUCT NAME: | Sabril® (Vigabatrin) |
| INDICATION: | Refractory complex partial seizures (rCPS) in Pediatrics aged 10 years and above |
| DOSAGE FORM: | Tablet / Sachet |
| ROUTE of ADMINISTRATION: | Oral |
| SUBMISSION DATE: | 04/26/2013 |
| SPONSOR: | Lundbeck Inc. |
| REVIEWER: | |
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# 1 REGULATORY BACKGROUND

Vigabatrin (Sabril®; NDA 20427) is approved as 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 vision loss. Sabril is not indicated as a first line agent for CPS.

Sabril® (NDA 22006) is approved as monotherapy for pediatric patients from 1 month to 2 years of age with infantile spasms (IS) for whom the potential benefits outweigh the potential risk of vision loss.

A deferred study under the Pediatric Research Equity Act (PREA) was required to evaluate the safety and efficacy of fixed doses of Sabril® versus placebo as adjunctive therapy in pediatric patients 10 years of age and above with refractory CPS (hereafter referred to as rCPS). A waiver for the lower age ranges was granted due to the difficulty in monitoring visual toxicity in children less than 10 years of age. Accordingly, a pediatric written request (hereafter PWR) was issued in 2011. In the PWR, the sponsor was requested to conduct a randomized efficacy study in subjects from 10 to 16 years of age with rCPS, comparing the effect of 2 doses (20 mg/kg/day and 60 mg/kg/day) to placebo. A long-term safety study in 50 patients for 6 months and 20 patients for 1 year was also requested. As a postmarketing requirement (PMR) from NDA 22006, a PK study in patients with infantile spasm in patients 1-5 months of age was also requested.

Two Type C meetings were held with the Agency on 10 November 2011 and 8 June 2012.

During these meetings, Lundbeck discussed available data in the intended population from studies conducted by the previous sponsor (Hoechst Marion Roussel [HMR]) which were terminated early. Available data include 3 controlled trials, including dose-response study 118 and 2 flexible-dose trials (Studies 192 and 221), as well as 2 open-label extension studies (Study 201 as an extension of Studies 118 and 221, and Study 294 as an extension of Study 192). Two European Medicines Agency Article 12 safety studies (Studies 4020 and R003) and 1 phase 3b/4 open-label study (Study 0098) also included pediatric patients with rCPS in addition to adult patients.

During the Type C meetings referenced above, the Agency agreed with Lundbeck's proposal to use data from the controlled studies in pharmacometric bridging-type analyses to address the PREA study listed in the PWR and support dosing recommendations in the vigabatrin labeling. The sponsor's modeling report was submitted and reviewed by pharmacometric reviewer (IND 17213, Appendix) and the sponsor's proposal was accepted by the Agency and PWR was amended in 2013.

In this supplementary NDA submission, the sponsor submitted two modeling reports: (1) revised dose-response modeling report which contains exposure-response analysis as well as revised dose-response analysis. (2) population PK analysis report. The proposed dosing regimen for pediatrics 10-16 years old with refractory complex partial seizures is shown in Table 1.

Table 1. Proposed Dosing Regimen for Sabril® in Pediatrics 10-16 years old With Refractory Complex Partial Seizures.

| Body Weight [kg] | Total Daily* Starting Dose [mg/day] | Total Daily* Maintenance Dose† [mg/day] |
|---|---|---|
| 25-60†† | 500 | 2000 |

*Administered in two divided doses.
†Maintenance dose is based on 3000 mg/day adult-equivalent dose
††Patients weighing more than 60 kg should be dosed according to adult recommendations

## 2 SUMMARY OF FINDINGS

### 2.1 Key Review Questions

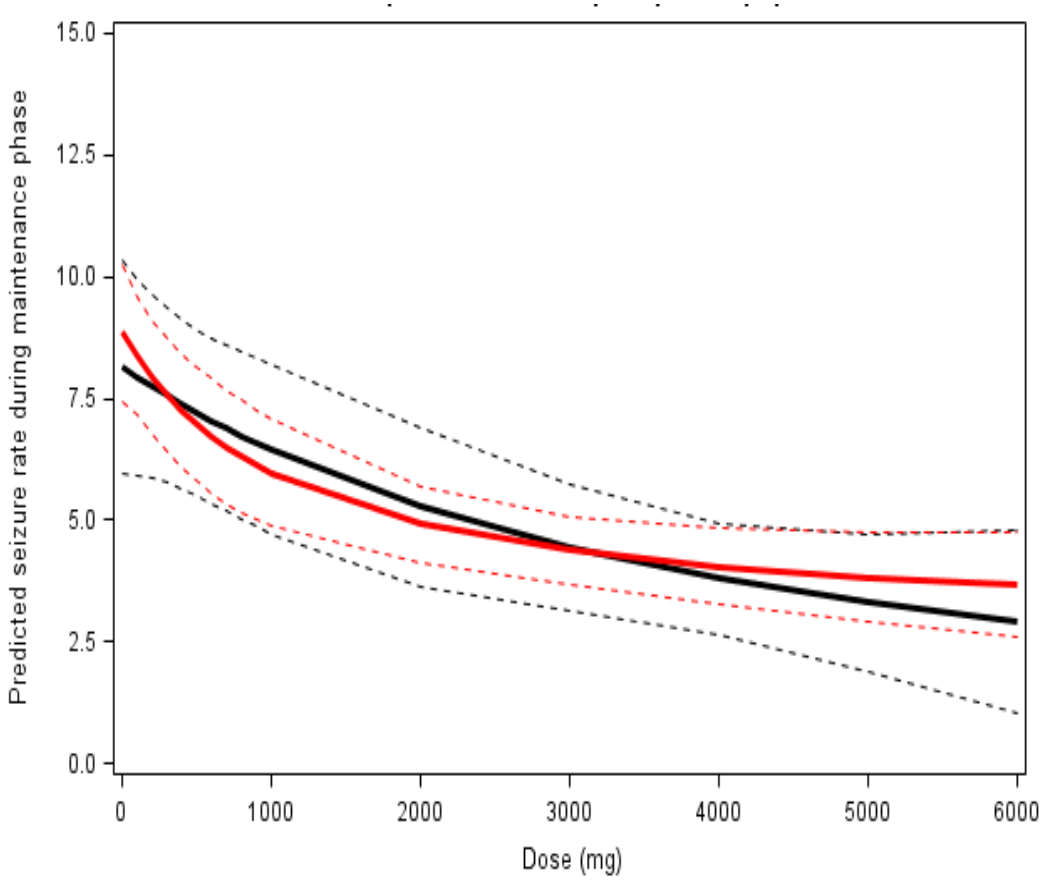
The purpose of this review is to address the following key questions.

#### 2.1.1 Is the dose/exposure-response relationship similar between adults and pediatric patients with refractory complex partial seizure?

Yes, the dose/exposure-response relationship is similar between adults and pediatrics. Data from 3 studies in pediatric (071754PRO118, 071754PRO192, and 071754PRO221) and two studies in adult (71754-3-C-024 and 71754-3-C-025) patients with uncontrolled complex partial seizures were used in the dose/exposure-response analysis.

Figure 1 shows the relationship between normalized dose and seizure rate during maintanence phase.

Figure 1. The model-predicted relationship between normalized dose and seizure rate during the maintenance phase. The red line is for adults and the black line is for pediatrics. The dot lines represent 95 % prediction interval.




The dose-response analysis performed by the sponsor showed similar dose-response relationship between adults and pediatrics, which was confirmed by the reviewer's independent assessment (see Appendix). The reviewer conducted exposure-response analysis to confirm the previous conclusion. Table 20 and Table 21 show the parameter estimates from the reviewer's log-linear model. Consistent with previously conducted dose-response analysis, age was not found to be significant covariate in the pooled analysis. Furthermore the parameter estimates (e.g., slope of dose-response relationship) are shown to be similar between pediatrics and adults.

### 2.1.2 Is the sponsor's proposed dosing regimen for pediatrics with refractory complex partial seizure acceptable?

Yes, the sponsor's proposed dosing regimen is acceptable.

The sponsor generated pediatric dose recommendations using the sponsor's final dose-response model. Since the dose-response model was determined to be similar in adult and pediatric patients, the predictions were driven entirely by the weight-based correction of normalized dose targeting two approved adult doses, 1000 mg and 3000 mg using following equation:

$$D_{NORM\,ij} = DOSE_{ij} \cdot \left(\frac{WT_i}{60}\right)^{-0.608}$$

The sponsor's final dosing recommendation is presented in Table 2.

**Table 2. Sponsor's Final Dosing Recommendation in Pediatrics.**

| Adult Dose | Body Weight (kg) | Proposed Dose (mg) | Drug Effect (% Reduction in Seizure Rate) | Drug Effect in 70 kg Adult (% Reduction in Seizure Rate) | Percent Change in Drug Effect Relative to Adults | Ratio of Drug Effect Relative to Drug Effect in 70 kg Adult |
|---|---|---|---|---|---|---|
| 1000 | 25.0 | 500 | 20.46 | 21.6 | -5.18 | 0.95 |
| 1000 | 42.5 | 500 | 15.65 | 21.6 | -27.47 | 0.73 |
| 1000 | 60.0 | 500 | 13.05 | 21.6 | -39.54 | 0.60 |
| 1000 | 70.0 | 1000 | 21.58 | 21.6 | 0.00 | 1.00 |
| 3000 | 25.0 | 2000 | 47.71 | 43.8 | 8.89 | 1.09 |
| 3000 | 42.5 | 2000 | 41.77 | 43.8 | -4.67 | 0.95 |
| 3000 | 60.0 | 2000 | 37.32 | 43.8 | -14.83 | 0.85 |
| 3000 | 70.0 | 3000 | 43.81 | 43.8 | 0.00 | 1.00 |

The reviewer performed independent assessment to evaluate if the sponsor's proposed dosing recommendation was supported based on exposure level in pediatrics.

Figure 2 presents the distribution of average vigabatrin concentration (Cavg) which was predicted from the sponsor's final population PK model at the doses of 1000 mg and 3000 mg in adult studies only, which shows dose-proportionality.

There were limited number of patients given 3000 mg in pediatric population. Therefore, the exposure level at the dose of 3000 mg in pediatric patients was compared to that in adult patients. As shown in Figure 3, Cavg appears to be higher in pediatrics than that in adults, the ratio of median Cavg between adolescents (10-16 years old patients) and adults ( > 16years old patients) was 0.58. This ratio was applied to match to the approved adult doses, 1000 mg and 3000 mg and the result is shown in Table 3. The reviewer's calculation using the exposure ratio between adults and pediatrics was similar to the sponsor's proposed doses.

**Figure 2. Distribution of Average Concentration (Cavg) by Dose in Adult Studies.**

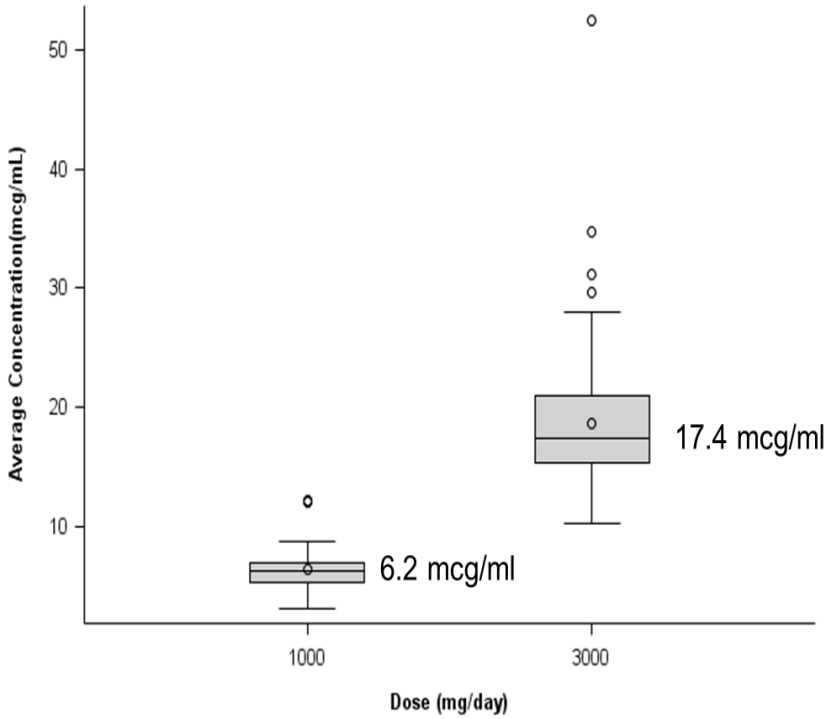



**Figure 3. Distribution of Average Concentration (Cavg) by Age Group at Dose of 3000 mg.**

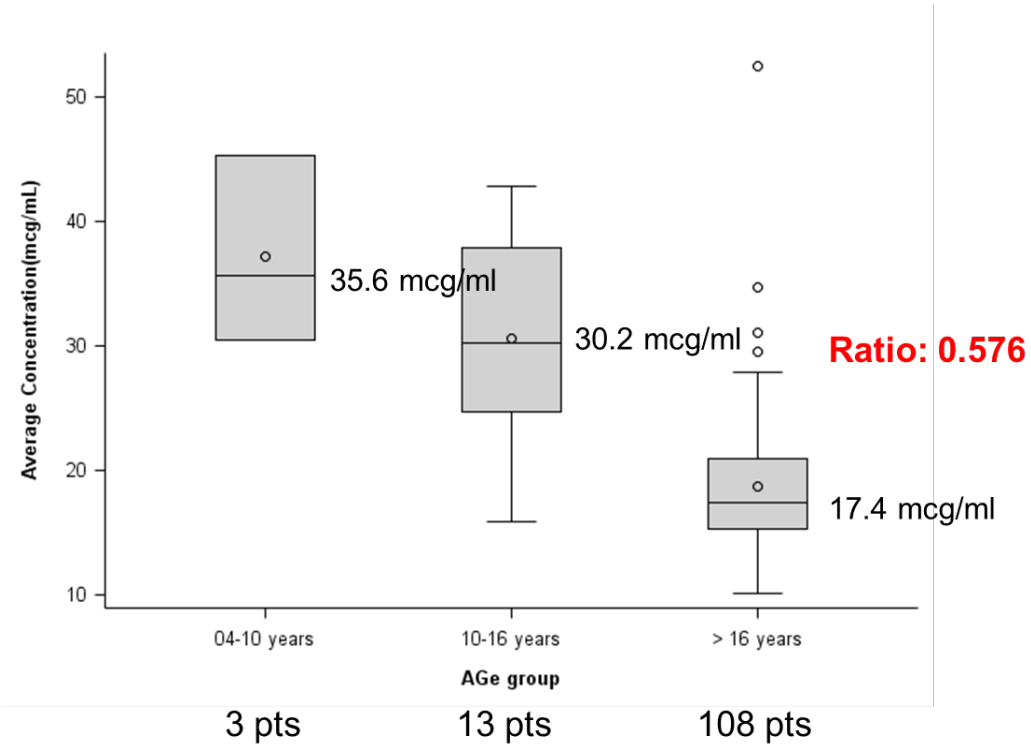
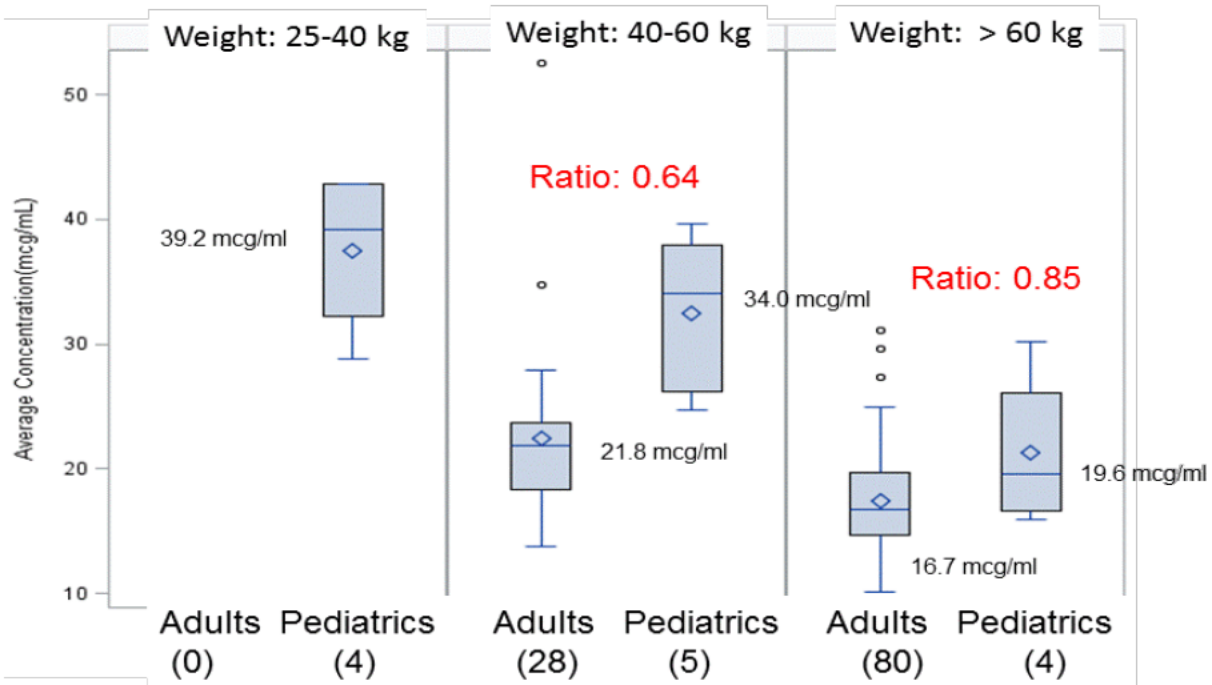


**Table 3. Comparison of Dose Between the Sponsor's Proposal and the Reviewer's Calculation Based on the Exposure Ratio.**

| | | Adult Approved Dose | |
|---|---|---|---|
| | | 1000 mg | 3000 mg |
| Cavg | Adults (>16 years) | 6.2 mcg/ml | 17.4 mcg/ml |
| | Pediatrics (10-16 years) | 10.8 mcg/ml | 30.2 mcg/ml |
| Predicted Dose for Peds | Based on Exposure Ratio | 576 mg (1000×0.576) | 1728 mg (3000×0.576) |
| | Sponsor's Proposal | 500 mg | 2000 mg |

To examine further whether the sponsor's proposal for the same dose for pediatrics as adults for those who weigh greater than 60 kg, the weight was broken down by 25-40 kg, 40-60 kg and > 60 kg. Although the sample size is limited, the ratio of Cavg for patients weighing greater than 60 kg is closer to 1 (Figure 4), which confirms the sponsor's proposal.

**Figure 4. Distribution of Average Concentration (Cavg) by Weight Category at Dose of 3000 mg.**

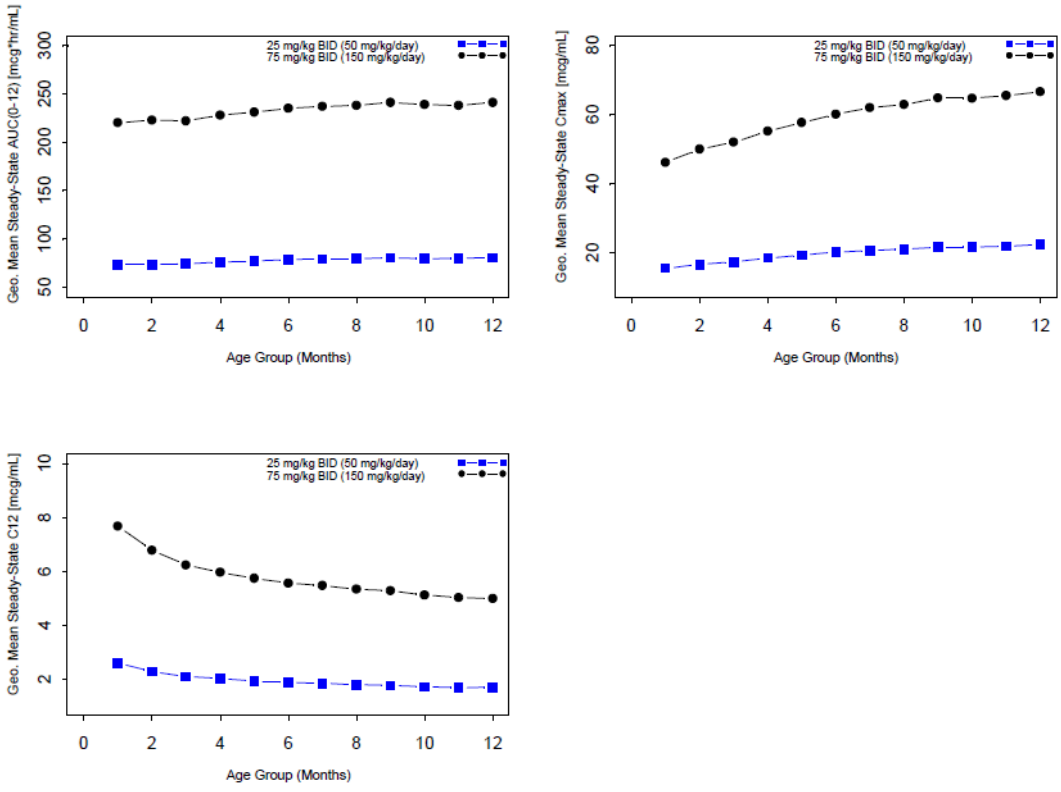


### 2.1.3 Is the sponsor's characterization of pharmacokinetics of Sabril® in patients 1-5 month age acceptable?

Yes. The sponsor's characterization of pharmacokinetics of Sabril® in patients 1-5 month age is acceptable. For details refer to Sponsor's DOSE-RESPONSE Analysis

Exposure predictions ($AUC_{0-12}$, $C_{max}$, and $C_{12}$) for pediatric patients less than or equal to one year of age are displayed in Figure 5.

**Figure 5. Steady-State AUC $_{0-12}$, C $_{max}$ and C $_{12}$ for Pediatric Patients 1 to 12 Months of Age**



### 2.1.4 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-marketed formulations for refractory complex partial seizures (rCPS) in pediatrics will be both tablet and powder formulations, which are the current commercial formulations approved for rCPS and infantile spasm indications, respectively. Liquid solutions, xylitol/benzoate or saccharin/paraben liquids, were used in the three pediatric rCPS efficacy trials (118, 192 and 221). Data were provided in this submission to bridge the liquid formulations with the tablet and powder for oral solution formulations as illustrated in the following figure. The study design and results of these studies were summarized in the table below.

**Figure 6. Bioequivalence bridging between vigabatrin saccharin/paraben or xylitol/benzoate liquid formulations used in Phase 3 pediatric clinical trial and commercial tablet and powder for oral solution dosage forms**

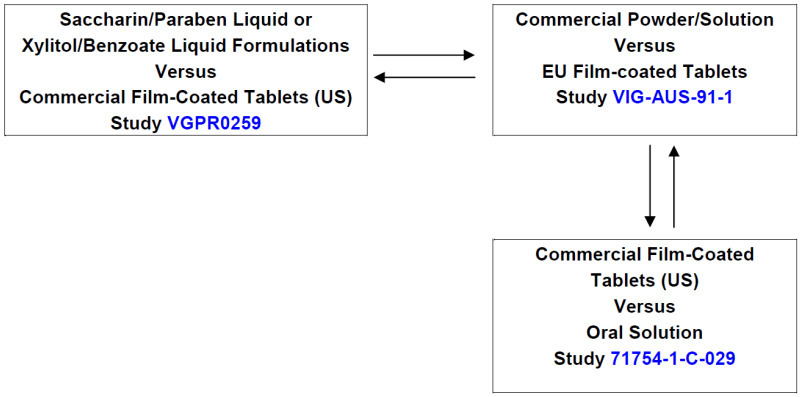


**Table 4. Summary (mean and %CV) of Bioavailability Studies**

| Study | # Subjects M/F | Vigabatrin Administration p.o. | Cmax (µg/mL) | Tmax (hr) (median, range) | AUC(0-t) (µg/mL*hr) | AUC(0-inf) (µg/mL*hr) |
|---|---|---|---|---|---|---|
| 71754-1-C-029 | 12 M | 500 mg uncoated tablets, US | 36.3 (14.3%) | 0.75 (0.50-1.00) | 137 (9.8%) | 141 (9.9%) |
| | | 500 mg film-coated tablets, US | 35.2 (13.9%) | 0.75 (0.33-1.25) | 143 (16.0%) | 147 (16.1%) |
| | | 100 mg/mL solution-US | 39.6 (18.7%) | 0.50 (0.33-0.75) | 139 (13.0%) | 142 (12.7%) |
| Study Design: Randomized open-label single-dose 3-period crossover in healthy volunteers.<br>Objectives: To establish the relative bioavailability of uncoated and film-coated vigabatrin tablets compared to an oral solution and the bioequivalence of vigabatrin uncoated and film-coated tablets in normal, healthy, male volunteers. | | | | | | |
| VGPR0259 | 16 M | 2 x 500 mg vigabatrin chewable tablets | 40.2 (18.1%) | 0.63 (0.50-1.00) | 154 (13.5%) | 160 (13.5%) |
| | | 10 mL of a 100 mg/mL liquid saccharin/paraben formulation | 38.7 (20.0%) | 0.75 (0.50-1.00) | 150 (12.8%) | 157 (13.1%) |
| | | 10 mL of a 100 mg/mL liquid xylitol/benzoate formulation | 40.2 (22.6%) | 0.50 (0.50-0.75) | 145 (16.6%) | 151 (16.7%) |
| | | 2 x 500 mg vigabatrin US commercial, film-coated tablets | 37.7 (24.1%) | 1.00 (0.75-1.50 ) | 151 (13.9%) | 157 (13.7%) |
| Study Design: Randomized open-label, single-dose complete 4-period crossover<br>Objectives: To determine bioequivalence of vigabatrin 500 mg chewable tablet and a liquid saccharin/paraben formulation to a liquid xylitol/benzoate formulation; to characterize bioavailability of the 3 treatments relative to the US commercial film-coated 500 mg tablet. | | | | | | |
| VIG/AUS/91/1 | 15 M | Ref: 2 x 500 mg vigabatrin tablets | 28.8 (13.3%) | 0.78 (0.72-1.03) | 118 (24.8%) | 133 (27.1%) |
| | | Test: 1 g vigabatrin powder | 33.3 (23%) | 0.73 (0.25-1.07) | 128 (26.0%) | 143 (28.9%) |
| Study Design: Randomized, single-dose crossover.<br>Objective: To demonstrate bioavailability of 100 mg vigabatrin powder in solution relative to two 500 mg tablets. | | | | | | |

1. Comparison between the commercial tablet formulation and the liquid formulations

The commercial tablet formulation was demonstrated to be bioequivalent to the liquid formulations, as shown by the following table. Study VGPR0259 has been reviewed before by Dr. John Duan in the Clinical Pharmacology review for NDA 22-006, which was submitted on December 28, 2007. Please refer to his review for more details.

**Table 5. Study VGPR0259: Bioequivalence (Dose = 1000 mg) Assessment of Vigabatrin Chewable Tablets, Saccharin/Paraben Liquid or Xylitol/Benzoate Liquid Formulation relative to U.S. Film-Coated Tablets**

| Parameter | Reference | Test | Ratio[%Ref] | 90% CI, Lower limit | 90% CI, Upper limit |
|---|---|---|---|---|---|
| Cmax | D | A | 108.00 | 99.61 | 117.09 |
| | D | B | 103.66 | 95.61 | 112.39 |
| | D | C | 107.44 | 99.01 | 116.58 |
| AUC(0-t) | D | A | 101.58 | 97.38 | 105.96 |
| | D | B | 99.57 | 95.45 | 103.86 |
| | D | C | 95.93 | 91.93 | 100.10 |
| AUC(0-inf) | D | A | 101.46 | 97.24 | 105.87 |
| | D | B | 99.43 | 95.29 | 103.75 |
| | D | C | 95.88 | 91.85 | 100.09 |

Treatment A: 2 x 500 mg vigabatrin chewable tablets
Treatment B: 10 ml of a 100 mg/ml liquid saccharin/paraben formulation
Treatment C: 10 ml of a 100 mg/ml liquid xylitol/benzoate formulation
Treatment D: 2 x 500 mg vigabatrin US commercial, film-coated tablets

2. Comparison between the powder for oral solution formulation and the tablet formulation

A study (VIG/AUS/91/1) was performed showing bioequivalence between powder and E.U. film-coated tablet formulation. The study has been reviewed before by Dr. John Duan in his review for NDA 22-006 submitted on December 28, 2007.

**Table 6. Study VIG/AUS/91/1 Bioequivalence (Dose = 1000 mg) Assessment of Vigabatrin Powder for Oral Solution (Treatment B) Relative to Vigabatrin Administered as 2 x 500 mg EU Film-Coated Tablets (Treatment A)**

| Parameter | Reference | Test | Ratio[%Ref] | 90% CI, Lower limit | 90% CI, Upper limit |
|---|---|---|---|---|---|
| **Cmax** | B | A | 87.22 | 80.64 | 94.33 |
| **AUC(0-t)** | B | A | 92.24 | 83.16 | 102.30 |
| **AUC(0-inf)** | B | A | 92.98 | 82.44 | 104.87 |

Treatment A: 2 x 500 mg vigabatrin EU film-coated tablets; Treatment B: 1 packet 1000 mg of vigabatrin powder dissolved in 200 mL of water

The E.U. film-coated tablet is comparable to the U.S. film-coated tablet based on the similarities in the compositions of the formulations. The components of the core tablet for the two formulations are identical. The difference lies in the film coating, which is considered as an insignificant, non-functional difference.

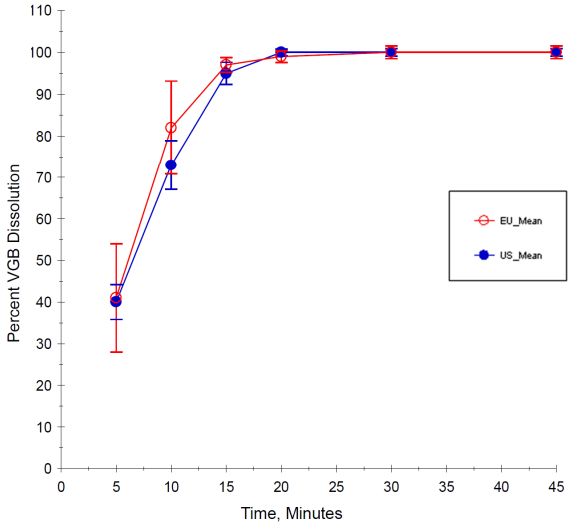
**Table 7. Quantitative Composition of Vigabatrin Film-Coated Tablets (Left panel: E.U. version; Right panel: current U.S. Formulation)**

| Component | Theoretical (mg/tablet) |
|---|---|
| Vigabatrin | 500.00 |
| Microcrystalline Cellulose | (b) (4) |
| Sodium Starch Glycolate | |
| Povidone K30 | |
| Magnesium Stearate | |
| (b) (4) | |
| **Total Core Tablet Weight** | |
| (b) (4) | |
| **Total Coated Tablet Weight** | |

| Component | Theoretical (mg/tablet) |
|---|---|
| Vigabatrin | 500.00 |
| Microcrystalline Cellulose | (b) (4) |
| Sodium Starch Glycolate | |
| Povidone K30 | |
| Magnesium Stearate | |
| (b) (4) | |
| **Total Core Tablet Weight** | |
| (b) (4) | |
| **Total Coated Tablet Weight** | |

The similarity between the E.U. film-coated tablet and the U.S. film-coated tablet is also demonstrated by the *in vitro* dissolution profiles. Thus, the data obtained with the E.U. film-coated tablets can be applied to the U.S. film-coated tablets.

**Figure 7. Summary of Dissolution Comparison Study Results for Sabril Tablets (500 mg) Lot No. 5370 (EU Tablets) and Lot No. PD097A-001 (US Tablets)**




3. Comparison between the powder for oral solution formulation and the liquid formulations

There was no BE study conducted to directly compare the powder dosage form to liquid forms. A cross-study comparison based on the two studies described above suggested that the powder/sachet for oral solution formulation has comparable bioavailability to the liquid formulations.

As shown in Table 5, the geometric mean ratios (GMR) of Cmax for the liquid formulation versus U.S. film-coated tablet formulation were 103.66% (90% confidence interval (CI): 95.61% to 112.39%) and 107.44% (90% CI: 99.01% to 116.58%), respectively, for saccharin/paraben formulation and xylitol/benzoate formulation. The corresponding values for powder formulation were similar, with a GMR of 115% (90% CI: 106% to 124%), using the E.U. film-coated tablet formulation as the reference (refer to Dr. John Duan's review for NDA 22-006).

The similarity was also observed for AUC of vigabatrin. Based on Study VGPR0259, the GMR values of AUCt were 99.57% (95.45%, 103.86%) and 95.93% (91.93%, 100.10%), respectively, for liquid saccharin/paraben formulation and liquid xylitol/benzoate formulation relative to the tablet formulation (Table 5). From Study VIG/AUS/91/1, the GMR of AUCt was 106.75% (97.26%, 117.16%) for powder form using tablet formulation as the reference (refer to Dr. John Duan's review for NDA 22-006).

The median and range of Tmax were also similar across different formulations (film-coated tablets, liquid formulations, and powder for oral solution), as shown in Table 4.

4. Permeability and Solubility of Vigabartrin

Vigabatrin has high permeability and is expected to have high solubility although it is not officially being approved as a Biopharmaceutical Classification System (BCS) class I drug. Thus, the minor difference among different formulations has less concern.

The sponsor stated that vigabatrin can be described as a BCS Class 1 drug, however, the sponsor did not submit complete data to support the claim and they did not pursue a formal BCS designation for vigabatrin in this submission. Per the labeling of Sabril®, 95% of total radioactivity (administered orally) was recovered in the urine over 72 hours with the parent drug representing about 80% of this. The results suggest that vigabatrin is very likely to be a compound with high permeability. Vigabatrin seems also having good aqueous solubility as indicated by the following table (extracted from the Clinical Pharmacology and Biopharmaceutical review for NDA 20-427 available at Drus@FDA). The vigabatrin tablet and powder for oral solution formulations are available with 500-mg strength, which is readily soluble in water considerably less than 250 mL. Since the solubility of vigabatrin under pH of 1.0 could not be found, a definitive judgment can not be made at this moment about whether vigabatrin is a BCS class 1 drug. However, considering its chemical structure, molecular weight (129 Da) and pKa (zwitterion; pka 4.0, carboxyl acid group; pka 9.7, amine group), vigabatrin is very likely to also have good solubility under low pH.

**Table E–1. Effects of pH Change on Physical/Chemical Properties of Vigabatrin**

| *Physical/Chemical Parameter* | *Lower pH (4.1–4.5)* | *Higher pH (8.0–8.4)* |
|---|---|---|
| Percent present as the neutral zwitterion | >70% | ≅100% |
| Log–partition coefficient (n–octanol/water) | –2.14 | –1.96 |
| Solubility in water (mg/mL) | 495 | 335 |

The claim that vigabatrin may be a BCS Class 1 drug is also supported by several BA/BE studies (Study VGPR0259, VIG/AUS/91/1 and 71754-1-C-029) which showed bioequivalence among different formulations of vigabatrin (film-coated tablets, uncoated tablet, chewable tablet, liquids, oral solution, powder for oral solution) (Figure 6). Study 71754-1-C-029 was reviewed previously by Dr. Vijay Tammara and the conclusion about BE was considered acceptable, as described by Dr. John Duan in his review for NDA 22-006.

5. Summary

The current available data are sufficient to demonstrate comparable bioavailability between the liquid formulations used in pediatric CPS efficacy trials and current commercial powder and tablet formulations which will also be marketed for pediatric CPS patients once the submission is approved.

### 2.1.5 Is the drug and/or the major metabolite a substrate, inhibitor or inducer of CYP enzymes on an in vitro basis?

When NDA 20-427 was approved, there was a Phase IV commitment: 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. The applicant conducted an *in vitro* study (OVNC-9066) to evaluate the

potential of vigabatrin as an inducer of CYP1A2 and CYP3A4/5 using fresh and cryopreserved primary cultures of human hepatocytes. The results suggested that Vigabatrin did not induce CYP1A2 or CYP3A4/5. This is in alignment with the current Sabril® labeling which states that vigabatrin induces CYP2C9, but does not induce other hepatic cytochrome P450 enzyme systems.

**Study XT093059 (OVNC-9066):** In vitro evaluation of Vigabatrin as an inducer of CYP1A2 and CYP3A4/5 in five fresh and one cryopreserved primary cultures of human hepatocytes [Study period: September 28, 2009 to April 30, 2010]

Objective: to investigate the induction effects of vigabatrin on the expression of CYP1A2 and 3A4/5.
Methods: Preparations of freshly cultured human hepatocytes from three separate livers were treated once daily for 72 hrs with dimethyl sulfoxide (DMSO, 0.1% v/v, vehicle control), one of three concentrations of vigabatrin (1, 10 or 100 µM; 129.16, 1291.6 or 12916 ng/mL) or known CYP inducers, omeprazole (100 µM) or rifampin (10 µM). Two additional preparations of freshly cultured human hepatocytes from two separate livers and one additional preparation of cryopreserved cultured human hepatocytes from a separate liver were treated once daily for 72 hrs with DMSO (0.1% v/v), one of four concentrations of vigabatrin (1000, 2500, 5000 or 10000 µM), omeprazole (100 µM) or rifampin (10 µM).

After treatment, the cells of the first three individual human hepatocyte preparations were harvested to isolate microsomes for the analysis of phenacetin O-dealkylation (marker for CYP1A2) and testosterone 6β-hydroxylation (marker for CYP3A4/5) by LC-MS/MS.

| Enzyme | Substrate | Substrate concentration (µM) | Final protein concentration (µg/mL) [a] | Incubation time (min) |
|---|---|---|---|---|
| CYP1A2 | Phenacetin | 80 | 40 | 30 |
| CYP3A4/5 | Testosterone | 250 | 40 | 10 |

a: Incubation volume = 200 µL

After treatment, the cells of the three additional human hepatocyte preparations were incubated with the appropriate marker substrates for the analysis of phenacetin O-dealkylation and testosterone 6β-hydroxylation by LC-MS/MS.

| Enzyme | Substrate | Substrate concentration (µM) | Incubation time (min) |
|---|---|---|---|
| CYP1A2 | Phenacetin | 100 | 30 |
| CYP3A4/5 | Testosterone | 250 | 30 |

a: Incubation volume = 200 µL

Fold increases were determined by dividing the enzymatic rate for each treatment group by that of the vehicle control.

Additional hepatocytes from the same treatment groups were harvested to isolate RNA, which was analyzed by quantitative reverse transcription-polymerase chain reaction (qRT-PCR) to measure mRNA levels. The relative quantity of the target cDNA compared

with that of the control cDNA (GAPDH) was determined by the ΔΔCt method. The level of mRNA expression relative to the positive control was calculated as follows:

$$\%\ \text{positive control} = \frac{[(\text{fold change in test item treated sample}) - 1]}{[(\text{fold change in positive control}) - 1]} \times 100$$

Results: Treatment of cultured human hepatocytes with up to 10000 µM (1291.6 µg/mL) vigabatrin caused little or no change on CYP1A2 and CYP3A4/5 activity and mRNA levels (less than 2-fold increase, on average). In contrast, the positive controls, omeprazole and rifampicin, caused significant increases in mRNA and activities of CYP1A2 and CYP3A4/5, respectively. The mean Cmax,ss of vigabatrin is approximately 107 to 196 µg/mL.

**Table 8. The effects of treating cultured human hepatocytes with 1, 10 or 100 µM Vigabatrin or positive controls on microsomal CYP enzyme activity (mean ± SD of three hepatocytes)**

| Treatment | Concentration | Fold increase [a] | |
|---|---|---|---|
| | | Phenacetin *O*-dealkylation (CYP1A2) | Testosterone 6β-hydroxylation (CYP3A4/5) |
| Dimethyl sulfoxide | 0.1% (v/v) | 1.00 ± 0.47 | 1.00 ± 0.84 |
| Vigabatrin | 1 µM | 1.04 ± 0.09 | 0.970 ± 0.023 |
| Vigabatrin | 10 µM | 0.892 (n=2) | 0.873 (n=2) |
| Vigabatrin | 100 µM | 0.943 ± 0.066 | 1.02 ± 0.10 |
| Omeprazole | 100 µM | **60.9 ± 16.1** | 3.87 ± 3.16 |
| Rifampin | 10 µM | 1.92 ± 0.21 | **12.4 ± 11.6** |

**Table 9. The effects of treating cultured human hepatocytes with 1000, 2500, 5000 or 10000 µM Vigabatrin or positive controls on *in situ* CYP enzyme activity (mean ± SD of three hepatocytes)**

| Treatment | Concentration | Fold increase [a] | |
|---|---|---|---|
| | | Phenacetin *O*-dealkylation (CYP1A2) | Testosterone 6β-hydroxylation (CYP3A4/5) |
| Dimethyl sulfoxide | 0.1% (v/v) | 1.00 ± 1.08 | 1.00 ± 0.28 |
| Vigabatrin | 1000 µM | 0.997 ± 0.027 | 0.976 ± 0.142 |
| Vigabatrin | 2500 µM | 0.874 ± 0.133 | 0.967 ± 0.137 |
| Vigabatrin | 5000 µM | 0.882 ± 0.038 | 0.946 ± 0.157 |
| Vigabatrin | 10000 µM | 0.781 ± 0.176 | 0.958 ± 0.164 |
| Omeprazole | 100 µM | **53.4 ± 45.4** | 1.56 ± 0.54 |
| Rifampin | 10 µM | 1.36 ± 0.82 | **3.28 ± 0.55** |

**Table 10. The effects of treating cultured human hepatocytes with 1, 10, 100, 1000, 2500, 5000 or 10000 µM Vigabatrin or positive controls on CYP mRNA levels (mean ± SD of three hepatocytes)**

| Treatment | Concentration | Fold increase [a] | |
|---|---|---|---|
| | | CYP1A2 | CYP3A4 |
| Dimethyl sulfoxide | 0.1% (v/v) | 1.00 ± 0.00 | 1.00 ± 0.00 |
| Vigabatrin | 1 µM | 0.952 ± 0.309 | 0.887 ± 0.350 |
| Vigabatrin | 10 µM | 0.875 (n=2) | 1.23 (n=2) |
| Vigabatrin | 100 µM | 0.763 ± 0.298 | 1.01 ± 0.21 |
| Omeprazole | 100 µM | **198 ± 103** | 4.60 ± 2.60 |
| Rifampin | 10 µM | 0.951 ± 0.174 | **22.0 ± 20.8** |

| Treatment | Concentration | Fold increase [a] | |
|---|---|---|---|
| | | CYP1A2 | CYP3A4 |
| Dimethyl sulfoxide | 0.1% (v/v) | 1.00 ± 0.00 | 1.00 ± 0.00 |
| Vigabatrin | 1000 µM | 1.12 ± 0.18 | 1.17 ± 0.18 |
| Vigabatrin | 2500 µM | 0.977 ± 0.323 | 1.11 ± 0.21 |
| Vigabatrin | 5000 µM | 0.959 ± 0.361 | 1.09 ± 0.43 |
| Vigabatrin | 10000 µM | 0.981 ± 0.361 | 1.15 ± 0.46 |
| Omeprazole | 100 µM | **118 ± 66** | ND |
| Rifampin | 10 µM | ND | **9.73 ± 4.57** |

Conclusion: *In vitro* study showed that vigabatrin did not induce CYP1A2 or CYP3A4/5 at its clinical relevant concentrations. Therefore, there is no concern on the clinical drug interactions with CYP1A2 and CYP3A4 substrates. No labeling update is needed as such information is already in the current Sabril® package Insert, which states that vigabatrin induces CYP2C9 but does not induce other hepatic cytochrome P450 enzyme systems.

## 2.2 Recommendations

Office of Clinical Pharmacology has reviewed the submission (NDA 20427-S11, 22006 S12) and found it acceptable. Appropriate changes to the label have been proposed.

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## 3 SPONSOR'S DOSE-RESPONSE ANALYSIS

***Population PK analyses (study-1533a.pdf)***

**Objectives:**

- Develop a population PK model to characterize the vigabatrin concentration-time profile in adults and children with complex partial seizures and children with infantile spasms
- Investigate the effects of selected covariates on pertinent PK parameters to derive a final predictive PK model
- Generate individual exposure predictions to support additional pharmacokinetic-pharmacodynamic (PK-PD) analyses.

**Data:**

Data from seven clinical trials were pooled for the analyses. Three studies (studies 71754-2-C-018, 71754-3-C-024, 71754-3-C-025) were conducted in adults with complex partial seizures, three studies (71754PRO118, 71754PRO192, 71754PRO221) were conducted in children with complex partial seizures, and one study (097-332.5) was conducted in children with infantile spasms.

**Pharmacokinetic Sample Collection:**

The actual elapsed time since the first and last dose of vigabatrin was expected to be available for PK samples collected in studies 18, 24, 25, and 97. For studies 118, 192, and 221 the actual time in which the PK sample was collected as well as the elapsed time since the most recent dose of vigabatrin were not available. For studies 118 and 221, it was inferred from the protocol, based on descriptions of study procedures and dose administration instructions, that trough vigabatrin PK samples were collected. For study 192, the protocol specifically stated that PK samples were to be collected prior to administration of study medication (i.e. trough). Details regarding the collection of PK samples are provided Table 11.

**Table 11. Vigabatrin Pharmacokinetic Sampling Schedules**

| Study | PK Sampling Times |
|---|---|
| 18 | Prior to each dose on Days 1-4 and 0.167, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after the dose on Day 4 |
| 24 | Prior to first dose of the day for each visit in Segments 2 and 3 |
| 25 | Prior to first dose of the day for each visit in Segments 2 and 3 |
| 118 | Prior to first dose of the day[a] for Baseline, Visit 7 (Week 6), and Final Visit (Week 14) |
| 192 | Prior to first dose of the day for Baseline, Visit 4 (Week 4), Visit 7 (Week 10), and Visit 8 (Week 17) |
| 221 | Prior to first dose of the day[a] for Baseline, Visit 4 (Week 4), Visit 7 (Week 10), and Final Visit (Week 17) |
| 97 | Pre-dose, 0.5, 1, 2, 3, 6, 9, 12, 24, 25, 48, 49, 72, 73, 96, 97, 120, and 121 hours after the first-dose of vigabatrin |

[a] This information was inferred from the study protocol but was not specifically stated

## Population Pharmacokinetic Analysis Methodology:

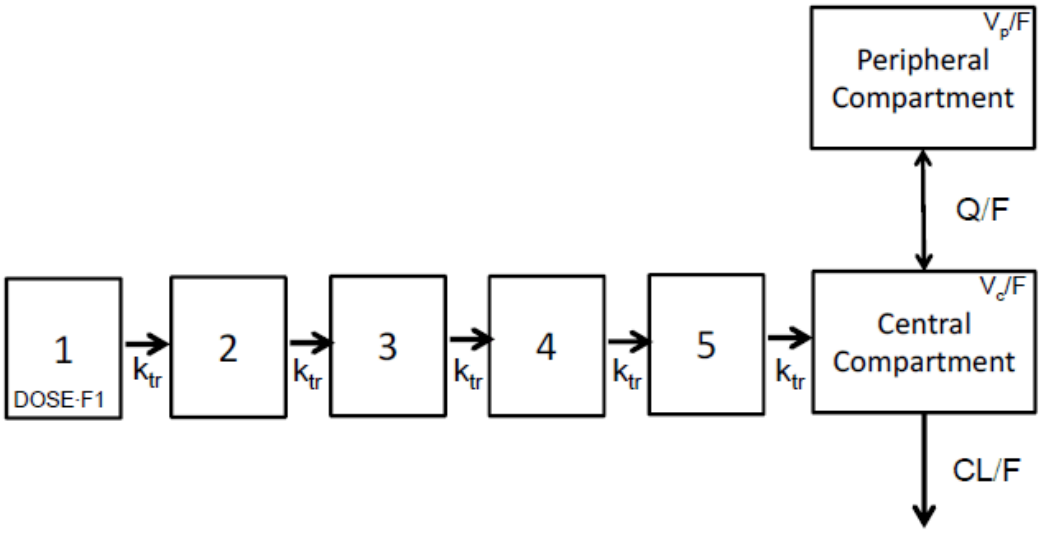
Nonlinear mixed effects modeling methodology was implemented in this analysis using the computer program NONMEM® (version 7.2). The first-order conditional estimation method was used to fit the vigabatrin concentration-time data. Covariates examined included age, body weight, sex, and creatinine clearance. Standard goodness-of-fit plots and predictive checks were used to determine if the model could adequately characterize the vigabatrin PK data in adults and children with complex partial seizures and children with infantile spasms. Table 12 summarizes the brief statistics of covariates included in the sponsor's population PK analysis.

**Table 12. Summary Statistics of Patient Covariates included in population PK analyses**

| Covariate | Statistic | Study 18 | Study 24 | Study 25 | Study 97 | Study 118 | Study 192 | Study 221 | Total |
|---|---|---|---|---|---|---|---|---|---|
| Age (yr) | N | 12 | 92 | 126 | 12 | 53 | 27 | 27 | 349 |
| | Mean (SD) | 34.6(9.97) | 34.3(8.99) | 34.4(9.41) | 4.86(4.88) | 10.6(4.1) | 11.2(3.37) | 11.6(2.98) | 26.2(13.9) |
| | Median | 33.5 | 34 | 33 | 3.2 | 11 | 12 | 12 | 28 |
| | Min-Max | 19-47 | 18-60 | 18-63 | 0.617-14.2 | 3-16 | 5-16 | 5-16 | 0.617-63 |
| Body Weight (kg) | N | 12 | 92 | 126 | 12 | 53 | 27 | 27 | 349 |
| | Mean (SD) | 74.4(14.3) | 75.8(20.2) | 74.6(18.2) | 19.2(16.1) | 45.6(23.2) | 59.5(26) | 51.9(23.7) | 65.6(25) |
| | Median | 77.3 | 72.3 | 71.8 | 13.4 | 44.5 | 54.1 | 47.6 | 65.3 |
| | Min-Max | 53.5-93.2 | 42.2-138 | 43.5-132 | 5.4-55 | 12.7-110 | 21.9-116 | 15-112 | 5.4-138 |
| Creatinine Clearance[a] (mL/min) | N | 12 | 92 | 126 | 5 | 53 | 27 | 27 | 342 |
| | Mean (SD) | 108(20) | 119(38.9) | 115(34.5) | 35.9(24.7) | 97.1(48.6) | 135(59.5) | 116(52.7) | 113(43.3) |
| | Median | 108 | 110 | 106 | 28.6 | 89.9 | 116 | 110 | 106 |
| | Min-Max | 70.2-131 | 57.6-239 | 52.2-263 | 19.7-79.2 | 29.1-277 | 54.5-283 | 34.8-240 | 19.7-283 |
| Sex | No. Male (%) | 7 (58.3) | 37 (40.2) | 65 (51.6) | 9 (75.0) | 30 (56.6) | 11 (40.7) | 17 (63.0) | 176 (50.4) |
| | No. Female (%) | 5 (41.7) | 55 (59.8) | 61 (48.4) | 3 (25.0) | 23 (43.4) | 16 (59.3) | 10 (37.0) | 173 (49.6) |
| Race | No. White (%) | 12 (100.00) | 83 (90.22) | 120 (95.24) | M | 50 (94.34) | 26 (96.30) | 25 (92.59) | 316 (90.54) |
| | No. Black (%) | 0 (0.00) | 6 (6.52) | 4 (3.17) | M | 1 (1.89) | 1 (3.70) | 2 (7.41) | 14 (4.01) |
| | No. Asian (%) | 0 (0.00) | 3 (3.26) | 2 (1.59) | M | 2 (3.77) | 0 (0.00) | 0 (0.00) | 7 (2.00) |
| | No. Missing (%) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 12 (100) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 12 (3.44) |

**Results:**

A two-compartment model with first-order elimination and transit compartment absorption (N=5) adequately characterized the vigabatrin concentration-time data in adults and children with complex partial seizures and children with infantile spasms.




The parameter estimates from the sponsor's final model presented in the Table 13 and the final model is described below:

$$k_{tr,ij} = 11.4\left[\left(\frac{AGE_i}{28}\right)^{0.3}\right] e^{\eta_{2i}+\kappa_{2ij}}$$

$$CL/F_{TV} = 6.52\left[\left(\frac{CRCL_i}{100}\right)^{0.538} \cdot e^{(-0.644 \cdot I_{ST118} + -0.285 \cdot I_{ST192} + -0.608 \cdot I_{ST221})}\right]$$

$$Vc/F_{TV} = 23.9\left[\left(\frac{WTKG_i}{70}\right)^{0.406}\right]$$

$$k_i = \left[\frac{CL/F_{TV}}{Vc/F_{TV}}\right] e^{\eta_{2i}}$$

$$Vc/F_i = [Vc/F_{TV}] e^{\eta_{1i}}$$

$$Q/F = 3.59\left[\left(\frac{WTKG_i}{70}\right)^{0.692}\right]$$

$$Vp/F = 32.3\left[\left(\frac{WTKG_i}{70}\right)^{1.08}\right]$$

$$F1_{ij} = 1 \cdot e^{\kappa_{2ij}}$$

where $I_{ST118}$, $I_{ST192}$, and $I_{ST221}$ are indicator variables equal to one if study is equal to 118, 192, or 221, respectively, and zero otherwise.

**Table 13. Parameter estimates from the sponsor's final population PK model.**

| Parameter | Final Model[a] | |
|---|---|---|
| **Fixed Effects** | **Estimate** | **95% CI** |
| $k_{tr}$ [1/hr] | 11.4 | (9.24,13.5) |
| AGE on ktr | 0.3 | (0.172,0.429) |
| CL/F [L/hr] | 6.52 | (6.16,6.89) |
| CRCL on CL/F | 0.538 | (0.445,0.632) |
| Study 118 on CL/F | -0.644 | (-0.766,-0.522) |
| Study 192 on CL/F | -0.385 | (-0.498,-0.273) |
| Study 221 on CL/F | -0.608 | (-0.721,-0.496) |
| $V_c$/F [L] | 23.9 | (20.9,26.9) |
| WTKG on Vc/F | 0.406 | (0.248,0.564) |
| Q/F [L/hr] | 3.59 | (2.95,4.24) |
| WTKG on Q/F | 0.692 | (0.232,1.15) |
| $V_p$/F [L] | 32.3 | (25.3,39.2) |
| WTKG on Vp/F | 1.03 | (0.751,1.31) |
| **Interindividual/Interoccasion Variability** | **Estimate (% CV[b])** | **95% CI** |
| IIV - $k_{tr}$ (log ω) | -1.42 (24.2) | (-2.23,-0.612) |
| IIV - k (log ω) | -1.92 (14.7) | (-2.22,-1.62) |
| IIV - $V_c$/F (log ω) | -1.72 (18) | (-2.31,-1.12) |
| IOV - $k_{tr}$ for Study 97 (log κ) | -0.543 (58.1) | (-0.984,-0.103) |
| IOV - F1 for Study 97(log κ) | -1.31 (26.9) | (-1.83,-0.793) |
| **Residual Variability** | **Estimate (% CV[b])** | **95% CI** |
| RV - Study 18 (σ) | 0.188 (18.8) | (0.17,0.206) |
| RV - Study 24 (σ) | 0.392 (39.2) | (0.365,0.42) |
| RV - Study 25 (σ) | 0.377 (37.7) | (0.357,0.398) |
| RV - Study 97 (σ) | 0.275 (27.5) | (0.205,0.345) |
| RV - Study 118 (σ) | 0.87 (87) | (0.718,1.02) |
| RV - Study 192 (σ) | 0.615 (61.5) | (0.494,0.736) |
| RV - Study 221 (σ) | 0.571 (57.1) | (0.451,0.69) |
| **OFV** | -1253.271 | |

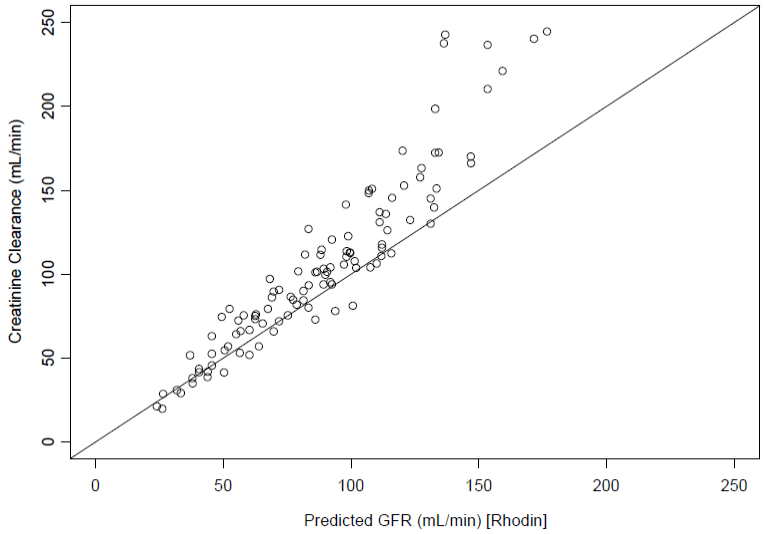
[a] Final Model excluded 7 patients with missing CRCL values
[a] Approximate % CV
CI = confidence interval, IIV = interindividual variability, IOV = interoccasion variability, NE = not estimated, RV = residual variability

The sponsor used the final vigabatrin PK model to predict exposures for pediatric patients between 1 month and 12 months of age. Day 1 and steady-state vigabatrin concentration-time profiles for the 25 mg/kg and 75 mg/kg BID dosing regimens were generated for 10000 patients in each of the following age groups: 1 month, 2 month, 3 month, 4 month, 5 month, 6 month, 7 month, 8 month, 9 month, 10 month, 11 month, and 12 month. Covariate information was sampled from the empirical distribution of patients in the Sabril® registry by age group. Since serum creatinine information was not available in the registry dataset, CRCL could not be calculated using the Cockroft-Gault or Schwartz formulas as was done in the analysis dataset. Instead a previously published population model by Rhodin et al. which characterized the relationship between glomerular filtration rate (GFR) and patient covariates (body weight and age) was used to calculate GFR from sampled age and weight information. It was assumed that the GFR predictions from the Rhodin model (pGFR) were equivalent to CRCL used in the final model. Figure 8 shows that there is reasonable agreement in pGFR and CRCL, especially at the lower values, for those pediatric patients with CRCL values in the final analysis dataset. The Rhodin model for predicting GFR is described by the following equation:

$$pGFR(mL/min) = \frac{PMA^{5.40}}{PMA^{5.40}+TM50^{5.40}} \cdot \left(\frac{WTKG}{70}\right)^{0.75} \cdot GFR_{Mature}$$

where *PMA* is the postmenstrual age in weeks and assumes a 40 week gestation period in addition to the postnatal age, *TM50* is the time to achieve half of the mature GFR and is equal to 47.7 weeks, and *GFRMature* is the GFR for a mature adult and is equal to 121 mL/min.

Figure 8. Predicted Glomerular Filtration Rate from Rhodin Model versus Creatinine Clearance in Pediatric Patients Less than 18 Years of Age in the Analysis Dataset




Exposure predictions (AUC(0-12), Cmax, and C12) for pediatric patients less than or equal to one year of age are displayed in Figure 5.

***Pediatric Dosing Derivation (Dose / Exposure-Response Analyses, study-1532a.pdf)***

**Objectives :**

- Assess the previously developed longitudinal dose-response model
- Determine if a concentration-response model using individual predicted exposure measures from the final population pharmacokinetic model explains additional variability in response relative to the dose-response model.

**Data :**

The sponsor's dose-response analysis included data from 3 studies in pediatric (071754PRO118, 071754PRO192, and 071754PRO221) and two studies in adult (71754-3-C-024 and 71754-3-C-025) patients with uncontrolled complex partial seizures. The detailed information on the study is presented in Table 14 and the brief statistics of demographics is summarized in Table 15.

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**Table 14. The summary of studies included in the sponsor's dose-response analysis.**

| Study | Population | Treatment[a,b] | Sample Size[c, d] | Key Inclusion (I) / Exclusion (E) Criteria |
|---|---|---|---|---|
| 118 | Pediatric | Placebo<br>VGB 20 mg/kg/day<br>VGB 60 mg/kg/day<br>VGB 100 mg/kg/day | 126 | I: 3-16 years of age (inclusive)<br>I: Diagnosis of complex partial epilepsy with or without secondary generalization<br>I: At least 6 CPS during last 8 weeks of baseline phase<br>I :Stable regimen of AEDs<br>E: Generalized epilepsy<br>E: Progressive neurological disorders<br>E: Treatable causes of seizures (e.g. infection)<br>E: Non-epileptic seizures (e.g. febrile seizures) |
| 192 | Pediatric | Placebo<br>0.5-1.5 g/day for 10-15 kg<br>0.5-2.0 g/day for 16-30 kg<br>1.0-3.0 g/day for 31-50 kg<br>1.0-4.0 g/day for > 50 kg | 55 | I: 3-16 years of age (inclusive)<br>I: Diagnosis of partial epilepsy with CPS or PSSG<br>I: At least four CPS or PSSG during the baseline phase<br>I: Stable regimen of AEDs<br>E: Generalized epilepsy<br>E: Progressive neurological disorders<br>E: Treatable causes of seizures (e.g. infection)<br>E: Non-epileptic seizures (e.g. febrile seizures) |
| 221 | Pediatric | Placebo<br>0.5-1.5 g/day for 10-15 kg<br>0.5-2.0 g/day for 16-30 kg<br>1.0-3.0 g/day for 31-50 kg<br>1.0-4.0 g/day for > 50 kg | 88 | I: 3-16 years of age (inclusive)<br>I: Diagnosis of complex partial epilepsy with or without secondary generalization<br>I: At least four CPS or PSSG during the baseline phase<br>E: Generalized epilepsy<br>E: Progressive neurological disorders<br>E: Treatable causes of seizures (e.g. infection)<br>E: Non-epileptic seizures (e.g. febrile seizures) |
| 024 | Adult | Placebo<br>VGB 3 g/day | 183 | I: 18-60 years of age (inclusive)<br>I: Documented CPS or PSSG<br>I: At least 6 CPS during last 8 weeks of baseline phase<br>I : Stable regimen of AEDs<br>E: Progressive neurological disorders<br>E: Treatable causes of seizures (e.g. infection) |
| 025 | Adult | Placebo<br>VGB 1 g/day<br>VGB 3 g/day<br>VGB 6 g/day | 174 | I: 18-60 years of age (inclusive)<br>I: Documented CPS or PSSG<br>I: At least 6 CPS during last 8 weeks of baseline phase<br>I : Stable regimen of AEDs<br>E: Progressive neurological disorders<br>E: Treatable causes of seizures (e.g. infection) |

VGB = vigabatrin
CPS = complex partial seizure
AED = Antiepileptic drug
PSSG = Partial seizures with secondary generalization
[a] Vigabatrin dose titrated in all studies. See narratives for additional details.
[b] Dosage regimen was twice daily (BID) in all studies
[c] Based on number of patients that were randomized
[d] Planned enrollment was not achieved for Studies 118, 192, and 221

**Table 15. Summary of statistics of covariates included in the sponsor's dose-response analysis.**

| Covariate | Statistic | Study 24 | Study 25 | Study 118 | Study 192 | Study 221 | Total |
|---|---|---|---|---|---|---|---|
| Age (yr) | Mean (SD) | 34 (9) | 35 (10) | 10 (4) | 11 (3) | 10 (4) | 24 (14) |
| | Median | 34 | 33 | 10 | 11 | 10 | 24 |
| | Min, Max | 18, 60 | 18, 63 | 3, 16 | 4, 16 | 3, 16 | 3, 63 |
| Baseline Body Weight (kg) | Mean (SD) | 75 (19) | 73 (17) | 44 (23) | 58 (23) | 43 (23) | 62 (25) |
| | Median | 72 | 70 | 41 | 55 | 38 | 62 |
| | Min, Max | 40, 132 | 44, 136 | 12, 112 | 22, 116 | 15, 112 | 12, 136 |
| Baseline Creatinine Clearance (mL/min) | Mean (SD) | 105 (24) | 101 (21) | 91 (50) | 126 (55) | 102 (59) | 102 (40) |
| | Median | 101 | 98 | 80 | 121 | 83 | 99 |
| | Min, Max | 65, 271 | 58, 168 | 21, 273 | 46, 243 | 28, 266 | 21, 273 |
| Sex | No. Male | 80 | 83 | 59 | 25 | 41 | 288 |
| | No. Female | 102 | 91 | 66 | 30 | 44 | 333 |
| Race | No. White | 165 | 165 | 113 | 53 | 72 | 568 |
| | No. Black | 12 | 5 | 7 | 1 | 9 | 34 |
| | No. Asian | 0 | 2 | 2 | 0 | 0 | 4 |
| | No. Other | 5 | 2 | 3 | 1 | 4 | 15 |

**Methodology:**

Nonlinear mixed effects modeling methodology was implemented in this analysis. A previously described dose-response model was re-fit with a revised dataset. In the study 118, accurate longitudinal dosing histories were not available and as a result the protocol specified titration scheme and maintenance doses were utilized. Following finalization of the dose-response modeling report, it was discovered that patients with body weights greater than 60 kg were dosed as if their body weight was equal to only 60 kg. This practice of capping the dosing weight resulted in the largest patients receiving less than the protocol specified mg/kg nominal dosage; this was not accounted for in the previous version of the dataset. Therefore, the previously constructed analysis dataset was revised based on the new information. The revised dataset was identical to previous version of the dataset in all other aspects.

The individual predicted empirical Bayes estimates of CL/F as well as the typical individual estimates of CL/F from the final population PK model were merged with the

revised analysis dataset. The average vigabatrin concentration (Cavg) was selected as the exposure measure to best characterize the relationship between concentration and seizure frequency.
Cavg was calculated from total daily dose and CL/F predictions

$Cavg = Dose / (CL/F \cdot \tau)$

Predictive checks were used to determine if the predictive performance of the final model was preserved in the revised dataset.

Concentration-response models were also evaluated in order to determine if individual predicted Cavg from the final population PK model could explain additional variability in the vigabatrin exposure response relationship relative to the dose-response model.

**Results:**

The dose-response model fit to the revised dataset resulted in similar parameter estimates to the original dataset.

**Table 16. Comparison of Parameter estimates between previous and revised analyses.**

| | Previous Analysis | | Revised Analysis | |
|---|---|---|---|---|
| **Parameter** | **Estimate** | **SE** | **Estimate** | **SE** |
| LN $\lambda$ – Adults | -1.07 | 0.0395 | -1.07 | 0.0394 |
| Age on LN $\lambda$ | -0.419 | 0.0592 | -0.418 | 0.0592 |
| LN *OVDP* – Adults | 0.0928 | 0.0194 | 0.0924 | 0.0195 |
| Δ LN *OVDP* -118 | -0.672 | 0.0413 | -0.671 | 0.0412 |
| Δ LN *OVDP* -192 | -0.937 | 0.0741 | -0.94 | 0.0743 |
| Δ LN *OVDP* -221 | -1.42 | 0.0729 | -1.42 | 0.073 |
| *AS* – Adults | -0.157 | 0.129 | -0.156 | 0.243 |
| Δ *AS* -118 | 0.132 | 0.25 | 0.12 | 0.406 |
| Δ *AS* -192 | -0.558 | 0.368 | -0.584 | 0.378 |
| Δ *AS* -221 | -0.356 | 0.289 | -0.374 | 0.364 |
| LN $k$ | -4.97 | 0.256 | -5 | 0.278 |
| LN $\alpha$ | -1.46 | 0.241 | -1.29 | 0.228 |
| LN $\beta$ | -0.187 | 0.108 | -0.122 | 0.118 |
| WT on $D_{NORM}$ | -0.705 | 0.162 | -0.608 | 0.174 |
| LN $\omega - \lambda$ – Adults ($\omega - \lambda$) | -0.318 (0.728) | 0.0554 | -0.319 | 0.0552 |
| Δ LN $\omega - \lambda$ -118 | 0.585 | 0.0872 | 0.586 | 0.0867 |
| Δ LN $\omega - \lambda$ -192 | 0.884 | 0.122 | 0.886 | 0.122 |
| Δ LN $\omega - \lambda$ -221 | 0.357 | 0.0986 | 0.358 | 0.0989 |
| *SHAPE* - Adults | 0.743 | 0.104 | 0.745 | 0.104 |
| LN $\omega - AS$ ($\omega - AS$) | 0.677 (1.97) | 0.193 | 0.694 | 0.213 |
| LN $\omega - \beta$ ($\omega - \beta$) | -0.116 (0.890) | 0.054 | -0.137 | 0.0699 |

The mean seizure rate was described by the following equations:

$$\lambda_{ij} = \lambda_i \cdot f_{TIME}(ij) \cdot f_{DRUG}(ij) \quad \textbf{[3a]}$$

$$\lambda_i = \exp(-1.07 + -0.418 \cdot (\ln(AGE_i) - \ln(24)) + \eta_\lambda) \quad \textbf{[3b]}$$

$$AS_i = -0.156 + 0.12 \cdot ST118_i + -0.584 \cdot ST192_i + -0.374 \cdot ST221_i + \eta_{AS} \quad \textbf{[3c]}$$

$$f_{TIME}(ij) = \exp(AS_i \cdot (1 - \exp(\exp(-5) \cdot TIME_{ij}))) \quad \textbf{[3d]}$$

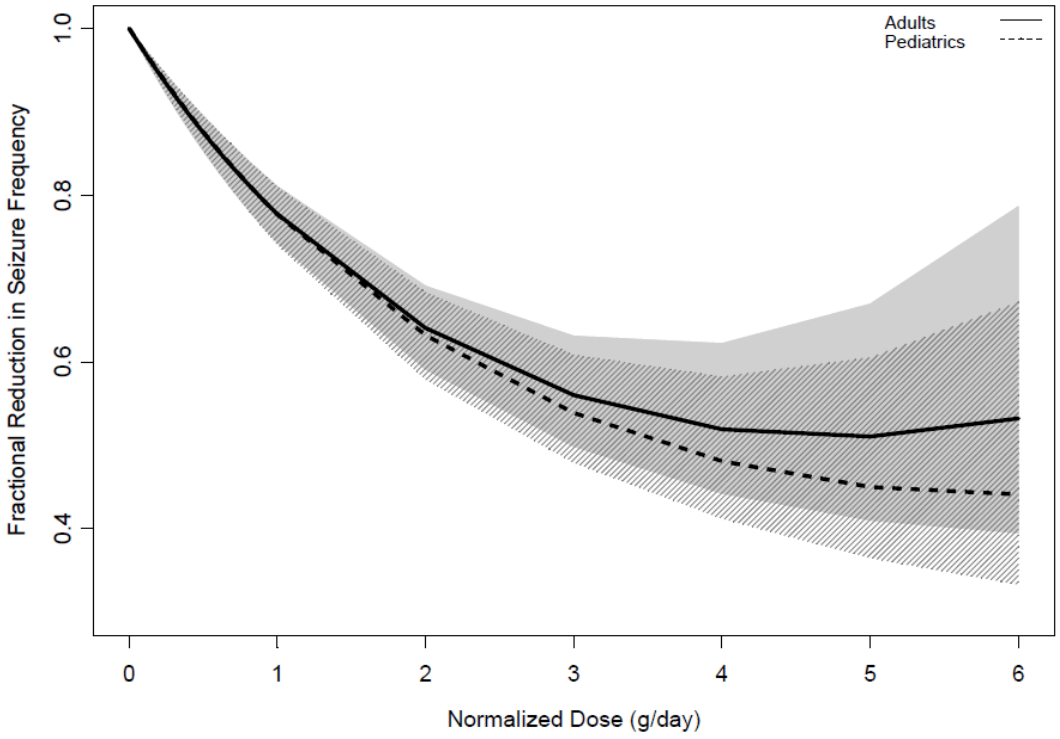
$$D_{NORM\,ij} = DOSE_{ij} \cdot \left(\frac{WT_i}{60}\right)^{-0.608} \quad \textbf{[3e]}$$

$$f_{DRUG}(ij) = \exp(\exp(-1.29) \cdot \left(\frac{D_{NORM\,ij}}{3000}\right)^2 - \exp(-0.122 + \eta_\beta) \cdot \left(\frac{D_{NORM\,ij}}{3000}\right)) \quad \textbf{[3f]}$$

where *ST118i*, *ST192i*, and *ST221i* are indicators equal to 1 if *ith* patient was from Study 118, Study 192, or Study 221, respectively, or zero otherwise.

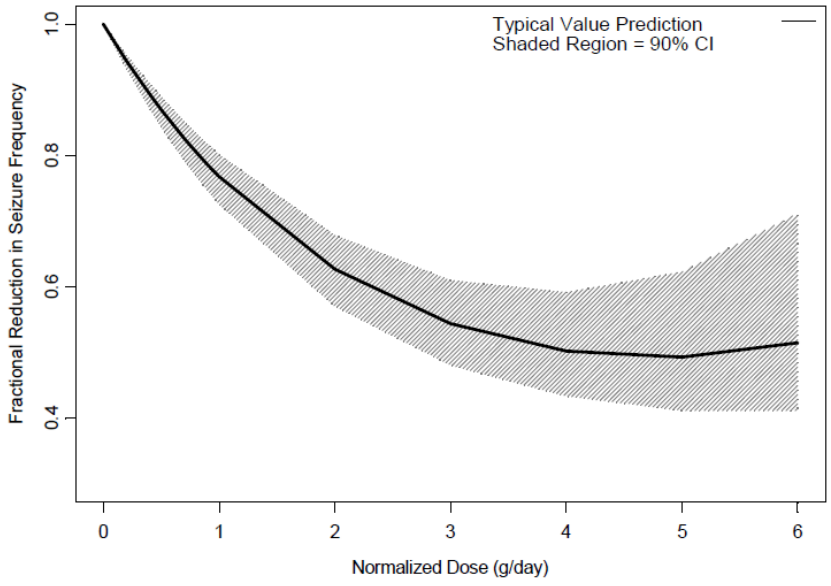
Figure 9 provides a graphical illustration of the difference between adult and pediatric patients in terms of the vigabatrin drug effect.

**Figure 9.** Dose-response Model (90% CI) with Separate Fixed-Effect Parameters for Adults and Pediatrics



Similarly, predictive checks indicated that the predictive performance of the dose-response model in the revised dataset was similar to that of the original dataset. The relationship between weight-normalized dose and the fractional seizure reduction attributed to vigabatrin is provided in the **Figure 10**. A total daily normalized dose of 1, 3, and 6 g/day is predicted to reduce seizure rate by 23.2%, 45.6%, and 48.5%, respectively. A total daily normalized dose of 1.065g represents half of the response relative to a total daily normalized dose of 6 g.
Concentration-response models which used model predicted Cavg as the exposure measure instead of normalized-dose did not explain additional variability in the response to vigabatrin.

**Figure 10. Vigabatrin Dose-Response Relationship from Previously Developed Dose-Response Model.**




Pediatric dose recommendations were generated using the final model. Since the dose-response model was determined to be similar in adult and pediatric patients, the predictions were driven entirely by the weight-based correction of normalized dose. Dosing recommendations for children weighing greater than or equal to 10 kilograms are provided in the table below.

**Table 17. Sponsor's Dosing Recommendations in Pediatric Patients.**

| Formulation | Target Dose in Adults (mg) | Body Weight (kg) | Proposed Dose (mg/day) | Drug Effect in 70 kg Adult (% Reduction in Seizure Rate) | Drug Effect (Range) | Percent Change in Drug Effect Relative to Adults (Range) |
|---|---|---|---|---|---|---|
| Sachet | 1000 | 10-15 kg | 350 | 21.6 | 19.7 – 24.0 | -8.6 - 11 |
| Sachet | 1000 | >15-20 kg | 450 | 21.6 | 21.0 – 24.0 | -2.8 - 11.4 |
| Tablet | 1000 | >20-35 kg | 500 | 21.6 | 17.3 – 22.8 | -19.8-5.6 |
| Tablet | 1000 | >35-60 kg | 750 | 21.6 | 18.5 – 24.0 | -14.5-11 |
| Tablet | 1000 | 70 kg | 1000 | 21.6 | 21.6 | 0-0 |
| Sachet | 3000 | 10-15 kg | 1050 | 43.8 | 41.6 – 46.3 | -5.2-5.7 |
| Sachet | 3000 | >15-20 kg | 1300 | 43.8 | 42.3 – 45.7 | -3.4-4.3 |
| Tablet | 3000 | >20-35 kg | 1750 | 43.8 | 41.5 – 47.7 | -5.4-9 |
| Tablet | 3000 | >35-60 kg | 2250 | 43.8 | 39.8 – 46.3 | -9.1-5.7 |
| Tablet | 3000 | 70 kg | 3000 | 43.8 | 43.8 | 0-0 |

Further refinement of the pediatric dosing predictions was performed by the sponsor to reflect weights encompassing adolescents 10 to 16 years of age.
According to CDC growth charts, the 5th percentile of weight for 10 year olds is approximately 25 kg. Therefore, the patients below 25 kg removed from dosing recommendation. The final dosing recommendation is presented in Table 18.

**Table 18. Sponsor's Final Dosing Recommendation in Pediatrics.**

| Adult Dose | Body Weight (kg) | Proposed Dose (mg) | Drug Effect (% Reduction in Seizure Rate) | Drug Effect in 70 kg Adult (% Reduction in Seizure Rate) | Percent Change in Drug Effect Relative to Adults | Ratio of Drug Effect Relative to Drug Effect in 70 kg Adult |
|---|---|---|---|---|---|---|
| 1000 | 25.0 | 500 | 20.46 | 21.6 | -5.18 | 0.95 |
| 1000 | 42.5 | 500 | 15.65 | 21.6 | -27.47 | 0.73 |
| 1000 | 60.0 | 500 | 13.05 | 21.6 | -39.54 | 0.60 |
| 1000 | 70.0 | 1000 | 21.58 | 21.6 | 0.00 | 1.00 |
| 3000 | 25.0 | 2000 | 47.71 | 43.8 | 8.89 | 1.09 |
| 3000 | 42.5 | 2000 | 41.77 | 43.8 | -4.67 | 0.95 |
| 3000 | 60.0 | 2000 | 37.32 | 43.8 | -14.83 | 0.85 |
| 3000 | 70.0 | 3000 | 43.81 | 43.8 | 0.00 | 1.00 |

*Reviewer's comments: The proposed dosing guidelines are acceptable.*

# 4 REVIEWER'S ANALYSIS

## 4.1 Introduction

The reviewer performed independent assessment to evaluate whether the sponsor's proposed dosing recommendation is reasonable or not based on exposure level in pediatrics.

## 4.2 Methods

### 4.2.1 Data Sets

Data sets used are summarized in Table 19.

**Table 19. Analysis Data Sets**

| Study Number | Name | Link to CDSNAS |
|---|---|---|
| pop-pk-1526-1.pdf | update-pkpd-29dec2012.xpt | \\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Vigabatrin_NDA20427_JYL\Sponsor Data and Reports |

### 4.2.2 Software

SAS® (Version 9.3)

### 4.2.3 Models

The data from five studies was used and a log-linear model was applied for exposure-response analysis to confirm whether there was similarity in exposure-response relationship between adult and pediatric patients. Standardized seizure rate during maintenance phase, which was calculated by

$$\frac{Total\ Number\ of\ Seizures}{Study\ Days} \times 28$$

The log-transformed standardized seizure rate was used as a response variable, and the standardized seizure rate during baseline phase was adjusted in the model. The average concentration (Cavg) which was predicted from the sponsor's population PK model was used as an exposure.
The effect of age was evaluated as a covariate in the pooled analysis, and the exposure-response relationship was examined separately by pediatrics and adults studies.

### 4.3 Results

Table 20 and Table 21 show the parameter estimates from the reviewer's log-linear model.

**Table 20. Parameter Estimates in the Reviewer's Log-linear Model:Pooled Analysis.**

| | Estimates | P-value |
|---|---|---|
| Intercept | 2.1 | <0.0001 |
| Base SZ | 0.08 | <0.0001 |
| Cavg | -0.01 | 0.0037 |
| Age | 0.0005 | 0.9001 |
| Cavg*age | -0.0002 | 0.3586 |

**Table 21. Parameter Estimates in the Reviewer's Log-linear Model: Separate Analysis by Pediatrics and Adults Studies. ( ) represents p-value.**

| | Adults | Pediatrics |
|---|---|---|
| Intercept | 2.12 (<0.0001) | 2.09 (<0.0001) |
| Baseline SZ | 0.09 (<0.0001) | 0.08 (<0.0001) |
| Cavg | -0.021 (<0.0001) | -0.016 (0.0002) |

As being consistent with previously conducted dose-response analysis, age was not found to be significant covariate in the pooled analysis. Furthermore the parameter estimates are similar between pediatrics and adults in the separate analysis.

As a next step the reviewer examined the distribution of exposure, Cavg to evaluate whether the sponsor's proposed dose was supported by the exposure level shown in two populations. Figure 2 presents the distribution of Cavg at the doses of 1000 mg and 3000 mg in adult studies only, which shows dose-proportionality.

There were limited number of patients given 3000 mg in pediatric population. Therefore, the exposure level at the dose of 3000 mg in pediatric patients was compared to that in adult patients. As shown in Figure 3, Cavg appears to be higher in pediatrics than that in adults, the ratio of median Cavg between adolescents (10-16 years old patients) and adults ( > 16years old patients) was about 0.58. This ratio was applied to match to the approved adult doses, 1000 mg and 3000 mg and the result is shown in Table 3. The reviewer's calculation using the exposure ratio between adults and pediatrics was similar to the sponsor's proposed doses.

To examine further whether the sponsor's proposal for the same dose for pediatrics as adults for those who weigh greater than 60 kg, the weight was broken down by 25-40 kg, 40-60 kg and > 60 kg. Although the sample size is limited the ratio of Cavg for patients weighing greater than 60 kg is closer to 1 (Figure 4), which confirms the sponsor's proposal.

In conclusion, the sponsor's proposed dose for pediatrics is acceptable.

## 5 LISTING OF ANALYSES CODES AND OUTPUT FILES

| File Name | Description | Location in \\cdsnas\pharmacometrics\ |
|---|---|---|
| ER.SAS | Exposure-response analysis | \\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Vigabatrin_NDA20427_JYL\ER Analyses |

# 6 APPENDIX : PHARMACOMETRIC REVIEW FOR PREVIOUS DOSE-RESPONSE ANALYSIS (IND 17213)

# Office of Clinical Pharmacology
# Pharmacometrics

| | |
|---|---|
| IND | 17213 (Pediatric Written Request) |
| Generic name | Vigabatrin |
| Dosing regimen | 1g / 3g |
| Indication | Refractory complex partial seizures (rCPS) |
| Applicant name | Lundbeck |
| Pharmacometrics Reviewer | Joo-Yeon Lee |
| Pharmacometrics Team leader | Atul Bhattaram |

**Background**

Two New Drug Applications (NDAs) for Sabril® were approved on 21 August 2009.
NDA 20-427 was approved as 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 vision loss. Sabril® is not indicated as a first line agent for CPS. NDA 22-006 was approved for the use of Sabril® as monotherapy for pediatric patients from 1 month to 2 years of age with infantile spasms (IS) for whom the potential benefits outweigh the potential risk of vision loss.
A deferred study under the Pediatric Research Equity Act (PREA) was required to evaluate the safety and efficacy of several fixed doses of Sabril® versus placebo as adjunctive therapy in pediatric patients 10 years of age and above with refractory CPS (hereafter referred to as rCPS). A waiver for the lower age ranges was granted due to the difficulty in monitoring visual toxicity in children less than 10 years of age. Accordingly, the sponsor submitted a Proposed Pediatric Study Request (PPSR) to Investigational New Drug (IND) 17,213 on 30 October 2009 (Serial No. 722). This submission contained a protocol for a placebo-controlled dose-response study in subjects ages 10-16. Comments from the Food and Drug Administration (FDA) were sent via email on 11 November

2010, the sponsor responded via email on 20 December 2010, and a duplicate response was formally submitted to the IND on 16 March 2011 (Serial No. 734). A second set of FDA comments was issued via email on 17 March 2011, followed by a draft Pediatric Written Request (PWR) via email on 06 June 2011. In the 06 June 2011 communication, FDA noted that the current PWR would include all pediatric post approval commitments issued for both NDA 20-427 and NDA 22-006, and that the draft was being issued to facilitate initiation of the controlled study. The current PWR, dated 25 August 2011, incorporating all post marketing requirements related to pediatrics, was received by the sponsor on 01 September 2011. In the PWR, the sponsor was requested to conduct a randomized study in subjects from 10 to 16 years of age with rCPS, comparing the effect of 2 doses (20 mg/kg/day and 60 mg/kg/day) to placebo. A long-term safety study in 50 subjects for 6 months and 20 subjects for 1 year was also requested.

A Type C Meeting was held on 10 November 2011 and summarized in the final FDA minutes dated 9 December 2011. During the Type C Meeting, the Agency noted that they were open to the sponsor's proposal to use pharmacometric-type bridging analyses to satisfy PREA and to support earlier implementation of appropriate pediatric labeling for Sabril®. However, before the Agency could consider amending the PWR, the results of the analyses would need to be reviewed. The results of the pharmacometric-type bridging analyses were submitted for review to the IND on 15 March 2012 as Serial No. 0748.

In the analyses the sponsor aimed to show similar dose-response relationship between adult and pediatric populations. Pediatric dosing guidelines were derived based on the dose- response relationship. Hence, the reviewer focused on the question of whether the sponsor's claim of similar dose-response relationship in adult and pediatric populations is acceptable or not.

**Sponsor's analyses**

Data from 3 studies in pediatric (071754PRO118, 071754PRO192, and 071754PRO221) and two studies in adult (71754-3-C-024 and 71754-3-C-025) patients with uncontrolled complex partial seizures were included in the analyses. Table 22 summarizes the data used in the analyses with the demographics in each study (

Table 23).

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Table 22. Summary of data included in the sponsor's analyses

| Population | Study | Treatment | # of Patients | # of Daily Seizure Counts Recorded |
|---|---|---|---|---|
| Adults with Complex Partial Seizures | Study 24 | Placebo | 90 | 17821 |
| | | Vigabatrin 3g/day | 92 | 17927 |
| | Study 25 | Placebo | 45 | 9360 |
| | | Vigabatrin 1g/day | 45 | 9186 |
| | | Vigabatrin 3 g/day | 43 | 8638 |
| | | Vigabatrin 6 g/day | 41 | 7954 |
| Children with Complex Partial Seizures | Study 118 | Placebo | 31 | 5169 |
| | | Vigabatrin 20 mg/kg/day | 30 | 4771 |
| | | Vigabatrin 60 mg/kg/day | 32 | 5098 |
| | | Vigabatrin 100 mg/kg/day | 32 | 5046 |
| | Study 192 | Placebo | 27 | 4292 |
| | | Vigabatrin 0.5-4 g/day | 28 | 4155 |
| | Study 221 | Placebo | 44 | 6664 |
| | | Vigabatrin 0.5-4 g/day | 41 | 6087 |

Table 23. The summary of demographics at the baseline from each study included in the analyses.

| Covariate | Statistic | Study 24 | Study 25 | Study 118 | Study 192 | Study 221 | Total |
|---|---|---|---|---|---|---|---|
| Age (yr) | Mean (SD) | 34 (9) | 35 (10) | 10 (4) | 11 (3) | 10 (4) | 24 (14) |
| | Median | 34 | 33 | 10 | 11 | 10 | 24 |
| | Min, Max | 18, 60 | 18, 63 | 3, 16 | 4, 16 | 3, 16 | 3, 63 |
| Baseline Body Weight (kg) | Mean (SD) | 75 (19) | 73 (17) | 44 (23) | 58 (23) | 43 (23) | 62 (25) |
| | Median | 72 | 70 | 41 | 55 | 38 | 62 |
| | Min, Max | 40, 132 | 44, 136 | 12, 112 | 22, 116 | 15, 112 | 12, 136 |
| Baseline Creatinine Clearance (mL/min) | Mean (SD) | 105 (24) | 101 (21) | 91 (50) | 126 (55) | 102 (59) | 102 (40) |
| | Median | 101 | 98 | 80 | 121 | 83 | 99 |
| | Min, Max | 65, 271 | 58, 168 | 21, 273 | 46, 243 | 28, 266 | 21, 273 |
| Sex | No. Male | 80 | 83 | 59 | 25 | 41 | 288 |
| | No. Female | 102 | 91 | 66 | 30 | 44 | 333 |
| Race | No. White | 165 | 165 | 113 | 53 | 72 | 568 |
| | No. Black | 12 | 5 | 7 | 1 | 9 | 34 |
| | No. Asian | 0 | 2 | 2 | 0 | 0 | 4 |
| | No. Other | 5 | 2 | 3 | 1 | 4 | 15 |

A negative binomial (NB) distribution model was selected as the starting point for structural model development based on two previously published reports in patients with refractory epilepsy as follows:

$$P(Y_{ij}=n)=\left[\frac{\Gamma\left(n+\frac{1}{OVDP}\right)}{n!\cdot\Gamma\left(\frac{1}{OVDP}\right)}\right]\cdot\left(\frac{1}{1+OVDP\cdot\lambda_{ij}}\right)^{\frac{1}{OVDP}}\cdot\left(\frac{\lambda_{ij}}{\frac{1}{OVDP}+\lambda_{ij}}\right)^{n}$$

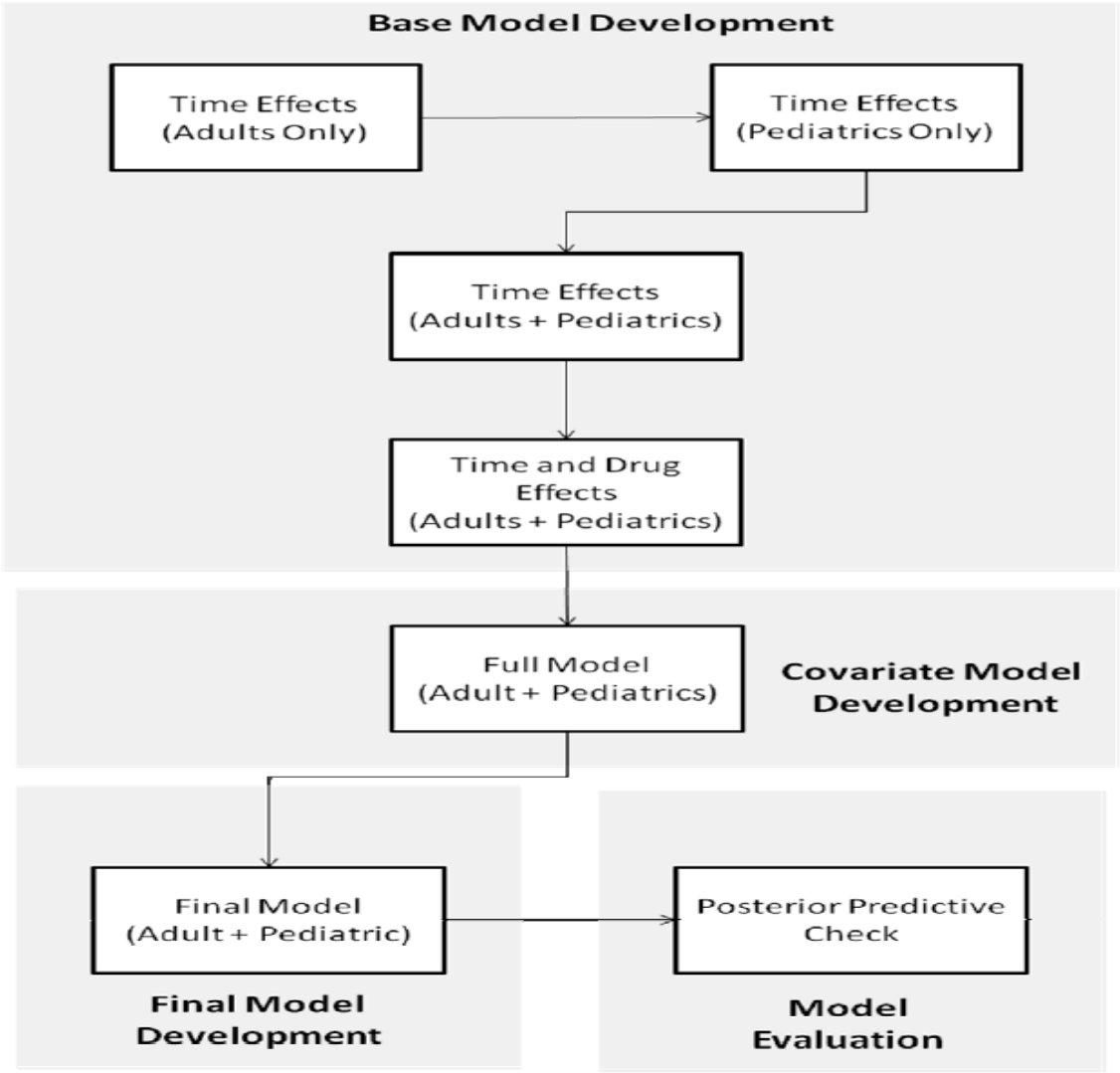
where $Y_{ij}$ is the observed number of seizures for the patient i on the day j, $\lambda_{ij}$ is the mean daily seizure count for the patient i on the day j with an exponential random effect, *OVDP* represents the degree of overdispersion, and Γ represents the gamma function.

Time effects and drug effects were incorporated on the $\lambda$ parameter in the basic NB distribution model to give the following overall functional form for mean daily seizure count.

Covariate model development was conducted in two stages. The Stage 1 Full Model included demographic covariates such as age, body weight (WT) and creatinine clearance

(CLCR). The Stage 2 Full Model evaluated the influence of other AEDs that were administered during the study period. Normalized dose was used instead of concentration as a surrogate measure. It was estimated in the model based on a patient's actual dose (in mg) and other patient covariates, body weight. Figure 11 presents the sponsor's model development process.

Figure 11. The sponsor's model development process.




The sponsor's final model is summarized below, and the parameter estimates are presented in Table 24.

$$\lambda_{ij} = \lambda_i \cdot f_{TIME}(ij) \cdot f_{DRUG}(ij)$$

$$\lambda_i = \exp(-1.07 + -0.419 \cdot (\ln(AGE_i) - \ln(24)) + \eta_\lambda)$$

$$AS_i = -0.157 + 0.132 \cdot ST118_i + -0.585 \cdot ST192_i + -0.356 \cdot ST221_i + \eta_{AS}$$

$$f_{TIME}(ij) = \exp(AS_i \cdot (1 - \exp(\exp(-4.97) \cdot TIME_{ij})))$$

$$D_{NORM\,ij} = DOSE_{ij} \cdot \left(\frac{WT_i}{60}\right)^{-0.705}$$

$$f_{DRUG}(ij) = \exp(\exp(-1.46) \cdot \left(\frac{D_{NORM\,ij}}{3000}\right)^2 - \exp(-0.187 + \eta_\beta) \cdot \left(\frac{D_{NORM\,ij}}{3000}\right))$$

where $\lambda_{ij}$ is the mean seizure count for the patient i on the day j, $\lambda_i$ is the mean seizure count at baseline for the patient i , $f_{time}(ij)$ is the function describing the time effects for the patient i on the day j, and $f_{drug}(ij)$ is the function describing the drug effects for the normalized dose administered in the patient i on the day j.
where $ST118_i$ , $ST192_i$, and $ST221_i$ are indicators equal to 1 if patient was from study 118, study 192, or study 221, respectively, or zero otherwise.

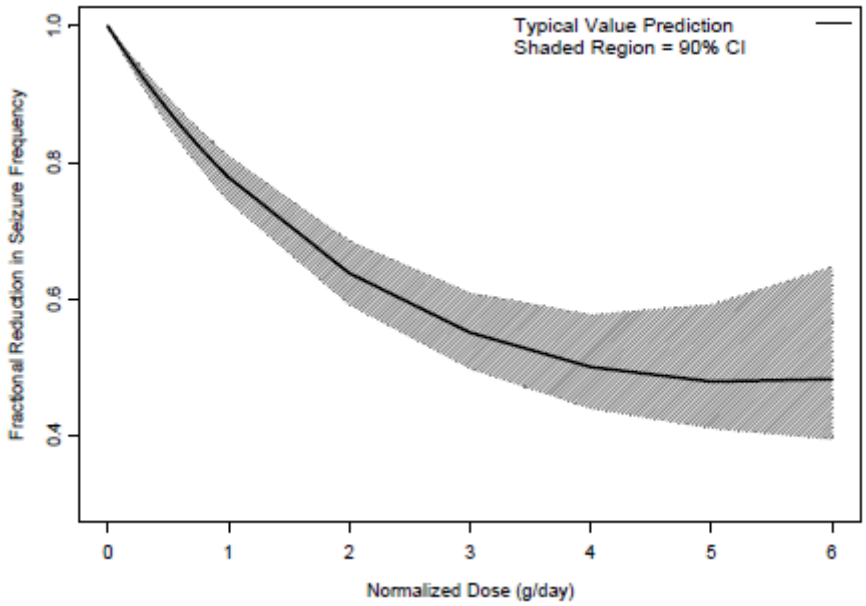
Table 24. The parameter estimates from the sponsor's final model.

| Parameter | Estimate | SE |
|---|---|---|
| LN $\lambda$ – Adults | -1.07 | 0.0395 |
| Age on LN $\lambda$ | -0.419 | 0.0592 |
| LN *OVDP* – Adults | 0.0928 | 0.0194 |
| Δ LN *OVDP* -118 | -0.672 | 0.0413 |
| Δ LN *OVDP* -192 | -0.937 | 0.0741 |
| Δ LN *OVDP* -221 | -1.42 | 0.0729 |
| *AS* – Adults | -0.157 | 0.129 |
| Δ *AS* -118 | 0.132 | 0.25 |
| Δ *AS* -192 | -0.558 | 0.368 |
| Δ *AS* -221 | -0.356 | 0.289 |
| LN $k$ | -4.97 | 0.256 |
| LN $\alpha$ | -1.46 | 0.241 |
| LN $\beta$ | -0.187 | 0.108 |
| WT on $D_{NORM}$ | -0.705 | 0.162 |
| LN $\omega - \lambda$ - Adults ($\omega - \lambda$) | -0.318 (0.728) | 0.0554 |
| Δ LN $\omega$ - $\lambda$ -118 | 0.585 | 0.0872 |
| Δ LN $\omega$ - $\lambda$ -192 | 0.884 | 0.122 |
| Δ LN $\omega$ - $\lambda$ -221 | 0.357 | 0.0986 |
| *SHAPE* - Adults | 0.743 | 0.104 |
| LN $\omega - AS$ ($\omega - AS$) | 0.677 (1.97) | 0.193 |
| LN $\omega - \beta$ ($\omega - \beta$) | -0.116 (0.890) | 0.054 |

$\lambda$ = Mean baseline seizure rate
*OVDP* = Overdispersion magnitude
*AS* = Asymptotic value dictating the maximum change in seizure rate due to time
$k$ = Constant governing the rate of decline in seizure rate over time
*SHAPE* = Parameter determining the shape and magnitude of skewness in random effect on $\lambda$
$\alpha$ = Quadratic parameter in drug effect model
$\beta$ = Linear parameter in drug effect model
$\omega$ = interindividual variability expressed as standard deviation
OFV = 195073.586
Condition Number = 102

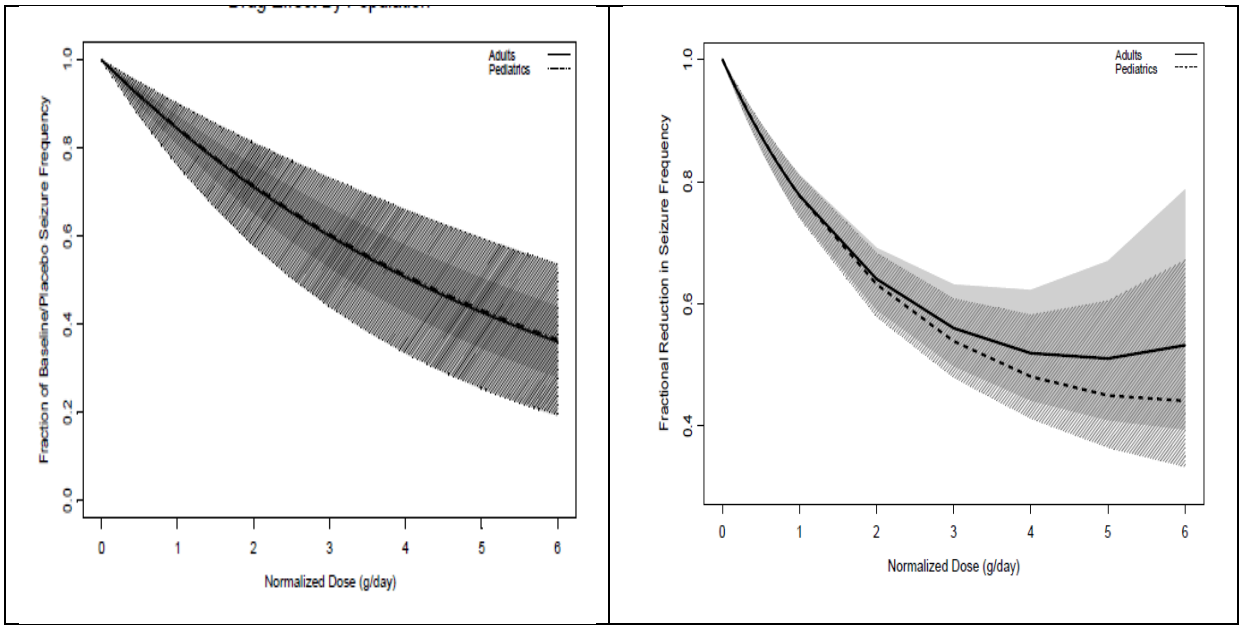
The sponsor's final model predicts to reduce seizure rate by 22%, 45% and 52% at the dose of 1, 3 and 6 g/day, respectively (Figure 12).

**Figure 12. The dose-response relationship from the sponsor's final model.**




A number of sensitivity analyses were fit to address specific questions pertaining to the usefulness or appropriateness of the final model. For example, a model which allowed separate drug effect parameters for pediatric patients compared to adults was fit in an attempt to further evaluate potential differences in drug effects between the two populations. Similarly, independent pediatric and adult dose-response models were fit in order to determine if data from one of the populations produced undue influence on the dose-response relationship in the combined model. Finally, a cross-validation procedure was conducted to determine the appropriateness of pooling the adult and pediatric data.

Figure 13. The dose-response relationship for adult and pediatric populations from the sponsor's sensitivity analyses. The left panel represents the dose-response relationship when the model was applied to pediatric and adult data separately; The right panel shows dose-response relationship when the model allowed separate drug effect parameter for pediatric population,




The final model was used to provide dosing recommendations for children with uncontrolled CPS. Predictions were made for both the sachet and tablet formulations based on the degree of dosage flexibility afforded by that specific formulation. For example, the lowest dose increment that was available for the tablet was 250 mg (i.e. ½ of a scored 500 mg tablet) while a 50 mg increment was selected for the sachet (25 mg in the morning and evening). Pediatric starting and maintenance doses were targeted to be within ± 15% of the drug effect for a 70 kg adult patient receiving the approved initial starting dose (1g/day) and maintenance dose (3/g day). The sponsor'dosing recommendation presents in Table 25.

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Table 25. The sponsor's Pediatric dosing Recommendation.

| Formulation | Target Dose in Adults (mg) | Body Weight (kg) | Proposed Dose (mg/day) | Drug Effect in 70 kg Adult (% Reduction in Seizure Rate) | Drug Effect (Range) | Percent Change in Drug Effect Relative to Adults (Range) |
|---|---|---|---|---|---|---|
| Sachet | 1000 | 10-15 kg | 300 | 20.3 | 18.5 – 23.2 | -9.2 - 14.2 |
| Sachet | 1000 | >15-20 kg | 400 | 20.3 | 19.8 – 23.3 | -2.7 - 14.4 |
| Tablet | 1000 | >20-35 kg | 500 | 20.3 | 17.2 – 23.6 | -15.6 - 16.2 |
| Tablet | 1000 | >35-60 kg | 750 | 20.3 | 17.5 – 23.8 | -13.7 - 17.2 |
| Tablet | 1000 | 70 kg | 1000 | 20.3 | 20.3 | 0 - 0 |
| Sachet | 3000 | 10-15 kg | 900 | 42.7 | 40.2 – 46.1 | -6 - 8 |
| Sachet | 3000 | >15-20 kg | 1150 | 42.7 | 41.1 – 45.3 | -3.8 - 6.1 |
| Tablet | 3000 | >20-35 kg | 1500 | 42.7 | 38.3 – 46.6 | -10.4 - 9 |
| Tablet | 3000 | >35-60 kg | 2250 | 42.7 | 38.8 – 46.8 | -9.1 - 9.4 |
| Tablet | 3000 | 70 kg | 3000 | 42.7 | 42.7 | 0 - 0 |

**Reviewer's analysis**

The sponsor's analysis was reviewed. The reviewer used change in seizure frequency (standardized seizure rate for 28 days) during the end of study (last 8 weeks during maintenance phase in the studies 24 and 25) from baseline as the endpoint for dose-response analysis. This endpoint was used in the approval decision for adults indication. As the pediatric study has different study duration, generally shorter than adult studies, a total maintenance phase was considered for the calculation of standardized seizure rate rather than the end of study as follows;

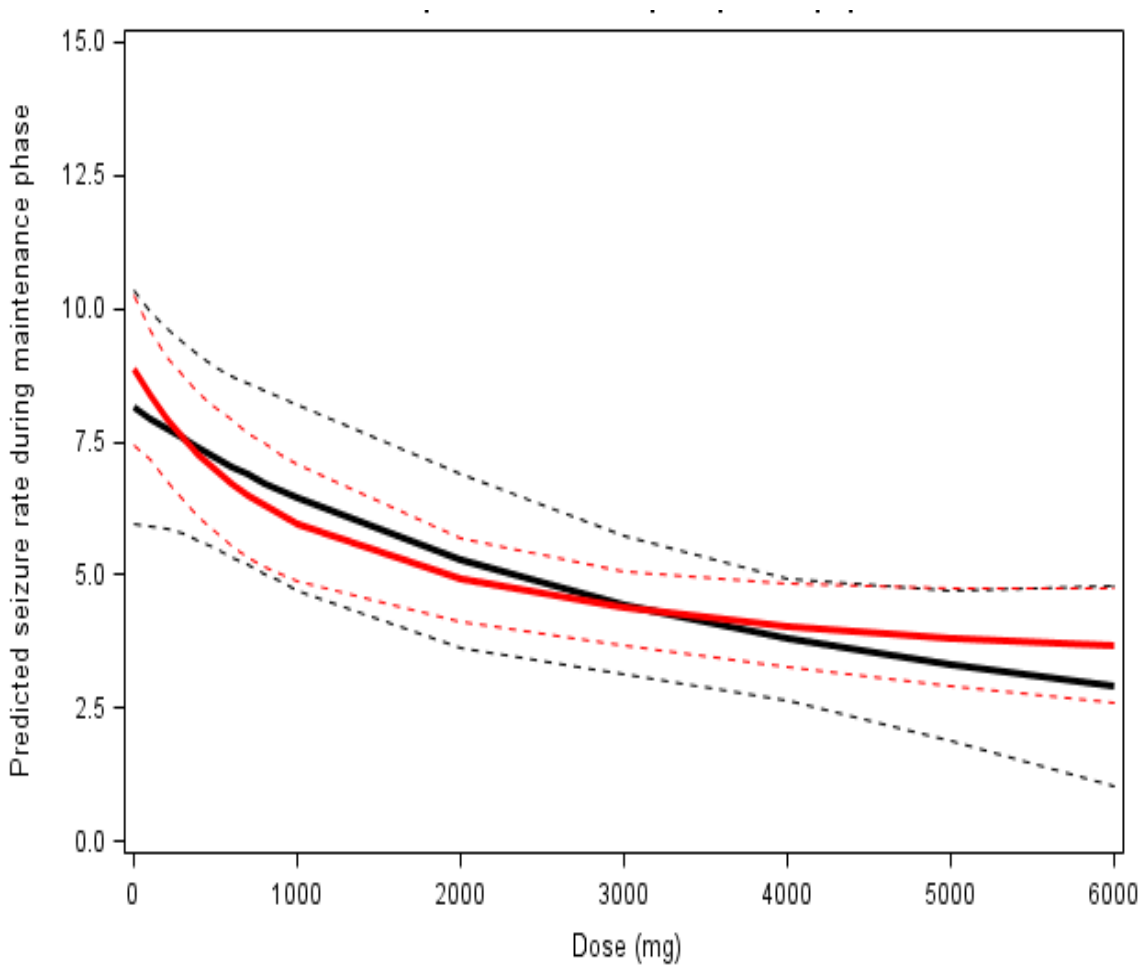
$$\frac{Total\ Number\ of\ Seizures}{Study\ Days} \times 28$$

The standardized seizure rate during the baseline phase was calculated in the same way using seizure frequency and study days during the baseline phase for each study.

The log-transformed endpoint was used as a response variable to ensure normal distribution, and the seizure rate during baseline phase was adjusted as a covariate. The several structural assumptions on the relationship between the endpoint and normalized dose such as Emax and linear relationship were examined, and Emax model was selected

for the final model based on Akaike Information Criteria (AIC). As a sensitivity analysis a linear model was also applied and compared the parameter estimates between two populations. Unlike the sponsor's analyses, data was analyzed separately for adults and pediatrics population. Figure 14 displays the reviewer's analysis result which confirms the sponsor's conclusion of similar dose-response relationship between two populations.

Figure 14. The model-predicted relationship between normalized dose and seizure rate during the maintenance phase. The red line is for adults and the black line is for pediatrics. The dot lines represent 95% prediction interval.



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VENKATESH A BHATTARAM
10/01/2013

XINNING YANG
10/01/2013

YUXIN MEN
10/01/2013