

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-014/S-003**

**CLINICAL PHARMACOLOGY AND**  
**BIOPHARMACEUTICS REVIEW(S)**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

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NDA	21-014/SE5-003
Submission Date	February 6, 2003
Drug Name	Trileptal® (Oxcarbazepine)
Tablet Strengths	Tablets (150, 300, 600 mg)
Sponsor	Novartis
OCPB Reviewers	Joga Gobburu, Ph.D. John Duan, Ph.D.
OCPB Team Leader	Ramana Uppoor, Ph.D.
Submission Type	Response to Approvable Letter for pediatric (4-16 yrs) monotherapy

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## Layout of the Review

The review is arranged into various sections. First, a brief regulatory history is provided (**Regulatory History**) capturing the different interactions between Novartis and FDA since 1/14/2000. Second, an overall summary of the contents of the current review is provided (**Executive Summary**). Third, empirical evidence regarding trileptal monotherapy in pediatrics are presented (**Empirical Findings**). Fourth, findings from the exposure-response modeling performed by the sponsor and the reviewers are elucidated (**Model-Based Findings**). Fifth, the proposed target concentration range (**Target Concentrations**) and Sixth, the proposed dosing recommendations are reviewed (**Dosing Regimen: Sponsor's Proposal**). Finally, the overall OCPB recommendations are provided (**Recommendations**). The previous review conducted by Dr. Vanitha Sekar, OCPB, sponsor proposed labeling and Dr. Machado and Dr. Shen's review of the equivalence testing are provided as **Appendices**.

## Regulatory History

Trileptal is being proposed for treatment of partial seizures, as monotherapy in pediatric patients. Current response from the sponsor is a follow-up to the previous submissions and communications summarized in Table 1.

Table 1. Regulatory history of the current submission for Trileptal monotherapy in pediatric patients (4-16 years old).

Submission (date)	Contents	Action (date)
NDA submission	Studies of adjunctive therapy for adults and children, and monotherapy for adults	Approval (1/14/2000) Letter
sNDA (SE5-003) submission 2/9/2001	"PK bridging" study for pediatric monotherapy	Approvable Issues (12/12/2001) Letter. identified.
Meeting 4/4/2002	Discussion of the sponsor's proposed response	
Telecon 10/11/02	Analysis using single measurement or repeated measurement	
Meeting 11/6/2002	Equivalence of PK/PD relationship	
Response 2/6/2003	Complete responses to Letter (12/12/01)	Under review

Originally, the approval letter (for adjunctive therapy in adults and pediatrics, and monotherapy in adults) dated 01/14/2000 stated that if the plasma oxcarbazepine (OXC) concentrations at a dose giving seizure control in the adjunctive setting in adults and pediatric patients were similar, it would be reasonable to conclude that plasma levels associated with seizure control would be similar in adults and pediatric patients during Trileptal monotherapy (PK-bridging). The letter also stated that dosing regimen to achieve these plasma levels might be determined. Table 2 lists the evidence that led to the previous approvals.

Table 2. Evidence that led to the approval of Trileptal for adjunctive therapy in adult and pediatric patients, and for monotherapy in adult patients.

	Adjunctive	Monotherapy
Adults	Trileptal approved on the basis of "positive" Phase 3 clinical trials (Study OT/PE1)	Trileptal approved on the basis of "positive" Phase 3 clinical trials
Children (4-16 years of age)	Trileptal approved on the basis of "positive" Phase 3 clinical trial (Study 011)	PK-bridging" approach proposed in submission SE5/003

In the submission dated 02/09/2001, the sponsor attempted to bridge the two populations using PK reasoning. In addition, the review team explored if the placebo effect and the relationship between trough 10-monohydroxy derivative (MHD, active moiety) concentrations (Cmin) and seizure reduction, in adults and pediatric patients (in the adjunct therapy trials) were different. The approvable letter dated 12/12/2001 asked the sponsor to (verbatim):

1. justify the construction of a concentration-response curve from the

- pediatric adjunctive study, given that the design was that of a flexible dose regimen,
2. address the question of how to determine the equivalence of any concentration-response relationships determined for pediatric and adult adjunctive therapy,
  3. if the first 2 points can be adequately addressed, address the question of the absolute effective concentration range, and
  4. if this can be done, develop dosing regimens in pediatric patients that will reliably yield these concentrations.

The current review first presents few additional considerations and an evaluation of the sponsor's response to the above issues.

### **Executive Summary**

The current review shows that there is considerable empirical evidence to believe that Trileptal monotherapy could be effective in pediatric patients and to provide reasonable dosing instructions in this population. Results from a randomized, double-blind, trial suggest that Trileptal monotherapy was not significantly different from phenytoin therapy. Another open-label, uncontrolled trial showed that 43% of the patients had at least 50% reduction in seizures upon monotherapy with Trileptal. The placebo response from the current label for adjunctive therapy is about 6% to 9% and drug effect is about 35% in pediatrics.

The PK/PD model developed by the sponsor is reasonably appropriate, although separate models for adults and pediatrics are proposed. A single model for both adults and pediatrics would have been ideal, but considering that the trial designs (adults: fixed dose; pediatrics: flexible dosing) in the two populations are quite different, it might be appropriate to conduct separate analysis. The medical reviewer needs to judge if the flexible dosing was indeed primarily toxicity driven and not effectiveness driven, before more conclusions can be drawn from the modeling.

The non-inferiority testing conducted by the sponsor is not acceptable. The review team conducted additional simulations, based on the adjunctive therapy trials, which suggest that for the same trough concentration the pediatrics might have only 85% of the effect that of adults. Nevertheless, the current label provides similar dosing instructions for pediatrics and adults for adjunctive therapy.

The sponsor proposed initial dosing, dosing increment and maintenance dosing for pediatric monotherapy are acceptable.

## Empirical Findings

### ***Adjunct therapy trials in adults and pediatrics***

Trileptal is currently approved as an anti-epileptic for adjunct use in adults and pediatrics and for monotherapy in adults. Hence, as indicated in the approval letter dated 01/14/2000 to some extent, to derive dosing instructions for monotherapy in pediatrics, the following conditions are satisfied, to avoid a controlled clinical trial:

1. PK in adults and pediatrics are not different.
2. Adjunctive therapy doses in adults and pediatrics are not different.
3. Adjunctive- and mono-therapy doses in adults are not different.
4. If points 1 to 3 are reasonably satisfied, then the dosing in pediatrics for monotherapy should not be different to that for pediatrics adjunctive therapy. Fine-tuning might be needed based on the observed C<sub>min</sub> values after monotherapy in pediatrics.

**PK in adults and pediatrics are not different:** The current labeling suggests that the pharmacokinetics of Trileptal are similar in older children (age >8 yrs) and adults, under adjunctive therapy section. The influence of interacting drugs in adults and pediatrics was also similar based on the examination of C<sub>min</sub> values of adjunctive therapy in both populations.

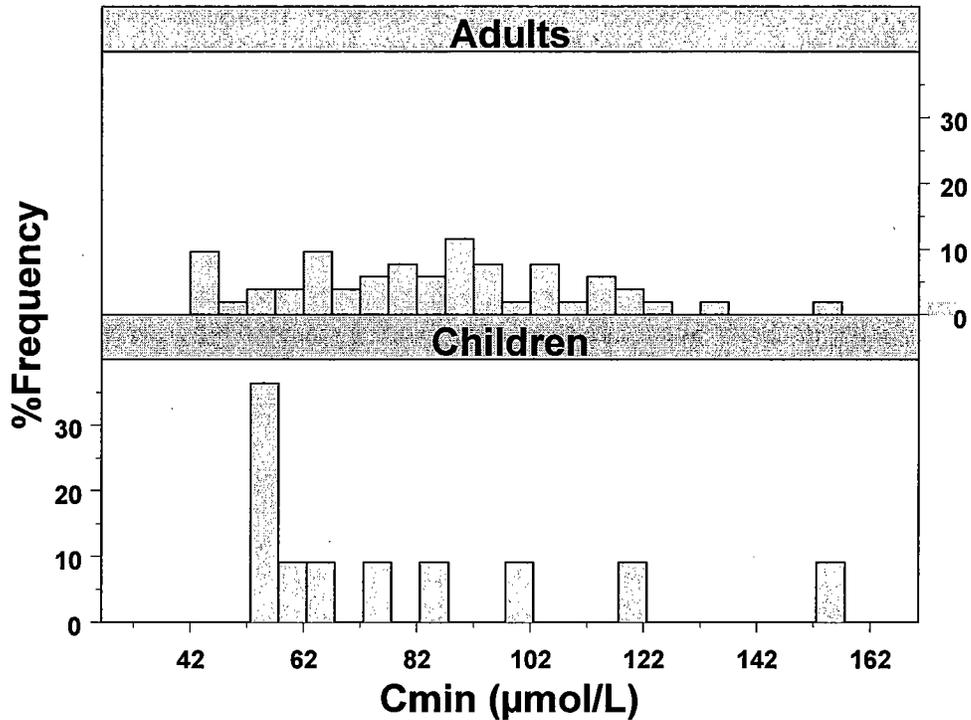
**Adjunctive therapy doses in adults and pediatrics are not different:** The starting dose, for adjunctive therapy, in adults is 600 mg/day and 8-10 mg/kg in pediatric patients. The starting dose in adult patients is equivalent to 8.6 mg/kg, very similar to that in pediatric patients. The highest maintenance dose in adults is 2400 mg/day or 34 mg/day/kg. Projected from this adult dose, the highest maintenance doses are 850 mg/day, 1190 mg/day and 1700 mg/day for 25, 35 and 50kg pediatric patients. These projected doses in pediatric patients are in agreement with the maintenance doses recommended for the adjunctive therapy in the current labeling.

**Adjunctive- and mono-therapy doses in adults are not different:** The current labeling recommends identical starting and maximum doses for adult adjunctive- and mono-therapies. The incremental dosing for adjunctive therapy (weekly increments of 600 mg/day) is not very different when compared to monotherapy (increments of 300 mg/day every third day).

**Adjunctive- and mono-therapy doses in pediatrics should not be different:** Since the aforementioned points are reasonably satisfied, it is a natural consequence to infer that dosing instructions for monotherapy should not be considerably different from those for adjunctive therapy in pediatric patients.

Figure 1 shows the distribution of C<sub>mins</sub> after monotherapy in adults and pediatrics.

Figure 1. Cmin distribution in monotherapy separated by age groups.



### Literature

1. Guerreiro MM et al. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. *Epilepsy Res.* 27:205-213, 1997.

This trial compared OXC monotherapy and phenytoin (PHT) in 193 patients aged 5-18 years with or without secondarily generalized seizures (PS) and generalized tonic-clonic seizures without partial onset (GTCS). After a retrospective baseline assessment, patients were randomized to OXC or PHT in a 1:1 ratio. The double-blind treatment phase comprised two periods: an 8-week flexible titration period; followed by 48 weeks maintenance treatment. During the titration phase, treatment began with 150 mg OXC or 50 mg PHT and increased gradually. During the maintenance phase, patients were to be on a t.i.d. regimen with 450-2400 mg/day OXC or 150-800 mg/day PHT. The effectiveness analyses showed that there were no statistically significant differences between OXC and PHT groups. Forty-nine (61%) patients in the OXC group and 46 (60%) in the PHT group were seizure-free during the maintenance period. Relevant results are presented in Table 3. Results from another publication (*Bill et al, A double-blind*

controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy, 27:195-204, 1997) reporting the results from a similar trial in adults are presented in Table 4, for comparison. Since the indication is not directly related to effectiveness in adults, more information from this adult trial are not presented here.

Table 3. Seizure frequency in pediatric patients in the monotherapy trial (Guerreiro et al).

	Baseline (N=97)	Maintenance Phase (N=81)
Mean/Median Seizure Frequency	0.68/0.25 per week	0.07/0 per week
Patients with 1 to 15 seizures	85 (88%) <sup>a</sup>	29 (36%)
Patients with zero seizures	0 (0%)	49 (61%)

<sup>a</sup> Patients with 2 to 10 seizures.

Table 4. Seizure frequency in adult patients in the monotherapy trial (Bill et al).

	Baseline (N=143)	Maintenance Phase (N=118)
Mean/Median Seizure Frequency	0.98/0.20 per week	0.08/0 per week
Patients with 1 to 15 seizures	102 (71%) <sup>a</sup>	43 (36%)
Patients with zero seizures	0 (0%)	113 (96%)

<sup>a</sup> Patients with 2 to 10 seizures.

Although such trials with no placebo control are not sufficient for approval, the results from the Guerreiro trial still indicate that Trileptal seems to be effective as monotherapy in this population. Further, the proportion of patients with 1 to about 15 seizures in the maintenance phase seems to be similar for adult and pediatric patients (36%). The end point used in these trials is different from the usual endpoint for anti-epileptic trials submitted to the Agency, which is the percentage of patients having a 50% reduction in the seizure rate for monotherapy trials. Because about 60% of the pediatric patients had a seizure-free 48 week maintenance phase, it might not be unreasonable to infer that the proportion of patients with 50% reduction would be at the least 60%. The same arguments also apply to the PHT group and PHT monotherapy is currently widely used to treat childhood epilepsy. In the primary effectiveness analysis (proportion of seizure-free patients who had at least one seizure assessment during the maintenance phase) no significant difference was seen between the OXC and PHT groups (p=0.91). This trial suggests that OXC is efficacious as first-line treatment in children and adolescents with PS and GTCS.

Although in this trial MHD concentration data were collected, primarily for assessing compliance, no results were reported. The mean daily OXC maintenance dose was 672.2 mg (range: 300-1350 mg). Guerreiro trial employed a flat starting dose of 150 mg in all patients, irrespective of their body weights. The lowest proposed initial monotherapy dose of Trileptal, by the sponsor, is 8 mg/kg/day. This translates to 128 mg and 576 mg in 16 kg and 72 kg pediatric patients (smallest and largest body weights in Guerreiro et al trial). However, interpreting the maintenance dose on a per kg basis is confounded by the responsiveness of the patients i.e., it might not be appropriate to conclude that the 300 mg maintenance dose was used in the patient with the lowest body weight.

However: 1) the medical reviewer needs to verify if the patient population and endpoints are reasonable and 2) the general caveats when interpreting published findings apply.

2. Gaily E et al. *Oxcarbazepine in the treatment of early childhood epilepsy. J. Child Neurol.* **12**:496-498, 1997.

53 children under 7 years of age were treated with OXC. Forty-three of these children had been intractable to one or more antiepileptic drugs, including carbamazepine, previously. Of these children, upon OXC treatment 13% became seizure free and 43% had a reduction of seizures of at least 50%.

3. Serdaroglu G et al. *Oxcarbazepine in the treatment of childhood epilepsy. Pediatr. Neurol.* **28**:37-41, 2003.

In this study, OXC was begun as monotherapy to evaluate the effectiveness and safety of the drug. Forty-two patients (19 females, 23 males) with partial or generalized epilepsy more than 4 years of age were included (mean age,  $11.9 \pm 3.4$  years). The mean age at epilepsy onset was  $8.9 \pm 4$  years. OXC dose was begun at 10 mg/kg/day twice daily and increased to 30 mg/kg/day at the end of the second week. Patients with inadequate seizure control even with the dose of 45 mg/kg/day or intolerable side effects were excluded. At the sixth month, 35 of the patients (87.5%) were seizure free (91.7% of the generalized epilepsy patients and 81.2% of the partial epilepsy patients).

4. Schmidt D et al. *Recommendations on the clinical use of oxcarbazepine in the treatment of epilepsy: a consensus view. Acta. Neurol. Scand.* **104**:167-170, 2001.

The authors (Epilepsy Research Group, Berlin) refer to the above publications and others in adults as well as the proceedings at two conferences in Oxford (August, 2000) and Copenhagen (October, 2000), to infer that OXC is a valuable antiepileptic drug for the treatment of adults and children with partial onset seizures both in initial monotherapy, for conversion to monotherapy and as adjunctive therapy. The clinically recommended titration scheme for all forms of

therapy in adults is to start with 150 mg/day at night and to increase by 150 mg/day every second day until a target dose of 900–1200 mg/day is reached. If necessary, one can go faster and start with up to 600 mg/day and titrate with weekly increments of up to 600 mg/day. In children, treatment can be initiated with 8–10 mg/kg/day body weight in two to three divided doses. Dosage can be increased by 8–10 mg/kg/day in weekly increments, if necessary for seizure control.

Critical details on what the considerations were for arriving at the recommended dosing are not provided. Interestingly, the initial dosing is identical to the one proposed by the sponsor. No upper dose limit was specified for monotherapy in pediatric patients.

### **Model-Based Findings: Sponsor’s Methods and Results**

The modeling efforts performed by the sponsor in support of the claim are presented below.

#### ***Dose-Cmin Relationship***

Pharmacokinetic model building had been done for Study 011 (pediatrics / adjunctive therapy) as part of the population pharmacokinetic analysis. It was also determined that apparent clearance was approximately proportional to body surface area. It was determined that each of three AEDs, carbamazepine, phenytoin, and phenobarbital, increased the apparent clearance of MHD by about 30%. These three AEDs are referred to herein as interacting AEDs. Empirical modeling of Cmin versus dose identified the following model for both Studies 011 and OT/PE1:

$$\log(C_{min}) = \beta_0 + \beta_1 \cdot AED + \beta_2 \cdot \log(\text{dose in mg/m}^2/\text{day}) + \varepsilon$$

where AED was an indicator variable for the presence of one of the three interacting AEDs. The parameter estimates are shown in Table 5.

Table 5. Final parameter estimates of Dose/PK model for study OT/PE1 (adults) and study 011 (pediatrics).

Study	Outlier	$\beta_0 \pm \text{s.e.}$	$\beta_1 \pm \text{s.e.}$	$\beta_2 \pm \text{s.e.}$
OT/PE1	With	-2.10 ± 0.41	-0.717 ± 0.213	0.981 ± 0.057
OT/PE1	W/out	-2.61 ± 0.30	-0.686 ± 0.156	1.06 ± 0.04
011	With	-2.90 ± 0.81	-0.313 ± 0.122	1.05 ± 0.12
011	W/out	-2.22 ± 0.60	-0.297 ± 0.089	0.953 ± 0.086

### ***Cmin-Seizure Reduction Relationship***

The sponsor used data from 464 adults from Study OT/PE1 and 16 adults from Study 011 to develop the PK/PD model for adults. Also, the sponsor used data from 221 pediatric patients from Study 011 and 9 pediatric patients from Study OT/PE1 to develop the PK/PD model for pediatric patients. These were studies of Trileptal as adjunctive treatment. The effectiveness measure was percent change in seizure frequency, namely,  $100*(N_{28}-N_0)/N_0$ , where  $N_{28}$  is the number of seizures that occurred in 28 days on the maintenance dose, and  $N_0$  is the baseline seizure frequency. Percent change from baseline was denoted as PCB. PCB takes the baseline seizure frequency into consideration. Each patient will have one PCB. The MHD exposure measure was  $C_{min}$ .

The empirical PK/PD model for adults was determined as:

$$\log(\text{PCB} + 110) = \beta_{0,A} + \beta_{1,A} * C_{min} + \beta_{2,A} * C_{min} * [\log(\text{baseline seizure freq.}) - 2.5] + \varepsilon_A \quad (1)$$

The empirical model for pediatric patients was:

$$\log(\text{PCB} + 110) = \beta_{0,P} + \beta_{1,P} * C_{min} + \varepsilon_P \quad (2)$$

The parameters,  $\beta_{0,A}$ ,  $\beta_{1,A}$  (adults) and  $\beta_{0,P}$ ,  $\beta_{1,P}$  (pediatric patients) are, respectively, intercepts and slopes, and the  $\beta_{2,A}$  is the coefficient for the interaction between baseline frequency and  $C_{min}$  (adults). The error terms,  $\varepsilon_A$ ,  $\varepsilon_P$ , are assumed independently normally distributed with zero means, and variances  $\sigma_A^2$ ,  $\sigma_P^2$ , respectively. The parameters estimated by the sponsor are shown in the Table 6.

Table 6. Final parameter estimates of the models presented in equations 1 and 2.

Parameter estimates (adults)	Adults	Parameter estimates (peds)	Pediatrics
$\beta_{0,A} \pm \text{s.e.}$	4.54±0.04	$\beta_{0,P} \pm \text{s.e.}$	4.55±0.06
$\beta_{1,A} \pm \text{s.e.}$	-0.0099±0.0011	$\beta_{1,P} \pm \text{s.e.}$	-0.0072±0.0015
$\beta_{2,A} \pm \text{s.e.}$	0.0031±0.0008	-	-
$\sigma_A$	0.6777	$\sigma_P$	0.7417
$R^2$	0.170	$R^2$	0.089

Baseline seizure frequency was an important covariate appearing in the model (equation 1) in an interaction term with  $C_{min}$  ( $p < 0.001$ ). The interpretation of this is that the dependence of seizure response on  $C_{min}$  depended on the

patient's baseline seizure frequency. Patients with higher baseline seizure frequencies needed higher concentrations to achieve a given percent seizure reduction. The  $\beta_{2,A}$  is the coefficient for the interaction between baseline frequency and  $C_{min}$  (adults) is on top of the correction for baseline in calculating PCB.

For Study 011, baseline seizure frequency was not significant ( $p > 0.3$ ) as a predictor of seizure response.

### ***Propriety of PK/PD analysis***

Examination of the possibility of influence of pharmacodynamics on pharmacokinetics. The pharmacological activity of oxcarbazepine is primarily exerted through the pharmacologically active metabolite, the 10-monohydroxy derivative (MHD). As evidence against any reverse causal influence of pharmacodynamics on pharmacokinetics, in both the flexible dose Study 011 and the fixed dose study OTPEI, three relevant features of MHD pharmacokinetics may be invoked.

**Dose linearity across a wide range of doses and subject groups.** MHD shows dose-linear steady-state pharmacokinetics at doses ranging from 300 mg/day to 2400 mg/day. Dose-linearity at steady state could be consistently demonstrated for both healthy subjects and patients with epilepsy, and in the latter population for both mono therapy and adjunct therapy.

**Lack of influence of baseline disease severity on pharmacokinetics.** Baseline seizure frequency was considered as a possible covariate for apparent clearance (CL/f) in the population pharmacokinetic modeling of Study 011. It was found to be not significant ( $p = 0.6$ ). For Study OT/PE1, baseline seizure frequency was explored as a potential predictor of the average, steady-state trough, i.e.,  $C_{min}$ . It was found to be nonsignificant ( $p > 0.7$ ).

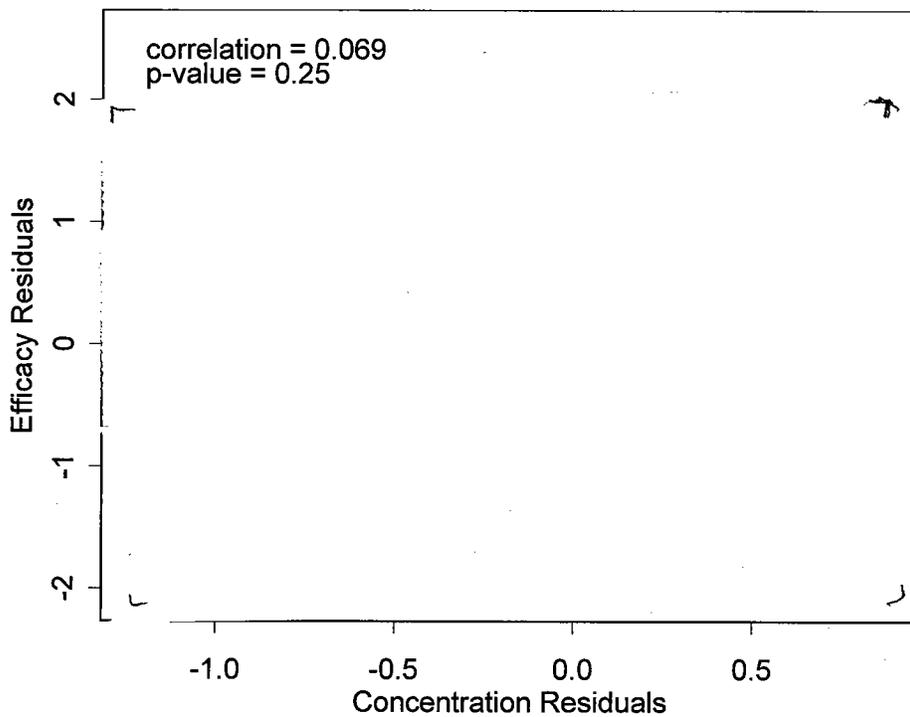
**Stability over time of pharmacokinetics.** In the population pharmacokinetic analysis of Study 011, Visit was also considered as a potential covariate and was found not to be significant ( $p = 0.08$ ). Thus, there was no change in MHD pharmacokinetics over time during maintenance treatment. For Study OT/PE1, Visit was explored as a potential predictor of observed, steady-state troughs, using a repeated-measures analysis. It was found to be nonsignificant ( $p > 0.2$ ). There was also a stable treatment effect (relative to placebo) over time during the entire maintenance period of the study. Therefore, it cannot be ruled out that the pharmacokinetic stability was influenced by the stability of the therapeutic response. Nonetheless, it is unlikely that pharmacodynamic responses, even in a flexible-dose study, would influence MHD pharmacokinetics.

**Investigation of confounding factors.** The sponsor stated that questions about the propriety of those inferences are essentially questions about confounding by unobserved covariates. Since patients were not randomized to concentration in either study, the potentially unobserved variables may have simultaneously

influenced both concentration and response. This is a phenomenon called confounding. For both studies, evidence is provided to support the absence or unimportance of confounding interactions between pharmacokinetics and pharmacodynamics. Evidence against confounding takes the following form.

Individual variation in dose-versus-concentration was uncorrelated with individual variation in concentration-versus-effectiveness. The correlation was examined between two sets of residuals: those from a regression of C<sub>min</sub> on dose and those from a regression of effectiveness on C<sub>min</sub>. Spearman correlation coefficients were computed because of non-gaussian distributions. Absence of significant correlation between those two sets of residuals supported the claim that variation in concentration given dose is independent of variation in response given concentration, as shown in Figure 2 for study OT/PE1. Similar results were obtained for study 011.

Figure 2. Scatterplots of the two sets of residuals for Study OT/PE1. Correlations could be assessed for patients on active drug only.



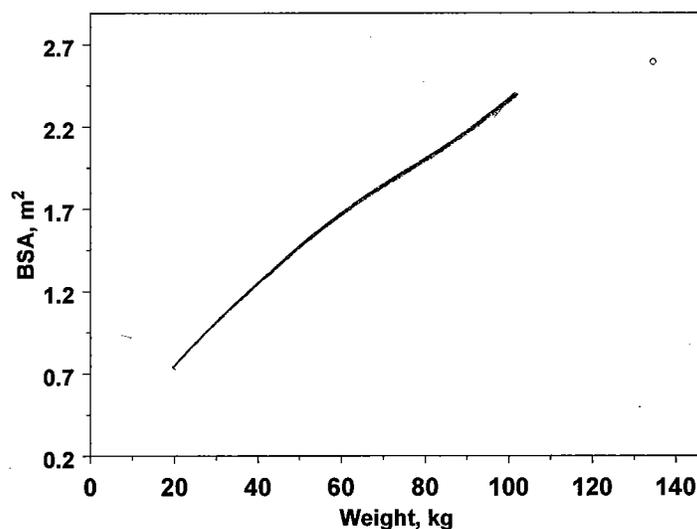
**Equivalence of PK/PD relationships in adults and pediatric patients.** Dr. Stella Machado and Dr. Meiyu Shen, Quantitative Methods Research Staff (QMRS), Office of Biostatistics, reviewed the sponsor's analysis. Their review is attached in Appendix B.

## Model-Based Findings: Reviewer's Comments

### *Dose-C<sub>min</sub> Relationship*

The dose-C<sub>min</sub> relationship is consistent with the known pharmacokinetics of MHD and population PK analysis conducted by the sponsor as part of the original submission. An important aspect to note is that the exposure is related to body surface area (BSA), but the dosing currently is provided as per kg. The relationship between BSA and body weight is curvilinear as shown in Figure 3, in patients with less than 18 years of age. Hence, per kg dosing is bound to result in some bias depending on the BSA and body weight.

Figure 3. Relationship between bodyweight and BSA in patients less than 18 years of age. All patients from studies OT/PE1 and 011 were included.



### *C<sub>min</sub>-Seizure Reduction Relationship*

Dr. Machado and Dr. Shen, and we find the sponsor's modeling assumptions to be generally reasonable. The data are extremely skewed and a log transformation helps to obtain some symmetry of distribution; this is needed to permit interpretation of hypothesis tests on the parameters of the prediction equations. The results obtained by the sponsor were confirmed by Dr. Machado and Dr. Shen, using the data set "adjunct". An important finding was the large between-patient variability in response, giving poor fit as evidenced by R<sup>2</sup> values between 0.09 and 0.17.

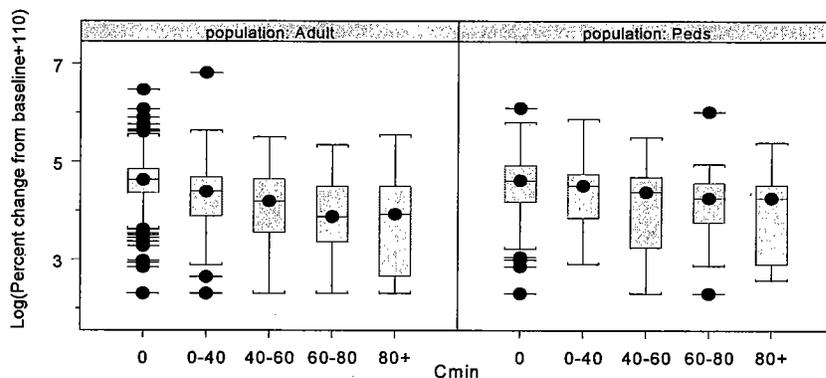
Previous review by Dr. Sekar (see Appendix) reported that the slope of the relationship between C<sub>min</sub> and seizure frequency was not different for adults and pediatrics. The slope for adults was estimated to be  $-0.33$  seizures/uMol/L and for pediatrics was estimated to be  $-0.251$  seizures/uMol/L. In spite of using all

the data collected (i.e., seizures at multiple visits) both the slopes were estimated with large standard errors of 95% and 130% and thus, concluded that there is a weak relationship, if at all there is one.

Glauser et al (Adjunctive therapy with oxcarbazepine in children with partial seizures, *Neurology*, 54:2237–2244, 2000) report the results of Study 011. Interestingly, the authors report that a regression analysis of the percentage change in seizure frequency with baseline seizure frequency as a covariate demonstrated that both treatment groups and minimum plasma MHD concentration during steady state (Cmin) were significantly correlated with reduction in seizure frequency ( $p < 0.001$ ). However, Cmin after incorporation of treatment group did not provide additional explanatory value for predicting seizure frequency. This is contrary to what the sponsor has presented in the response to the Agency's approvable letter and what the reviewers found.

Figure 4 shows box plots comparing the (geometric) means and inter-quartile ranges of the log(PCB+110) values for pediatric and adult patients. The average response to treatment for pediatric patients is less steep than that for adults. This could be partly due to different study design. Also, the range of log(PCB+110) values for pediatric and adult patients for each Cmin bin seems comparable.

Figure 4. Distribution of Log(PCB+110) at various ranges of Cmins for adults and pediatrics.



### **Propriety of PK/PD analysis**

#### *Justification of the PK/PD analysis*

For Study 011, titration was to fixed dose levels. Dose adjustments, when needed, were almost exclusively due to safety, not effectiveness. The medical reviewer needs to assess if the sponsor's claim is reasonable.

The sponsor provided reasonably convincing arguments that the Cmin and the effect are not driven by a third unknown intrinsic or extrinsic factor.

The sponsor conducted extensive analyses to demonstrate that the relationship between  $C_{min}$  and seizure reduction is not confounded by a common covariate. This was not *per se* the concern of the Agency. The Agency's concern was to evaluate the causal relationship between  $C_{min}$  and effectiveness i.e., is the effectiveness driving  $C_{min}$  or  $C_{min}$  driving the effectiveness? This question cannot simply be answered without a controlled clinical trial that randomizes  $C_{min}$ s rather than dose. However, there is abundant empirical and mechanistic evidence that effectiveness driving  $C_{min}$ s is unlikely. All the drug interaction studies and the special population studies evaluate pharmacokinetics only. The labeling for Trileptal lists the results from various drug interaction studies and suggests that lower phenytoin doses should be used when using with Trileptal. Such a recommendation has to come only with the belief that concentrations are driving the effect, not the other way.

#### *Equivalence of PK/PD relationships in adults and pediatric patients*

A complete review of this part of the submission (by Dr. Machado and Dr. Shen) is provided in Appendix A of this review. The relevant findings are presented below. To demonstrate similarity of two concentration-response relationships, it should be shown not only that the relationships have the same shape (eg, straight lines, or  $e_{max}$  curves), but also that the predicted responses to a given concentration achieved by the two relationships are similar, over the range of concentrations likely to be experienced. Independently it was shown that the  $C_{min}$ s in adults and pediatrics are similar. Critically also, the patient-to-patient variability evidenced in the substantial lack of fit of the models was not taken into account. Dr. Machado and Dr. Shen consider it more reasonable to assess equivalence of the responses between adult and pediatric populations, rather than noninferiority which is one-sided.

The sponsor stated that the data are sufficient to demonstrate that pediatric patients on adjunctive therapy with oxcarbazepine preserved at least 0.38 of the effect in adults (with baseline seizure frequency of 12/month) and varied from 0.32 to 0.45 for different assumed adult baseline seizure rates. In addition, the sponsor said that the predicted reduction for pediatric patients was insensitive to assumptions about adult baseline frequency, and the seizure frequencies predicted to be attained on maintenance therapy were generally comparable for adults and pediatric patients. Specifically, the sponsor concluded that "the noninferiority analysis demonstrates the equivalence of the PK/Effectiveness relationships for adults and patients on adjunctive therapy" and that "This result validates the premise of the PK-bridging approach, and allows doses for pediatric patients on monotherapy to be recommended as doses that achieve  $C_{min}$  values equal to those achieved by adults at effective monotherapy doses".

The sponsor compared predictions of percent change from baseline on seizure frequency at various  $C_{min}$  values; these are shown in Table 7. The computations were done by bootstrapping. This was concluded, by QMRS reviewers, as an

appropriate approach.

Table 7. Comparison of the model-predicted percent change from baseline in seizure frequency between adult and pediatric patients.

Cmin (umol/L)	Percent change from baseline		Difference: Pediatric patients-Adults	
	Pediatric patients	Adults	Estimated difference (% relative to adults)	95% Confidence interval for difference
0.0	-16.7	-14.1	-2.5 (-17.9%)	(-15.0, 9.9)
17.0	-27.2	-29.5	2.3 (7.8%)	(-6.5, 11.1)
40.8	-40.0	-47.0	7.0 (14.8%)	(-2.5, 16.4)
68.0	-52.2	-62.3	10.1 (16.2%)	(-1.9, 22.1)
73.8	-54.5	-65.1	10.6 (16.2%)	(-1.5, 22.6)

The sponsor concluded that all 95% confidence intervals for the differences between adults and pediatric patients contained zero, implying that the differences were not statistically significant. The QMRS review notes that: (i) This statement does not establish equivalence. (ii) These Cmin concentrations were chosen by the sponsor. See below for some predictions requested by the Medical Reviewer for Cmin values 59.1  $\mu\text{Mol/L}$  and 112  $\mu\text{Mol/L}$ .

A requirement before PK-bridging is to demonstrate similarity of the concentration-response relationships in the adult and the pediatric populations. Similarity is demonstrated statistically by equivalence testing, or non-inferiority testing which is one-sided equivalence testing. The "goal-posts" or non-inferiority margin,  $f$ , are set in advance by the agency. A common example, used for evaluate pharmacokinetics of generic and innovator products, is to attempt to establish that the ratio of the average response measure in one population versus that in another lies within the interval 0.8 to 1.25, with high probability.

Via simulations, using the sponsor's models, QMRS reviewers conducted an equivalence analysis of the effectiveness responses for adults and pediatric patients at the same concentrations, for a range of concentrations. It appears (Table 7 above) that the sponsor pursued similar idea, but not as far as they did.

QMRS reviewers fit the regression models and obtained the same results as the sponsor, however, omitting the interaction term between baseline seizure and slope for adults. The following parameter estimates were found:

Table 8. Parameter estimates obtained using the reviewer's model.

Population	N	$\beta_0$ (s.e.)	$\beta_1$ (s.e.)	$\sigma$	$R^2$
Adults	480	4.55036 (0.04169)	-0.01028 (0.00114)	0.68698	0.14
Peds	230	4.54554 (0.06259)	-0.007164 (0.001513)	0.74166	0.09

To examine the similarity of the PK/effectiveness relationships in the two populations, for various values of Cmin, 2000 pairs of independent trials (one for 480 adults and one for 230 pediatric patients) were simulated. For each pair, the ratio of the (geometric) mean PCB for pediatrics to the (geometric) mean PCB for adults was calculated. The percentiles of the 2000 average PCB's for adults, the percentiles of the 2000 average PCB's for pediatric patients, and the percentiles of the 2000 ratios were obtained.

The results are shown in Table 9. Columns 2 and 3 give the Sponsor's results, directly from Table 7 above. Columns 4 and 5 give the simulated median PCB's for pediatric and adult patients, and columns 6,7 and 8 give the 50<sup>th</sup>, 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles of the distribution of ratios. Included are results for 2 additional Cmin values, 59.1 and 112. Apart from the similarity of the placebo responses, the average response expected for pediatrics is 82% to 88% that of adults. Confidence intervals are a little wider for lower concentrations than higher ones. For Cmin = 40.8, the average response ratio is 83% with 95% confidence interval 51% to 119%. Clinical judgement is required to interpret the importance of these results.

Table 9. Effectiveness responses and equivalence assessment for selected Cmin values.

Cmin	PCB*		PCB**		Ratio		
	Peds	Adults	Peds	Adults	Median	2.5%	97.5%
0	-16.7	-14.1	-15.7	-15.4	1.037	-0.01	3.458
17	-27.2	-29.5	-26.6	-30.4	0.875	0.377	1.462
40.8	-40	-47	-39.6	-47.9	0.828	0.509	1.185
59.1			-48.1	-58.5	0.828	0.558	1.121
68	-52.2	-62.3	-51.8	-62.9	0.822	0.544	1.085
73.8	-54.5	-65.1	-54.5	-65.8	0.829	0.551	1.084
112			-68	-80.1	0.848	0.598	1.047

\* predicted by the sponsor (Table 6); \*\* predicted using the same models for both populations, via the simulations by QMRS reviewers.

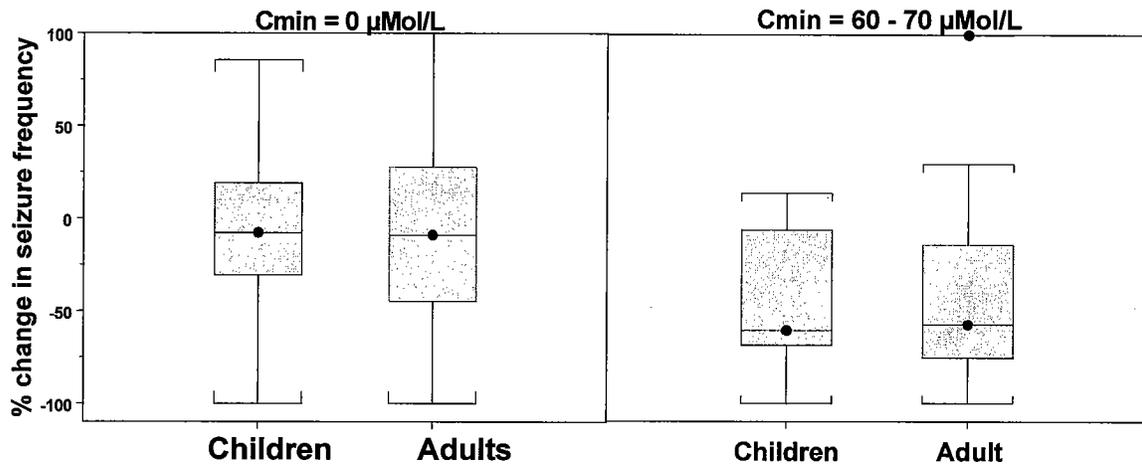
Table 10 shows the estimated increased Cmin levels that would be needed for pediatric patients to achieve response levels closely similar to those for the adult patients. Whether these values are useful targets depends on evaluation of the adverse event profile in pediatric patients. Also, more importantly, the simulations assume that the model derived from titration dose study (study 011)

adequately estimates the Cmin-PCB relationship. The empirical evidence presented earlier is not in agreement with this finding of a need to target different concentration for similar effects.

Table 10. Cmin levels for pediatric and adults patients to achieve similar responses.

Cmin		PCB		Ratio		
Peds	Adults	Peds	Adults	Mean	2.5%	97.5%
24	17	-30.5	-30.5	1.000	0.494	1.620
58	40.8	-47.7	-47.8	1.004	0.644	1.374
84	59.1	-58.6	-58.4	1.002	0.696	1.316
98	68	-63.2	-63.0	1.006	0.696	1.294
107	73.8	-65.8	-65.8	1.000	0.713	1.262
161	112	-79.9	-80.0	1.002	0.744	1.200

To compare the responses between adults and children at similar Cmin's in adjunctive therapy, box plots was generated. As shown in the following figure, at Cmin=0 (placebo) and Cmin ranging from 60-70  $\mu\text{mol/L}$  (in the identified target Cmin range in adult monotherapy), the responses (% change in seizure frequency) are comparable between adults and children.



### Target Concentrations: Sponsor's Proposal

In the previous submitted sNDA, the median Cmin values associated with the doses 1200 mg/day and 2400 mg/day for adults on monotherapy were identified as plasma levels associated with seizure control in adults during Trileptal monotherapy. The Agency requested additional justification of the proposed dosing regimen for children in regard of using the established PK/PD model to propose a suitable dosing regimen in children. Simulations should be performed to assess the distribution of predicted response using the proposed dosing regimen.

PK/Effectiveness models were fitted to data from adults and pediatric patients on mono therapy. The data come from three double-blind, placebo-controlled monotherapy studies: 004, 006, and 025. The models that have been found suitable for adjunctive therapy were refitted to adults and pediatric patients on monotherapy, starting with the following model.

$$\log(\text{percent change} + 110) = \beta_0 + \beta_1 * C_{\text{min}} + \beta_2 * C_{\text{min}} * [\log(\text{baseline seizure frequency}) - 2.5] + \epsilon$$

For both adults and pediatric patients on monotherapy, the term involving baseline seizure frequency was not found to be significant. Results are summarized in Table 11.

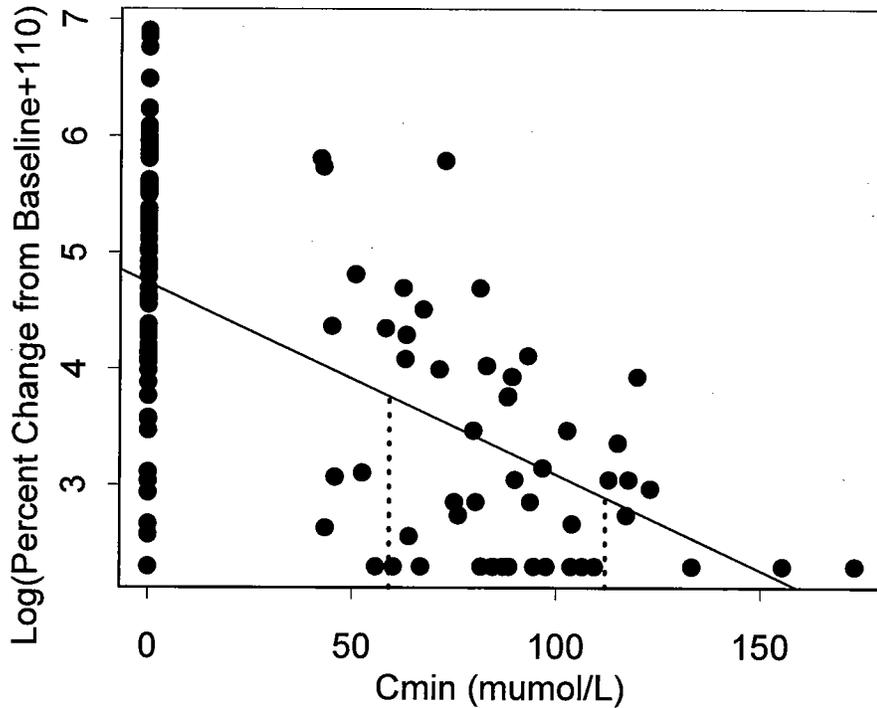
Table 11. C<sub>min</sub>-Seizure reduction models developed using the monotherapy data in adult and pediatric patients.

Group	$\beta_0 \pm \text{SE}$	$\beta_1 \pm \text{SE}$ (p-value)	$\beta_2 \pm \text{SE}$ (p-value)	Residual standard deviation
Adults (full model) n=132	4.73 $\pm 0.12$	-0.0156 $\pm 0.0031$ (0.0000)	-0.0007 $\pm 0.0018$ (0.7)	1.11
Adults (reduced model) n=132	4.74 $\pm 0.12$	-0.0165 $\pm 0.0021$ (0.0000)		1.10
Pediatric (full model) n=30	4.03 $\pm 0.36$	-0.0116 $\pm 0.0068$ (0.10)	0.0008 $\pm 0.0033$ (0.8)	1.59
Pediatric (reduced model) n=30	4.02 $\pm 0.35$	-0.0115 $\pm 0.0066$ (0.09)		1.56

The reduced model without the baseline seizure frequency term was accepted as the model for both adults and children. For pediatric patients even the dependence on C<sub>min</sub> was not significant (p-value=0.09). The data set was composed of only 30 patients. The inferred difference between  $\beta_1$  for adults and pediatric patients was not statistically significant (p=0.5). Figure 6 displays a plot of log(percent change from baseline in seizure frequency + 110) versus C<sub>min</sub> for adults on monotherapy in Studies 004 and 025. The fit of the linear regression model is superimposed. The two vertical dashed lines show the position of the two median C<sub>min</sub> values associated with doses of 1200 mg/day and 2400 mg/day: 59.1 and 112  $\mu\text{mol/L}$ , respectively.

Figure 6. Log (percent change from baseline in seizure frequency + 110) versus

Cmin for adults on monotherapy in Studies 004 and 025. The fit of the linear regression model is superimposed.

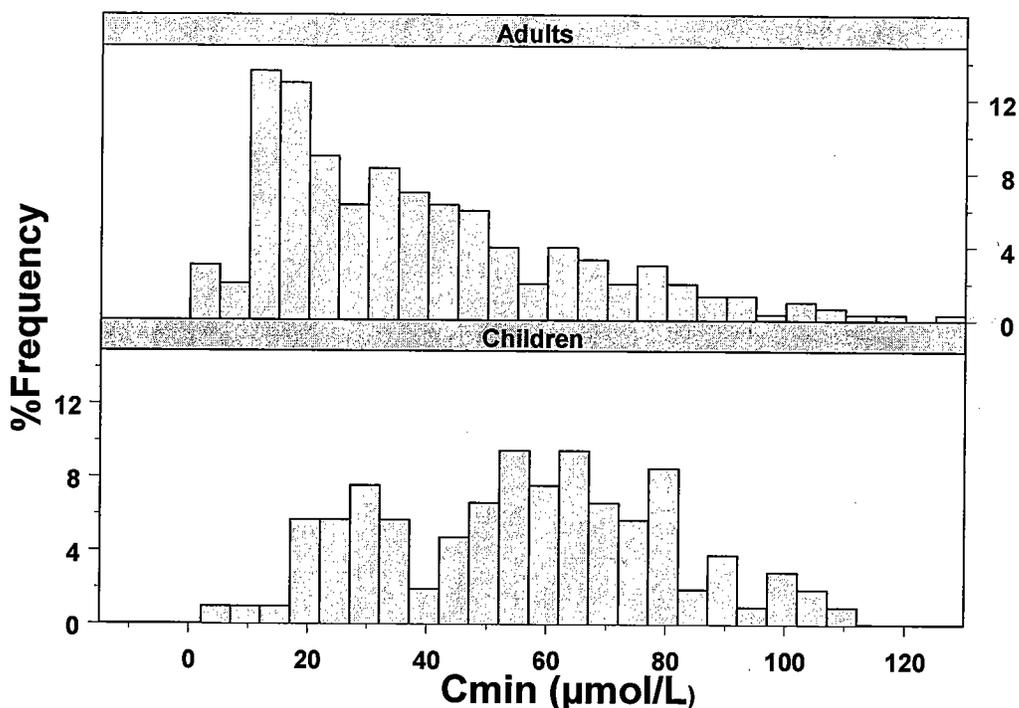


The sponsor states that 59.1 and 112  $\mu\text{mol/L}$  are their choices as target concentrations for seizure control. These concentrations are near the low and high end achieved by non-placebo patients in the two monotherapy studies. And both provide substantial average reductions in seizure frequency relative to placebo. The values of the ordinate on the linear regression curve for placebo, 59.1  $\mu\text{mol/L}$ , and 112  $\mu\text{mol/L}$  are 4.74, 3.76, and 2.89, respectively. These correspond to percent changes from baseline in seizure frequency of +4.2%, -67%, and -92%, respectively.

#### Target Concentrations: Reviewer's Comments

Cmin values reached in adjunctive therapy and monotherapy both in adults and in children are investigated. Figure 7 shows the Cmin distribution in adjunctive therapy OT/PE1 and 011 separated by age group. As can be seen, there is limited experience for Cmin to be above 110  $\mu\text{mol/L}$  in either adults or children.

Figure 7. Distribution of Cmins in adults and pediatrics after adjunctive therapy.



Compared to adjunctive therapy, the Cmin values in monotherapy seem higher, as shown in Figure 1 (see Empirical Findings section above). This could be explained by the dose and Cmin relationship. Empirical modeling of Cmin versus dose identified the following model for both Studies 011 and OT/PE1:

$$\log(\text{Cmin}) = \beta_0 + \beta_1 \cdot \text{Interact} + \beta_2 \cdot \log(\text{dose in mg/m}^2/\text{day}) + \varepsilon$$

where Interact was an indicator variable (carbamazepine, phenytoin, and phenobarbital) for the presence of one of the three interacting AEDs. Parameter estimates are displayed in Table 12.

Table 12. Parameter estimates for Dose/PK models

Study (N)	$\beta_0 \pm \text{SE}$	$\beta_1 \pm \text{SE}$	$\beta_2 \pm \text{SE}$
OT/PE1 (284)	-2.61±0.30	-0.686±0.155	1.06±0.04
011 (107)	-2.22±0.60	-0.297±0.089	0.953±0.086

The coefficients of the interaction term are negative, indicating the co-administered AEDs decrease Cmin, by increasing the clearance by about 30%. The lower Cmin values observed in adjunctive therapy compared to monotherapy

could be due to the drug interactions between trileptal and AEDs.

The above arguments suggest that the maintenance dose for monotherapy in children should be more or less similar to that in adjunctive therapy. Dr. Machado and Dr. Shen reported that, although the ratio of mean effect in pediatrics over adults is about 0.85, toxicity also needs to be considered to decide appropriate dosing recommendations. There are several drug related toxicities such as dizziness, vomiting, nausea, ataxia, somnolence reported for Trileptal. Additionally, given the large amount of patient-to-patient variability and the typical clinical practice to titrate the dosing for anti-epileptic drugs in general, the sponsor's target concentrations are not unreasonable.

### Dosing Regimen: Sponsor's Proposal

Trileptal should be initiated at a dose of 8-10 mg/kg/day given in a BID regimen. If clinically indicated, the dose may be increased by 5 mg/kg/day every third day to achieve the desired clinical response. Based on extrapolation from adult monotherapy studies, daily doses of approximately 20-50 mg/kg/day as shown in the table below achieve plasma concentrations in the effective range. In clinical studies, pediatric patients have received monotherapy up to 60/mg/kg/day.

Table 13 displays recommended maintenance doses for pediatric patients by body weight. These were determined from the population pharmacokinetic model fitted to the pooled pediatric monotherapy data, as reported in the sNDA. The exact doses in mg/day were determined as those that would achieve the target concentrations on average. For the lower target concentrations, doses were rounded up to the nearest multiple of 300 mg/day; and for the upper target concentration, doses were rounded down to the nearest multiple of 300 mg/day. These daily doses correspond to bid dosing in multiples of 150 mg, the smallest tablet strength available. The recommended doses provided differ slightly from those provided in the sNDA because of the rounding.

Table 13. Sponsor recommended maintenance doses for pediatric patients for monotherapy.

Weight (kg)	MHD plasma levels during monotherapy: C <sub>min</sub> (µmol/L)			
	59.1 (median concentration at 1200 mg/day in adults)		112 (median concentration at 2400 mg/day in adults)	
	Dose (mg/day)	Dose (mg/kg/day)	Dose (mg/day)	Dose (mg/kg/day)
20	600	30.0	900	45.0
25	900	36.0	1200	48.0
30	900	30.0	1200	40.0
35	900	25.7	1500	42.9
40	900	22.5	1500	37.5
45	1200	26.7	1500	33.3
50	1200	24.0	1800	36.0

55	1200	21.8	1800	32.7
60	1200	20.0	2100	35.0
65	1200	18.5	2100	32.3
70	1500	21.4	2100	30.0

### Dosing Regimen: Reviewer's Comments

Table 14 shows the initial doses. As in adults, the proposed initial dose for children monotherapy is the same as in adjunctive therapy.

Table 14 Initial Dose

Initial	Adjunctive	Monotherapy
<b>Adults</b>	600 mg/day	600 mg/day
<b>Children</b>	8-10 mg/kg not exceed 600 mg/day	8-10 mg/kg/day

Table 15 gives the dose increment during titration. Although the dose increment for children adjunctive therapy is not indicated in the currently labeling, the proposed dose increment is similar to that for adults. In adults, the dose increment in monotherapy is half of that in adjunctive therapy, which is the same as initial therapy. Similarly, in children, the dose increment in monotherapy is proposed to be half of the initial therapy.

Table 15. Dose Increment

Increment	Adjunctive	Monotherapy
<b>Adults</b>	< 600 mg/day, weekly	300 mg/day every third day
<b>Children</b>	No specific instructions	5 mg/kg/day every third day

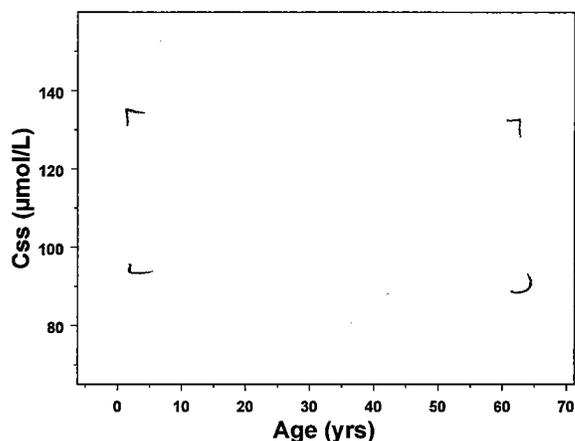
For adults, the monotherapy maintenance dose is the same as in adjunctive therapy. For children, as in Table 16, the proposed monotherapy maintenance dose (shown in Table 13) seems reasonable.

Table 16. Maintenance Dose

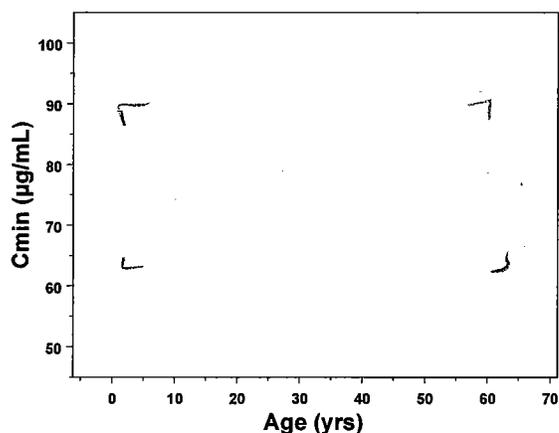
Maintenance	Adjunctive	Monotherapy
<b>Adults</b>	1200 mg/day	1200 mg/day
<b>Children</b>	20-29 kg – 900 mg/day 29.1-39 kg – 1200 mg/day >39 kg – 1800 mg/day	Table 13

The starting dose and the increment dose seem appropriate. In the current labeling, the maintenance dose for adult monotherapy is between 1200 mg/day and 2400 mg/day. Please note that in adult monotherapy, the recommended maintenance dose for initiation of trileptal therapy is 1200 mg/day whereas the maintenance dose for conversion from AEDs is 2400 mg/day. However, based on the Medical Division, this difference is due to different design in clinical trials. To investigate the appropriateness of the sponsor's proposal, a simulation is done by using the body weight and body surface area data of patients in trial

OT/PE1 and 011 whose body weight is less than 70 kg. For each patient, the dose is based on the body weight adjusted dose (upper limit) provided by the sponsor. The clearance is calculated based on the population PK model, which is related to the body surface area. The steady state average concentration across the dosing interval ( $C_{ss}$ ) is, then, calculated based on the clearance and dose. The resulted  $C_{ss}$  vs. age plot is shown below (Please note:  $C_{ss}$  here stands for the average concentration across the dosing interval at the steady state).



Based on the half life of MHD (about 9 hours) and dosing interval (12 hours), the fluctuation factor is approximately 2. Following figure shows the  $C_{min}$  (converted from  $C_{ss}$ ) vs. age.



From these plots, we can see that the  $C_{ss}$ 's or  $C_{min}$ 's are in the same range among patients in different ages and the range is in the proposed concentration range (59-110  $\mu\text{mol/L}$ ). Therefore, the proposed dosing regimen by the sponsor is deemed to be appropriate.

## Recommendations

1. The empirical evidence from the current approved labeling of Trileptal and more importantly the published clinical trial results substantially support that the dosing instructions for Trileptal use in pediatrics as monotherapy should be similar to those for monotherapy in adults (body weight adjusted).
2. The PK/effectiveness models proposed by the sponsor are reasonable, but due to considerable patient-to-patient variability (on and off treatment) the models do not fit well. ( $R^2 = 0.09$  for pediatrics, 0.14 for adults).
3. The sponsor assessed noninferiority (or equivalence) on the slope of the  $C_{min}$ -PCB relationship, which was considered inappropriate by the review team. The sponsor also obtained a non-inferiority margin around 38% when pediatric patients are compared with adults with baseline seizure frequencies in adults of 12/month.
4. The equivalence analyses using the effectiveness response PCB showed that the (geometric) average for the pediatric patients was around 85% of that for all adults, with 95% confidence limit 51% to 119%, at  $C_{min}=40.8$ ; the width of the confidence intervals is greater/narrower for  $C_{min}$  values less than/greater than 40.8. For  $C_{min}$  values  $> 40.8$ , the "effect preserved" would be 51% and above. Interpreting the interaction, when pediatric patients are compared with adults with more/fewer baseline seizures than the average, the effectiveness response ratio is greater/less than 0.85. The simulations for comparing adults and pediatric patients assumed trials of 480 adult patients and trials of 230 pediatric patients. These are the sizes of the (pooled) studies available for adults and pediatric patients. The choice of these same sizes for simulation is arbitrary, but was made to reflect the same quantity of information from which other inferences are being made. To generate the PCB values for a given concentration  $C_{min}$ , all patients in the trial were assumed to have this same  $C_{min}$ . This is not a realistic reflection of the observed trial data, where all patients have differing  $C_{min}$  values, but is a reasonable approach.
5. It is to be noted that there is substantial patient-to-patient variability and it needs to be taken into account along with the mean ratio. More importantly, it is to be noted that the data used for the modeling arises from the adjunctive therapy trials. The current labeling in a way considers that from a clinical point of view adjunctive therapy in adults and pediatrics are not different.
6. If the sponsor's responses are accepted, we provide the following recommendation regarding dosing regimen for monotherapy in pediatrics.
7. The target effective concentrations identified by the sponsor seem to be reasonable.
8. Dosing for conversion to monotherapy and the dosing for initiation of monotherapy (in patients previously untreated with AEDs): The dosing regimens proposed by the sponsor seems to be appropriate.

## Labeling Recommendations

The following changes are recommended in DOSAGE AND ADMINISTRATION section.

### **Conversion to Monotherapy:**

Patients receiving concomitant antiepileptic drugs may be converted to monotherapy by initiating treatment with Trileptal at approximately 8-10 mg/kg/day, given in a BID regimen, while simultaneously initiating the reduction of the dose of the concomitant antiepileptic drugs. The concomitant antiepileptic drugs can be completely withdrawn over 3-6 weeks while Trileptal may be increased as clinically indicated by a maximum increment of 10 mg/kg/day at approximately weekly intervals to achieve the desired clinical response. Patients should be observed closely during this transition phase.

Based on extrapolation from adult monotherapy and children adjunctive therapy studies, maintenance doses of approximately 20-50 mg/kg/day, as shown in the table below, achieve plasma concentrations in the effective range.

### **Initiation of Monotherapy**

Patients not currently being treated with antiepileptic drugs may have monotherapy initiated with Trileptal. In these patients, Trileptal should be initiated at a dose of 8-10 mg/kg/day given in a BID regimen. If clinically indicated, the dose may be increased by 5 mg/kg/day every third day to achieve the desired clinical response. Based on extrapolation from adult monotherapy studies, daily doses of approximately 20-50 mg/kg/day as shown in the table below achieve plasma concentrations in the effective range.

**Range of estimated maintenance doses of Trileptal for children by weight during monotherapy**

	From		To	
Weight in kg	Dose (mg/day)	Dose/body wt. (mg/kg/day)	Dose (mg/day)	Dose/body wt. (mg/kg/day)
20	600	30.0	900	45.0
25	900	36.0	1200	48.0
30	900	30.0	1200	40.0
35	900	25.7	1500	42.9
40	900	22.5	1500	37.5
45	1200	26.7	1500	33.3
50	1200	24.0	1800	36.0
55	1200	21.8	1800	32.7
60	1200	20.0	2100	35.0
65	1200	18.5	2100	32.3
70	1500	21.4	2100	30.0

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 HFD-860 R. Uppoor, J. Gobburu, J. Duan  
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Appendix I. Statistical Consult for the Office of Clinical Pharmacology and Biopharmaceutics

**Drug Product:** NDA 21-014 (s-003) Trileptal (oxcarbazepine) Tablet  
**Document Reviewed:** Pediatric Monotherapy Supplement Response to Approvable Letter  
**Proposed by:** Novartis Pharmaceutical Corporation  
**Review Requested by:** Review Team for N21-014/SE5-003, Division of Pharmaceutical Evaluation - I  
**Statistical Reviewers:** Stella G Machado, Ph.D., Mathematical Statistician  
Meiyu Shen, Ph.D., Mathematical Statistician  
HFD-705, QMRS/Office of Biostatistics  
**Date Requested:** April 15, 2003  
**Date Completed:** July 1, 2003

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## I INTRODUCTION

Trileptal is approved for treatment of partial seizures as adjunctive therapy in adults and children over four years of age, and as monotherapy in adults.

In February 2001, Novartis submitted a Supplemental NDA (sNDA) for the use of Trileptal (oxcarbazepine) as monotherapy in pediatric patients. In December 2001, the FDA issued an Approvable Letter for pediatric monotherapy, in which additional justification of the PK/Efficacy analysis was requested. Subsequently, the FDA raised four points of concern to be addressed by the sponsor. These four points are listed as follows:

Justification of the PK/Efficacy analysis  
Equivalence of PK/Efficacy relationships in adults and pediatric patients  
Methods of determining effective concentrations and doses  
Strength of evidence from the meta-analyses of efficacy.

We were requested by OCPB to review item 2.

## ***II SPECIFIC OCPB REQUESTS***

Please evaluate the following.

1. The propriety of the noninferiority approach used. The methodology used by the applicant was in the setting different from the usual application of this approach. Is it reasonable?
2. The interpretation of the analysis. Did the analysis address the Agency's concern and demonstrate the similarity of oxcarbazepine treatment in two different patient populations, adults and pediatric patients?

As requested, this statistical review is focused primarily on issues relating to the equivalence of the PK/Efficacy relationships in adults and pediatric patients.

## ***III. DESCRIPTION OF THE PROBLEM***

The PK bridging approach of the sNDA begins with the demonstration of similarity between adults and pediatric patients on adjunctive therapy with respect to their PK/efficacy relationships. While reviewing the sNDA, the previous FDA reviewers conducted independent data analyses to compare the PK/Efficacy relationships between adults and pediatric patients. Linear regression models were fitted to a log-transform of the change in seizure frequency from baseline as a function of  $C_{min}$  using data from studies of adjunctive therapy in both patient populations. It was determined that the PK/PD

relationships in adults and pediatric patients do not differ statistically. The sponsor was requested to provide a convincing argument that these relationships are indeed, essentially equivalent, and not just not statistically significantly different.

#### IV EQUIVALENCE CRITERIA AND TEST PROPOSED BY THE SPONSOR

Empirical PK/efficacy models for adults and pediatric patients

The sponsor used data from 464 adults from Study OT/PE1 and 16 adults from Study 011 to develop the PK/PD model for adults. Also, the sponsor used data from 221 pediatric patients from Study 011 and 9 pediatric patients from Study OT/PE1 to develop the PK/PD model for pediatric patients. These were studies of trileptal as adjunctive treatment. The efficacy measure was percent change in seizure frequency, namely,  $100 \cdot (N_{28} - N_0) / N_0$ , where  $N_{28}$  is the number of seizures that occurred in 28 days on the maintenance dose, and  $N_0$  is the baseline seizure frequency. We labeled percent change from baseline as PCB. The trileptal exposure measure was  $C_{min}$ .

**The empirical PK/PD model for adults was determined as:**

$$\log(\text{PCB} + 110) = \beta_{0,A} + \beta_{1,A} \cdot C_{min} + \beta_{2,A} \cdot C_{min} \cdot [\log(\text{baseline seizure freq.}) - 2.5] + \varepsilon_A \quad (1)$$

**The empirical model for pediatric patients was**

$$\log(\text{PCB} + 110) = \beta_{0,P} + \beta_{1,P} \cdot C_{min} + \varepsilon_P \quad (2)$$

The parameters,  $\beta_{0,A}$ ,  $\beta_{1,A}$  (adults) and  $\beta_{0,P}$ ,  $\beta_{1,P}$  (pediatric patients) are, respectively, intercepts and slopes, and the  $\beta_{2,A}$  is the coefficient for the interaction between baseline frequency and  $C_{min}$  (adults). The error terms,  $\varepsilon_A$ ,  $\varepsilon_P$ , are assumed independently normally distributed with zero means, and variances  $\sigma_A^2$ ,  $\sigma_P^2$ , respectively. The parameters estimated by the sponsor are shown in the Table 1. We confirmed these results.

Table 1 Estimated parameters for the PK/efficacy relationships for adults and pediatric patients

Parameter estimates (adults)	Adults	Parameter estimates (peds)	Pediatric patients
$\beta_{0,A} \pm \text{s.e.}$	4.54 ± 0.04	$\beta_{0,P} \pm \text{s.e.}$	4.55 ± 0.06
$\beta_{1,A} \pm \text{s.e.}$	- 0.0099 ± 0.0011	$\beta_{1,P} \pm \text{s.e.}$	-0.0072 ± 0.0015
$\beta_{2,A} \pm \text{s.e.}$	0.0031 ± 0.0008	-	-
$\sigma_A$	0.6777	$\sigma_P$	0.7417
$R^2$	0.170	$R^2$	0.089

## Noninferiority

Noninferiority comparisons are used when a new treatment cannot be compared with placebo for ethical or strategic reasons. Instead, the new treatment is compared with an active control that has been demonstrated to be superior to placebo in previous clinical trials.

The goal here is somewhat different, namely, to establish the similarity of a given treatment, oxcarbazepine, in two different patient populations, adults and pediatric patients, on adjunctive therapy, where in both populations the treatment has been tested directly against placebo.

**Reviewers' note:** establishing similarity for adults and pediatric patients would ideally use data from *monotherapy* studies, not *adjunctive* studies.

### Basic concepts of noninferiority

Noninferiority is about showing that a test treatment is similar to an active control treatment. Let  $\mu_T$ ,  $\mu_A$ , and  $\mu_0$  be the mean responses for the test, the active control, and placebo, respectively. Then noninferiority is about demonstrating that

$$|\mu_T - \mu_0| > f |\mu_A - \mu_0| \quad (3)$$

for some fraction  $f$ . The fraction  $f$  is selected in advance of the new trial.

### How the current situation is different

The setting here differs from the usual assessment of non-inferiority, which is carried out using data from the same trial, with a predetermined  $f$ , to show that a new treatment is similar to an active control in a given patient population. Here, the objective is to show that the same treatment performs similarly in two different patient populations (adults and pediatric patients), knowing that the treatment was demonstrated to be superior to placebo in separate trials. Similarity is required at all concentrations, including placebo. Moreover, the fraction  $f$  is unknown.

### Methodology used by the sponsor

For oxcarbazepine, adults on adjunctive therapy in Studies OT/PE1 and 011 played the role of the "active control", and pediatric patients from those two studies represented the "test treatment". We use P (pediatrics) instead of T (test) for the subscript.

Let  $\mu_{A,x,b}$  = expected value of  $\log(\text{PCB} + 110)$  at  $C_{\min}=x$  for adults with log

baseline seizure frequency of  $\log(N_0)$ , and  $\mu_{P,x}$  = expected value of  $\log(\text{PCB} + 110)$  at  $C_{\min}=x$  for pediatric patients. Recall from equations (1) and (2):

**The empirical structural model for adults is**

$$\mu_{A,x,b} = \beta_{0,A} + \beta_{1,A} * x + \beta_{2,A} * x * [\log(N_0) - 2.5]$$

**The empirical structural model for pediatric patients was**

$$\mu_{P,x} = \beta_{0,P} + \beta_{1,P} * x$$

Since the mean response for adults depends on the baseline frequency, the sponsor chose compare the models for adults and pediatric patient for adults with  $\log$  baseline frequency of 2.5 (seizure frequency 12), thus eliminating the interaction term and permitting comparison of the two fitted regression lines.

The sponsor said that non-inferiority may be demonstrated based on the slopes, since the intercepts are the placebo responses.

**Reviewers' note:** we show shortly that we don't agree with this.

Per the sponsor: the hypothesis of noninferiority to be tested is:

$$H_0: \beta_{1,P} \geq f * \beta_{1,A} \quad \text{vs.} \quad H_a: \beta_{1,P} < f * \beta_{1,A}$$

This is the same as:

$$H_0: \beta_{1,P} / \beta_{1,A} \leq f \quad \text{vs} \quad H_A: \beta_{1,P} / \beta_{1,A} > f$$

The sponsor used the available data and estimated the 95% confidence interval of the ratio  $\beta_{P,1} / \beta_{A,1}$ . They used the lower bound of this interval to estimate  $f$ . This is the largest fraction that can be estimated from the available data for which (1) is plausible by acceptable statistical criteria.

$f$  hat was found as the smaller quadratic root of the following equation (details given in the sponsor's response):

$$\left( \hat{\beta}_{1,T} - f * \hat{\beta}_{1,A} \right)^2 = F_{1,v,0.95} \left( \hat{\sigma}_{\hat{\beta}_{1,T}}^2 + f^2 * \hat{\sigma}_{\hat{\beta}_{1,A}}^2 \right)$$

**Reviewers' note:** demonstration of similarity of two response curves should be based on all parameters that define the curve, including the intercepts. The sponsor is making the assumption that the mean of interest for equivalence assessment is the  $\log$ (percent change from baseline) rather than the **percent change from baseline**. We consider this assumption to be incorrect.

To make the equivalence test using the **percent change from baseline** measure, equation (3) becomes (assuming  $\log(N_0)=2.5$  for simplicity of exposition):

$$|\exp(\beta_{0,P} + \beta_{1,P}x) - \exp(\beta_{0,P})| > f * |\exp(\beta_{0,A} + \beta_{1,A}x) - \exp(\beta_{0,A})| .$$

which reduces to

$$\{\exp(\beta_{0,P}) [\exp(\beta_{1,P}C_{min}) - 1]\} > f \{\exp(\beta_{0,A}) [\exp(\beta_{1,A}C_{min}) - 1]\} \tag{4}$$

Only if one can assume that  $\beta_{0,p} = \beta_{0,A}$ , a strong assumption for different populations, does the hypothesis to be tested, (4), reduce to a function of the 2 slopes,  $\beta_{1,P}$  and  $\beta_{1,A}$ ; however, it is not the function evaluated by the sponsor, namely,  $\beta_{1,P}/\beta_{1,A}$ .

Sometimes the noninferiority problem may be stated as requiring that  $|\mu_T - \mu_0| - |\mu_A - \mu_0| \leq C$  for some positive value  $C$  of interest. We explored the impact of this, and found again that the expression to be tested still includes the placebo responses. End of note.

## Results and discussion

Table 2 displays the estimated values of  $f$  in the comparison of pediatric patients and adults with a baseline seizure frequency of 12 seizures per month.

Table 2 Estimated values of  $f$  in the comparison of the slopes of the PK/Efficacy relationships between pediatric patients and adults with baseline seizure frequency of 12.

Data set	$\hat{\beta}_{1,A}$	$\hat{\beta}_{1,P}$	$\frac{\hat{\beta}_{1,P}}{\hat{\beta}_{1,A}}$	$f^*$ ="non-inferiority margin"
Without outliers	-0.0103	-0.0071	0.68	0.38
With outliers	-0.0099	-0.0072	0.72	0.41

The point estimate of the ratio of slopes was 0.68. The 95% confidence interval for the ratio of  $\beta_{P,1}/\beta_{A,1}$  was found as 0.38 to 1.05. Thus, 0.38 was the estimated value of the fraction of the effect for adults preserved by the pediatric patients.

Further quantification of the differences between adults and children

To compare pediatric patients and adults further with respect to their PK/Efficacy relationships, the sponsor compared predictions of percent change from baseline on seizure frequency at various  $C_{min}$  values; these are shown in Table 3. The computations were done by bootstrapping. This is an appropriate approach.

Table 3. Comparison of the model-predicted percent change from baseline in seizure frequency between adult and pediatric patients.

Cmin (umol/L)	Percent change from baseline		Difference: Pediatric patients-Adults	
	Pediatric patients	Adults	Estimated difference (%) relative to adults	95% Confidence interval for difference
0.0	-16.7	-14.1	-2.5 (-17.9%)	(-15.0, 9.9)
17.0	-27.2	-29.5	2.3 (7.8%)	(-6.5, 11.1)
40.8	-40.0	-47.0	7.0 (14.8%)	(-2.5, 16.4)
68.0	-52.2	-62.3	10.1 (16.2%)	(-1.9, 22.1)
73.8	-54.5	-65.1	10.6 (16.2%)	(-1.5, 22.6)

The sponsor concluded that all 95% confidence intervals for the differences between adults and pediatric patients contained zero, implying that the differences were not statistically significant.

**Reviewers' note:** (i) this statement does not establish equivalence. (ii) these  $C_{min}$  concentrations were chosen by the sponsor. See below for some predictions requested by the Medical Office for  $C_{min}$  values 59.1 and 112.

## 2.7 Summary remarks on noninferiority

The sponsor stated that the data are sufficient to demonstrate that pediatric patients on adjunctive therapy with oxycarbazepine preserved at least 0.38 of the effect in adults (with baseline seizure frequency of 12/month) and varied from 0.32 to 0.45 for different assumed adult baseline seizure rates. In addition, they said that the predicted reduction for pediatric patients was insensitive to assumptions about adult baseline frequency, and the seizure frequencies predicted to be attained on maintenance therapy were generally comparable for adults and pediatric patients. Specifically, they concluded that "the noninferiority analysis demonstrates the equivalence of the PK/Efficacy relationships for adults and patients on adjunctive therapy" and that "This result validates the premise of the PK-bridging approach, and allows doses for pediatric patients on monotherapy to be recommended as doses that achieve  $C_{min}$  values equal to those achieved by adults at effective monotherapy doses".

## V REVIEWERS' COMMENTS

## The PK/Efficacy models

We examined the sponsor's modeling assumptions and found them to be generally reasonable. (Equations (1) and (2) in section IV.1). The data are extremely skewed and a log transformation helps to obtain some symmetry of distribution; this is needed to permit interpretation of hypothesis tests on the parameters of the prediction equations. Note that  $\log(\text{PCB} + 110)$  may be expressed as  $\log(100N_{28}/N_0 + 10) = \log(100) + \log(N_{28}/N_0 + 0.1)$ , so one might ask why 0.1, and not 0.15 or 0.2, but this is a minor point.

When developing models for different populations, one would generally use the same model form (eg, linear, emax) for each one. We consider it would have been better practice to have used model (1) for the pediatric population, where the interaction term between baseline frequency and  $C_{\min}$  is included, even if not statistically significant.

We verified the results given in Table 1 above, using the data set "adjunct". An important finding was the large between-patient variability in response, giving poor fit as evidenced by  $R^2$  values between 0.09 and 0.17.

Figure 1a is a scatter plot, for categorized  $C_{\min}$  values, of observed PCB responses for the pediatric and adult patients; note the considerable skewness of distribution, and the large variability relative to the response to treatment. Figure 1b is a similar plot of  $\log(\text{PCB} + 100)$ , showing little skewness, but still considerable variability relative to response.

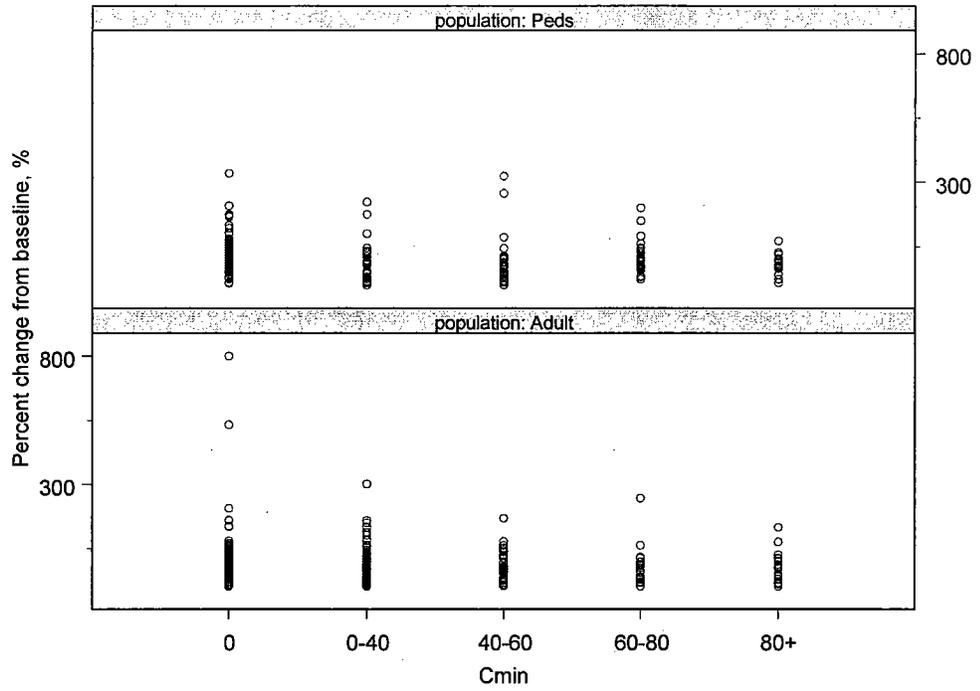


Figure 1a. Scatter plot of observed PCB responses for adult and pediatric patients, by categorized Cmin.

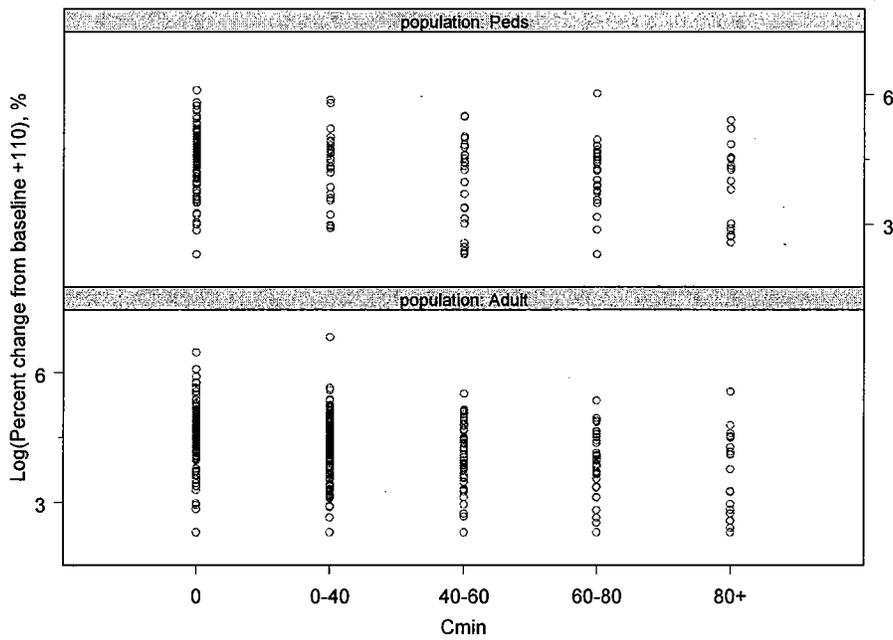
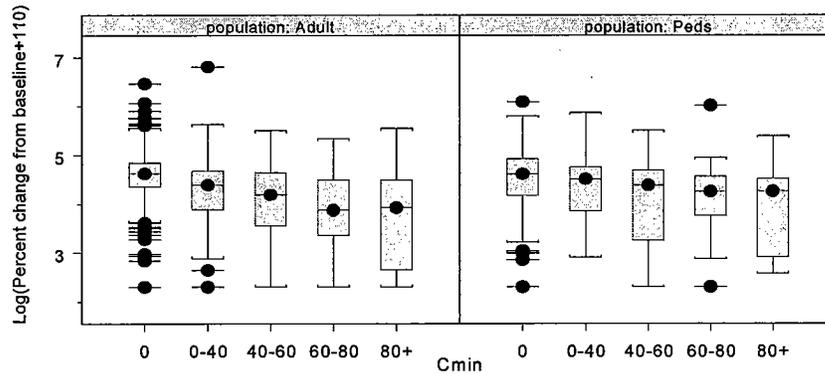


Figure 1b. Scatter plot of log(PCB+110) for adult and pediatric patients, by categorized Cmin.

Figure 2 shows box plots comparing the (geometric) means and inter-quartile ranges of the log(PCB+110) values for pediatric and adult patients. The average response to treatment for pediatric patients is less steep than that for adults.

Figure 2 Box plots of log(PCB+110) versus categorized Cmin for adult and pediatric patients



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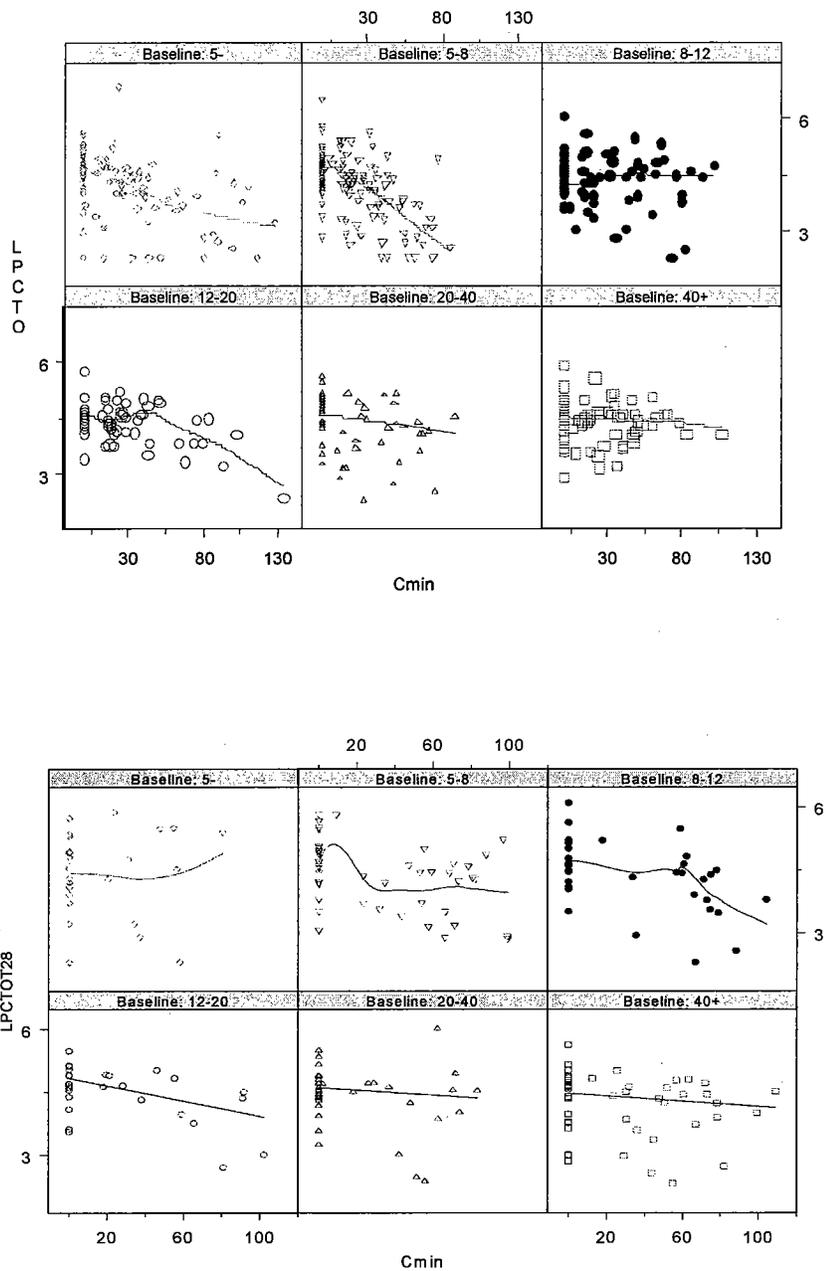


Figure 3:  
Scatter plots and loess fits of  $\log(\text{PCB}+110)$  versus  $C_{\text{min}}$  for adult patients (top) and pediatric patients (lower), for categorized values of the baseline seizure frequency.

Figure 3 shows scatter plots and loess fits of  $\log(\text{PCB}+110)$  values versus  $C_{\text{min}}$  for the adult and pediatric patients, for categorized values of the baseline seizure frequency. In spite of the variability, one can see some evidence for an interaction for adults between baseline frequency and slope of response; there is almost no exposure response apparent for adults with baseline seizure frequency  $> 40$  (13% of the 472 adults in the analysis). The pattern for pediatric patients is somewhat similar but not as clear.

### Equivalence of two PK/PD relationships.

A requirement before PK-bridging is to demonstrate similarity of the concentration-response relationships in the adult and the pediatric populations. Similarity is demonstrated statistically by equivalence testing, or non-inferiority testing which is one-sided equivalence testing. The “goal-posts” or non-inferiority margin,  $f$ , are set in advance by the agency. A common example is to attempt to establish that the ratio of the average response measure in one population versus that in another lies within the interval 0.8 to 1.25, with high probability.

To demonstrate similarity of two concentration-response relationships, it should be shown not only that the relationships have the same shape (eg, straight lines, or emax curves), but also that the predicted responses to a given concentration achieved by the two relationships are similar, over the range of concentrations likely to be experienced.

As already discussed, the sponsor compared the PK/PD relationships by comparing only the estimated slopes. Critically also, the patient-to-patient variability evidenced in the substantial lack of fit of the models was not taken into account.

Via simulations, using the sponsor’s models, we conducted an equivalence analysis of the efficacy responses for adults and pediatric patients at the same concentrations, for a range of concentrations. It appears (Table 3 above) that the sponsor pursued similar idea, but not as far as we did.

### 3. Reviewers’ equivalence analyses.

We fit the regression models and obtained the same results as the sponsor, however, omitting the interaction term between baseline seizure and slope for adults. The following parameter estimates were found:

Table 4.

Population	N	$\beta_0$ (s.e.)	$\beta_1$ (s.e.)	$\sigma$	$R^2$
Adults	480	4.55036 (0.04169)	-0.01028 (0.00114)	0.68698	0.14
Peds	230	4.54554 (0.06259)	-0.007164 (0.001513)	0.74166	0.09

To examine the similarity of the PK/efficacy relationships in the two populations, for various values of  $C_{min}$ , 2000 pairs of independent trials (one for 480 adults and one for 230 pediatric patients) were simulated. For each pair, the ratio of the (geometric) average PCB for pediatrics to the (geometric) average PCB for

adults was calculated. The percentiles of the 2000 average PCB's for adults, the percentiles of the 2000 average PCB's for pediatric patients, and the percentiles of the 2000 ratios were obtained.

The results are shown in Table 5. Columns 2 and 3 give the Sponsor's results, directly from Table 3 above. Columns 4,5 give the simulated median PCB's for pediatric and adult patients, and columns 6,7,8 give the 50<sup>th</sup>, 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles of the distribution of ratios. Included are results for 2 additional Cmin values, 59.1 and 112. Apart from the similarity of the placebo responses, the average response expected for pediatrics is 82% to 88% that of adults. Confidence intervals are a little wider for lower concentrations than higher ones. For Cmin = 40.8, the average response ratio is 83% with 95% confidence interval 51% to 119%. This interval is not contained in (80%, 125%). However, clinical judgement is required to interpret the importance of these results.

Table 5. Efficacy responses and equivalence assessment for selected Cmin values.

Cmin	% change*		% change**		ratio(median)	2.50%	97.50%
	Peds	Adults	Peds	Adults			
0	-16.7	-14.1	-15.7	-15.4	1.037	-0.01	3.458
17	-27.2	-29.5	-26.6	-30.4	0.875	0.377	1.462
40.8	-40	-47	-39.6	-47.9	0.828	0.509	1.185
59.1			-48.1	-58.5	0.828	0.558	1.121
68	-52.2	-62.3	-51.8	-62.9	0.822	0.544	1.085
73.8	-54.5	-65.1	-54.5	-65.8	0.829	0.551	1.084
112			-68.0	-80.1	0.848	0.598	1.047

\* predicted by the sponsor (Table 3); \*\* predicted using the same models, via our simulations

Table 6 shows the estimated increased Cmin levels that would be needed for pediatric patients to achieve response levels closely similar to those for the adult patients. Whether these values are useful targets depends on evaluation of the adverse event profile in pediatric patients.

Table 6. Cmin levels for pediatric and adults patients to achieve similar responses

Cmin peds	Cmin adults	%change	% change	Ratio	2.50%	97.50%
		peds	adults			
24	17	-30.5	-30.5	1.000	0.494	1.620
58	40.8	-47.7	-47.8	1.004	0.644	1.374
84	59.1	-58.6	-58.4	1.002	0.696	1.316

98	68	-63.2	-63.0	1.006	0.696	1.294
107	73.8	-65.8	-65.8	1.000	0.713	1.262
161	112	-79.9	-80.0	1.002	0.744	1.200

Table 7 shows simulation results from a comparison of adults (trial of 480) versus adults (trial of 230). The purpose is to examine the influence of the large patient-to-patient variability on the confidence intervals when we know the populations are the same.

Table 7. Simulated efficacy comparisons for adults versus adults.

Cmin	% change*				
	Adults (230)	Adults (480)	ratio(median)	2.50%	97.50%
0	-15.4	-15.6	1.001	0.317	2.332
17	-30.4	-30.3	1.001	0.728	1.309
40.8	-47.7	-47.8	1.001	0.858	1.142
59.1	-58.5	-58.5	1.001	0.901	1.102
68	-63.0	-62.9	1.001	0.915	1.088
73.8	-65.7	-65.6	1.001	0.924	1.078
112	-79.8	-80.0	1.000	0.958	1.044

Note that the ratios are centered at 1.0, as expected. Note also that the 95% confidence intervals are narrower than those at each corresponding Cmin in Table 5, due to a lower estimate for  $\sigma_A$  than for  $\sigma_P$  (Table 3).

## VI ANSWERS TO OCPB REQUESTS

The propriety of the noninferiority approach used. The methodology used by the applicant was in the setting different from the usual application of this approach. Is it reasonable?

It is reasonable to test for noninferiority or equivalence with data from different studies, but of course, the discussion of results should explain the differences in population, dosing regimens, and etc. For the purposes of predicting results to pediatric patients, all efforts should be made to use available data, including accounting for sources of variability.

We consider it more reasonable to assess equivalence of the responses between adult and pediatric populations, rather than noninferiority which is one-sided.

We consider the Sponsor's approach to assessing noninferiority inappropriate, since they did not assess the equivalence of the efficacy results, at each value of Cmin. They based assessment on a comparison of the log-transforms of the

efficacy response, which reduced to a comparison of the slopes of the linear regression lines; this approach did not take into account the possible difference in intercepts of the two different patient populations. In addition, they neglected to account for the patient to patient variability, which was considerable.

The interpretation of the analysis. Did the analysis address the Agency's concern and demonstrate the similarity of oxcarbazepine treatment in two different patient populations, adults and pediatric patients?

To demonstrate similarity of PK/efficacy, one needs to establish that the predicted efficacy responses in the two populations are closely similar, for each C<sub>min</sub> in the range that will be encountered clinically. The sponsor did not demonstrate this, even though they stated that they had done so. (see the quote, end of section 2.7).

We examined an equivalence assessment of the efficacy endpoint, PCB; the measure of similarity we used was the ratio of the (geometric) mean PCB for pediatric patients versus that in adults. This measure is scale-free, and may be interpreted in reference to familiar ranges, such as (0.8, 1.25), or (0.67, 1.50), as determined using medical judgement.

We found that the PCB response for pediatric patients ranged from 82% to 85% of the PCB response for adults, for C<sub>min</sub> in the range 40.8 to 112. The 95% confidence intervals for these percentages were broad: for C<sub>min</sub> = 40.8, the interval was 51% to 119% and for C<sub>min</sub> = 112, from 60% to 105%. The "effect preserved" is actually greater than the 0.38 arrived at by the sponsor (except for 0.377 at C<sub>min</sub>=17), but is far from 0.80 or other familiar measure. Since, however, there are no established "goal-posts" for this situation, medical judgement is necessary to assess the implications of the results.

We did not explore analyses linking dose to C<sub>min</sub> to efficacy, considering that out of scope of the consult request.

## **VII SUMMARY**

the PK/efficacy models proposed by the sponsor are reasonable, but due to considerable patient –to – patient variability (on and off treatment) the models do not fit well. ( $R^2 = 0.09$  for pediatrics, 0.14 for adults).

the sponsor assessed noninferiority (or equivalence) on the log-scale for efficacy response, which we consider inappropriate, and obtained a non-inferiority margin around 38% when pediatric patients are compared with adults with baseline seizure frequencies in adults of 12/month.

Our equivalence analyses using the efficacy response PCB showed that the (geometric) average for the pediatric patients was around 85% of that for all adults, with 95% confidence limit 51% to 119%, at  $C_{min}=40.8$ ; the width of the confidence intervals is greater/narrower for  $C_{min}$  values less than/greater than 40.8. For  $C_{min}$  values  $> 40.8$ , the “effect preserved” would be 51% and above. Interpreting the interaction, when pediatric patients are compared with adults with more/fewer baseline seizures than the average, the efficacy response ratio is greater/less than 0.85.

### **VIII NOTES ON THE SIMULATIONS**

The simulations for comparing adults and pediatric patients assumed trials of 480 adult patients and trials of 230 pediatric patients. These are the sizes of the (pooled) studies available for adults and pediatric patients. The choice of these same sizes for simulation is arbitrary, but was made to reflect the same quantity of information from which other inferences are being made. To generate the PCB values for a given concentration  $C_{min}$ , all patients in the trial were assumed to have this same  $C_{min}$ . This is not a realistic reflection of the observed trial data, where all patients have differing  $C_{min}$  values, but is a reasonable approach.

Each trial was simulated 2000 times, for each scenario. For each trial,  $i$ , the intercept and slope were set at  $\beta_{0i} = \beta_0 + z_0 * s.e.(\beta_0)$  and  $\beta_{1i} = \beta_1 + z_1 * s.e.(\beta_1)$ , respectively, where the estimates and their standard errors are from Table 4, and  $z_0$  and  $z_1$  are independently generated random  $N(0,1)$  variates. For each patient in the trial, the PCB value was generated as  $110 * \exp(\beta_{0i} + \beta_{1i} * C_{min} + z_2 * \sigma)$ , where  $z_2$  is an independently generated random  $N(0,1)$  variate. For the adult patients, the 2000 PCB values were ordered, and the percentiles identified. The same was done for the 2000 PCB values for the pediatric patients. The trials for adults and pediatrics were arbitrarily paired (by the order in which they were generated), the ratio of the mean PCB value for the pediatric patients to that of the adults was calculated, and the percentiles of the distribution identified from the sorted values.

To be finalized:

Stella G. Machado, Mathematical Statistician  
QMR/OB/OpaSS/CDER

Meiyu Shen, Mathematical Statistician  
QMR/OB/OPaSS/CDER

Concur:

\_\_\_\_\_  
Charles Anello, Deputy Director  
OB/OpaSS/CDER

Cc: HFD-705

Appendix II. Previous Review by Dr. Vanitha Sekar

**CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW**

**DRUG:** Trileptal® (Oxcarbazepine)  
**FORMULATION:** Tablets (150, 300, 600 mg)  
**TYPE:** Pediatric Efficacy Supplement  
**NDA:** 21014 SE5-003

**PRIMARY REVIEWER:** Vanitha Sekar  
**APPLICANT:** Novartis  
**DATE OF REVIEW:** 11/30/ 2001

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## OVERALL SUMMARY OF FINDINGS

Trileptal is currently indicated as monotherapy and adjunctive therapy for the treatment of partial seizures in adults and only as adjunctive therapy in children 4-16 years of age (Table 1). This supplement has been submitted for the approval of Trileptal as monotherapy in children aged 4-16 years. As opposed to conducting a controlled clinical efficacy trial to support this indication, a "PK-bridging" approach is being utilized. No new studies have been submitted, however, reanalysis of studies from the original NDA has been submitted.

Table 1

	Adults	Children (4-16 years of age)
Adjunctive	Trileptal approved on the basis of "positive" Phase 3 clinical trials	Trileptal approved on the basis of "positive" Phase 3 clinical trials
Monotherapy	Trileptal approved on the basis of "positive" Phase 3 clinical trials	"PK-bridging" approach proposed in this submission

In order to support the request for approval of Trileptal for pediatric monotherapy (in ages 4-16 years), the sponsor has submitted the following analysis: 1) comparison of concentrations achieved in children and adults during adjunctive therapy at the approved doses, 2) meta-analysis to confirm the effectiveness of Trileptal during monotherapy in children, 3) a dose-concentration analysis to determine an effective dose in children during monotherapy, and 4) evaluation of the seizure data to confirm the effectiveness of Trileptal at the recommended doses in children during monotherapy. However, the sponsor has not addressed the issue of pharmacodynamic equivalence or similarity between adults and children.

A summary of our analysis to address this issue is presented below:

- 1) Our analysis established that the relationship between plasma concentrations of MHD and the clinical endpoint (reduction in 28-day seizure frequency) are not statistically different ( $\alpha=0.05$ ) between adults and children. (n=280 adults on drug and 165 on placebo and n=120 children on drug and 136 on placebo) in the adjunctive therapy setting (Figure 1).
- 2) Based on (1), we assumed that the relationship between plasma concentrations of MHD and the clinical endpoint (28-day seizure frequency) in the monotherapy setting are not significantly different. This assumption was supported by our analysis of the observed data, which suggested that the relationship between plasma concentrations of MHD and the clinical endpoint (28-day seizure frequency) are not statistically different ( $\alpha=0.05$ ) between adults and children in the monotherapy setting. However the number of children in this analysis was small, n=12 on drug (Figure 2).
- 3) Plasma MHD concentrations were compared in adults and children following monotherapy at different doses (Figure 3). It appears that the average MHD trough concentrations in adults are slightly higher than those observed in children at a given dose (on a mg/kg basis) during monotherapy. Please refer to the Clinical Pharmacology section of this review for additional plots evaluating the effects of age and body weight on plasma MHD steady-state concentrations. A dosing regimen for monotherapy in pediatrics will be selected based on this data (subject of a future review after the applicant responds to our comments from this review).

Figure 1 (PK-PD analysis using repeated measures)

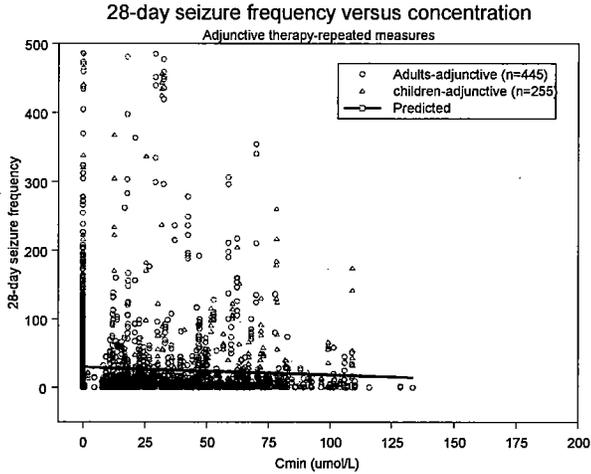


Figure 2 (PK-PD analysis using single PD measure)

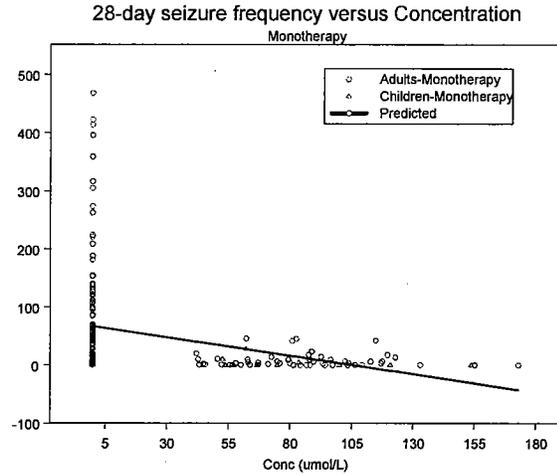
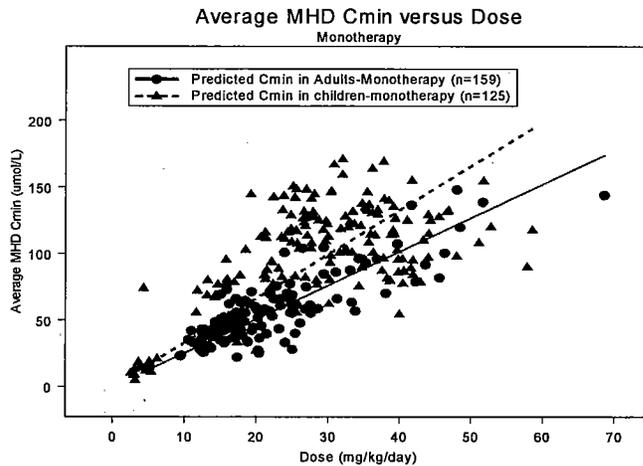


Figure 3

The figure is mis-labeled. The red triangle is for adults and blue circle is for children.



## RECOMMENDATION AND COMMENTS TO APPLICANT

The Clinical Pharmacology review of the data provided in this supplement is adequate to support approvability of Trileptal as monotherapy in children 4-16 years of age, provided that the following comments are addressed by the applicant.

The following comments should be forwarded to the applicant:

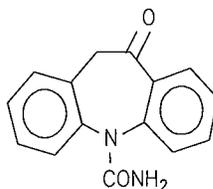
1. Although our analysis of the placebo-response and concentration-response relationship for patients on adjunctive and monotherapy suggests that these relationships are not statistically different between adults and children, this is not the same as stating that there is "pharmacodynamic (PD) equivalence" between the two populations. We request that you submit to us a compelling argument to support PD equivalence between adult and pediatric populations and provide a justification as to what difference observed between children and adults from these analyses should not be considered clinically relevant.
2. Based on review of the applicant's response to (1), if it is concluded that the PK-PD relationship is sufficiently similar between children and adults, a dosing regimen in which these (adult) exposure levels could be reliably achieved when Trileptal is given to pediatric patients as true monotherapy should be determined.

## INTRODUCTION AND BACKGROUND

Oxcarbazepine (OXC), the keto-analog of carbamazepine, is an orally active anticonvulsant that is presently marketed in the US as 150, 300 and 600 mg film coated tablets and suspension (60 mg/ml). The parent compound, oxcarbazepine ( OXC) is rapidly reduced by cytosolic enzymes to a monohydroxylated derivative (MHD) which is pharmacologically active. MHD is the moiety that is measured in plasma in all of the clinical trials.

## CHEMISTRY

The drug substance, OXC (10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide), is a tricyclic diarylazepine compound with anticonvulsant activity. OXC is a non-chiral, white to faintly orange crystalline powder with a molecular weight of 252.28. OXC has a pKa of  $10.7 \pm 0.2$  and a partition coefficient of 1.31 (octanol/phosphate buffer pH 7.4, 25°C). It is slightly soluble in chloroform, dichloromethane, acetone and methanol and practically insoluble in ethanol, ether and water. No polymorphs of the solvent free drug substance have been observed.



## PROPOSED MECHANISM OF ACTION

The anticonvulsant properties of OXC and MHD are possibly mediated by blocking voltage dependant sodium channels, decreasing high voltage activated calcium channels and interaction with potassium channels. The blockade of voltage dependant sodium channels in the brain has been proposed as the most plausible mechanism of action. This is based on results from: 1) in-vitro studies in which OXC and MHD limited sustained high frequency repetitive firing of sodium-dependant action potentials of cultured mouse neurons, and 2) in-vivo study (maximal electroshock) which evaluates the ability of drugs to prevent electrically induced tonic hind limb extension seizures in rodents. Efficacy in the maximal electroshock model has been shown to correlate with the ability to prevent partial and generalized tonic-clonic seizures in humans; also drugs that are active in this test (e.g. carbamazepine, phenytoin) often interact with voltage dependant sodium channels.

## INDICATION AND PROPOSED DOSAGE AND ADMINISTRATION

Trileptal is recommended for use either as monotherapy (in adults) or in combination with other antiepileptic drugs (in adults and children 4-16 years of age).

In monotherapy in children 4-16 years of age, the applicant recommends: "initiating Trileptal treatment at 8-10 mg/kg/day given in a bid regimen. Doses may be increased every third day by 5 mg/kg/day to achieve the desired clinical response. Based on extrapolation from adult monotherapy studies, daily doses of 20-55 mg/kg/day achieve plasma concentrations in the effective range".

## ANALYTICAL METHODS

The bioanalytical methods used to quantify MHD in plasma in the studies submitted to this supplement were reviewed as part of the original NDA for Trileptal and found to be acceptable.

## FORMULATION

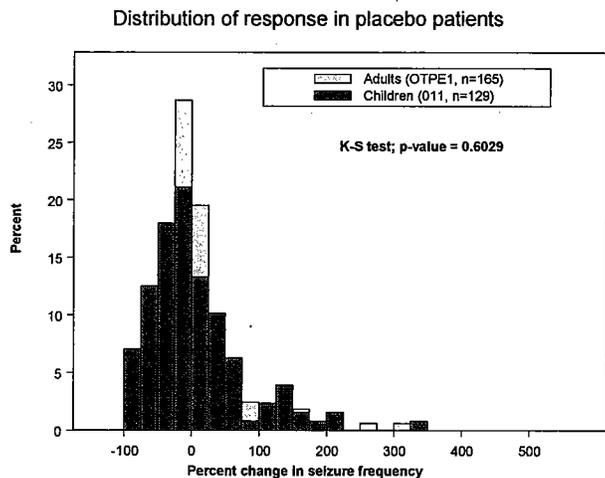
The formulation that was used in the clinical trials was Trileptal tablets 150, 300 and 600 mg.

## CLINICAL PHARMACOLOGY

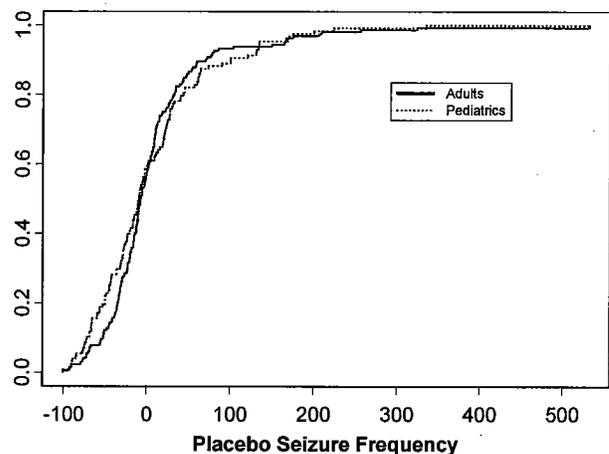
*Is the placebo-response similar between adults and children?*

The placebo response in children and adults was compared from two adjunctive therapy trials, OTPE1 and 011. A description of the study designs is attached as part of the Appendix 1. The placebo data from these trials were analyzed using the Kolmogorov-Smirnov (K-S) goodness-of-fit test to compare the distribution of placebo response in adults and children during adjunctive therapy. The results from this analysis suggest that the distribution of the placebo response is not different in children and adults during adjunctive therapy (Figures 4 and 5),  $p=0.6029$ .

**Figure 4**



**Figure 5**



*Is the relationship between plasma concentrations of MHD (PK) and the clinical (PD) endpoint (reduction in 28-day seizure frequency) similar between adults and children?*

In order to answer this question, the PK-PD relationship was compared in children and in adults in the adjunctive therapy setting. Data from 2 Phase 3 clinical trials (OTPE1 and 011) were used. A description of the study designs is attached as part of the Appendix 1.

The concentration-response relationship in the adjunctive therapy setting was examined for adults using the data from clinical trial OTPE1 and for children from trials OTPE1 and 011. The PD end point that was used in the analysis was the reduction in 28-day seizure frequency. This was also an efficacy endpoint for the adjunctive clinical trials. The 28-day seizure frequency was calculated as the number of seizures that occurred during a 28-day period during the baseline and double blind phase of the studies (See Appendix 1 for details). Two approaches were used to assess the PK-PD relationship in the adjunctive setting:

- 1) PD consisted of a single measurement of the clinical response after the baseline period – the average double blind 28-day seizure frequency that was used as the clinical end point,
- 2) PD consisted of repeated measurements of seizure frequency by visit during the double blind period of the study (following the baseline period). This approach was used in an attempt to increase the robustness of the PK-PD analysis.

(In the monotherapy setting, only approach (1) were used since data was unavailable to use

approach (2) because of the study designs and conduct.)

The parameter that was used to summarize the pharmacokinetics of MHD was Cmin or trough concentrations of MHD. Trough concentrations were either actual observed concentrations or predicted by the applicant using a one compartment pharmacokinetic model with first order absorption and elimination. For details regarding this PK model, please refer to the Pharmacometrics review (Appendix 2).

PK-PD relationships in adults and children during adjunctive Trileptal therapy using the two approaches were modeled using non-linear mixed effects modeling approaches. The results from the PK-PD modeling in adjunctive therapy is summarized below. For additional details, please refer to the Pharmacometrics review (Appendix 2):

- 1) The effects of MHD trough concentrations on the 28-day seizure frequency were described using a linear function (see equations below):

$E0 = INT(0) + SLOPE(0) * TIME$ ; calculates the PD response for placebo patients

$EFF = E0 + SLOPE * CONC$ ; calculates PD effect for drug treated patients

- 2) In the clinical trials, patients were randomized to dose and not concentrations; these analyses to determine concentration-response relationships are therefore retrospective and exploratory in nature. The trials were not designed to enable determination of a "therapeutic range" of plasma MHD concentrations. Also, the study designs for adjunctive therapy were different in adults (OTPE1) and children (011). OTPE1 was designed as a fixed dose study, while 011 was designed as a flexible dose study. Plasma concentrations of MHD were obtained only during the maintenance phases and not during the titration phases of the studies. Therefore in light of these limitations, this data is useful to compare the pediatric and adult populations, but is not considered sufficient to develop complete PK-PD relationships.
- 3) The relationship between PD effect and trough MHD concentrations is not strong; however the data shows a trend for increased effect with increasing MHD concentrations (Figures 6-7).
- 4) The relationship between plasma MHD concentrations and the reduction in 28-day seizure frequency are not statistically different ( $\alpha=0.05$ ) between adults and children in the adjunctive therapy setting (Figures 6a and 6b). (statistical test that was used was the Log-likelihood ratio test). Additional plots of percent change of seizure frequency from baseline versus concentration (in adjunctive therapy) are included in Appendix 3.
- 5) As stated in (2), the study designs for adjunctive therapy were different in adults (OTPE1) and children (011). OTPE1 was designed as a fixed dose study, while 011 was designed as a flexible dose study. However, OTPE1 also had a small number (n=18) children included. PK-PD analysis was performed to determine whether the children within Study OTPE1 had a different concentration-response relationship compared to adults from the same study. This analysis suggested that the relationship between plasma MHD concentrations and the reduction in 28-day seizure frequency are not statistically different ( $\alpha=0.05$ ) between adults and children within Study OTPE1.
- 6) Based on (4) and (5), we assumed that the relationship between plasma concentrations of MHD and the 28-day seizure frequency in the monotherapy setting are not significantly different. This assumption was also supported by our analysis of the observed data for monotherapy. The monotherapy studies used in this analysis were studies 004, 006, 025. A brief description of the study designs is attached as part of the Appendix 1. The results suggest that the relationship between plasma concentrations of MHD and the PD endpoint

(28-day seizure frequency) are not statistically different ( $\alpha=0.05$ ) between adults and children in the monotherapy setting. However the number of children in this analysis was small,  $n=12$  on drug of which 1 was under the age of 8), (Figure 7a and 7b).

- 7) Our analysis of the concentration-response relationship for patients on adjunctive and monotherapy suggests that this relationship is not statistically different between adults and children. However, in discussions with the Medical Division, the issue was raised that this is not the same as stating that there is "pharmacodynamic equivalence" between the two populations. The applicant will be requested to submit a justification regarding the clinical relevance of this difference.

Figure 6a

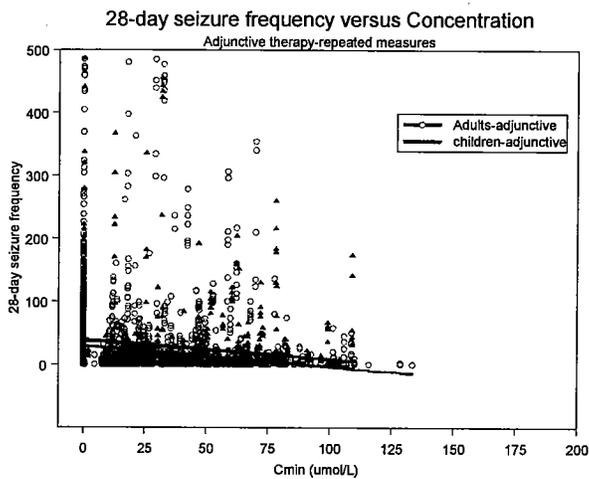


Figure 6b

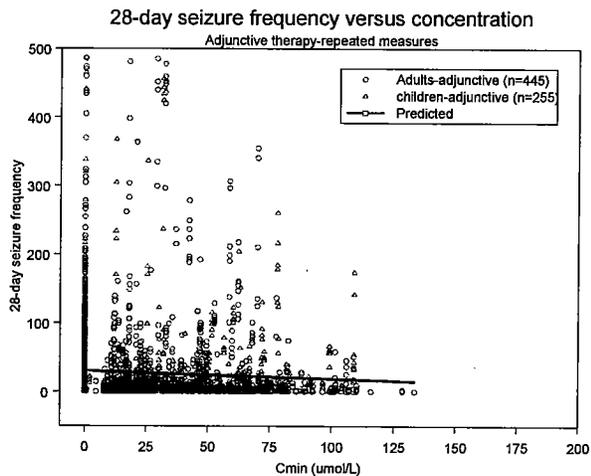


Figure 7a

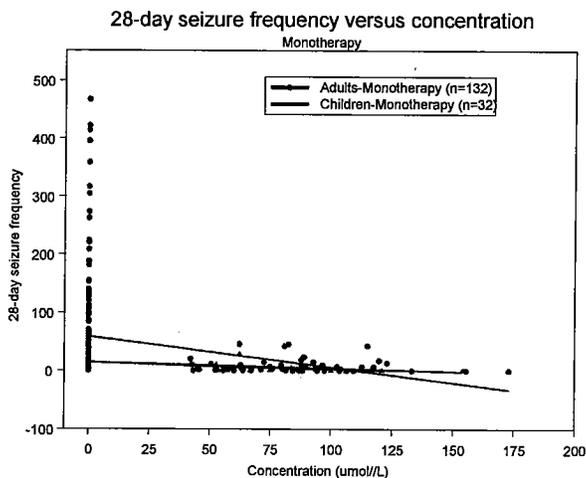
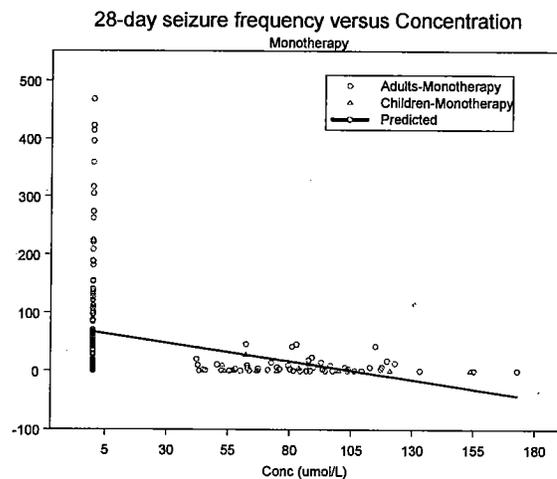


Figure 7b



LABELING COMMENTS

No labeling or dosing recommendations will be made at this time (See recommendations and comments to applicant).

Vanitha J. Sekar, Ph.D.  
Reviewer, Neuropharmacological Drug Section, DPE I  
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

Ramana Uppoor, Ph.D.  
Team Leader, Neuropharmacological Drugs  
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Jogarao Gobburu, Ph.D.  
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cc: HFD-120 NDA 21-014 (S005)  
/MO/ N. Hershkowitz  
/CSO/M. Fanari  
/Biopharm/V. Sekar  
/TL Biopharm/R. Uppoor, J. Gobburu  
HFD-860 /DD DPE1/M. Mehta

26 Page(s) Withheld

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✓ § 552(b)(4) Draft Labeling

\_\_\_\_\_ § 552(b)(5) Deliberative Process

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Jogarao Gobburu  
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BIOPHARMACEUTICS

Ramana S. Uppoor  
7/30/03 01:30:14 PM  
BIOPHARMACEUTICS

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## CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

**DRUG:** Trileptal® (Oxcarbazepine)  
**FORMULATION:** Tablets (150, 300, 600 mg)  
**TYPE:** Pediatric Efficacy Supplement  
**NDA:** 21014 SE5-003

**PRIMARY REVIEWER:** Vanitha Sekar  
**APPLICANT:** Novartis  
**DATE OF REVIEW:** 11/30/ 2001

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## OVERALL SUMMARY OF FINDINGS

Trileptal is currently indicated as monotherapy and adjunctive therapy for the treatment of partial seizures in adults and only as adjunctive therapy in children 4-16 years of age (Table 1). This supplement has been submitted for the approval of Trileptal as monotherapy in children aged 4-16 years. As opposed to conducting a controlled clinical efficacy trial to support this indication, a "PK-bridging" approach is being utilized. No new studies have been submitted, however, reanalysis of studies from the original NDA has been submitted.

Table 1

	Adults	Children (4-16 years of age)
Adjunctive	Trileptal approved on the basis of "positive" Phase 3 clinical trials	Trileptal approved on the basis of "positive" Phase 3 clinical trials
Monotherapy	Trileptal approved on the basis of "positive" Phase 3 clinical trials	"PK-bridging" approach proposed in this submission

In order to support the request for approval of Trileptal for pediatric monotherapy (in ages 4-16 years), the sponsor has submitted the following analysis: 1) comparison of concentrations achieved in children and adults during adjunctive therapy at the approved doses, 2) meta-analysis to confirm the effectiveness of Trileptal during monotherapy in children, 3) a dose-concentration analysis to determine an effective dose in children during monotherapy, and 4) evaluation of the seizure data to confirm the effectiveness of Trileptal at the recommended doses in children during monotherapy. However, the sponsor has not addressed the issue of pharmacodynamic equivalence or similarity between adults and children.

A summary of our analysis to address this issue is presented below:

- 1) Our analysis established that the relationship between plasma concentrations of MHD and the clinical endpoint (reduction in 28-day seizure frequency) are not statistically different ( $\alpha=0.05$ ) between adults and children. (n=280 adults on drug and 165 on placebo and n=120 children on drug and 136 on placebo) in the adjunctive therapy setting (Figure 1).
- 2) Based on (1), we assumed that the relationship between plasma concentrations of MHD and the clinical endpoint (28-day seizure frequency) in the monotherapy setting are not significantly different. This assumption was supported by our analysis of the observed data, which suggested that the relationship between plasma concentrations of MHD and the clinical endpoint (28-day seizure frequency) are not statistically different ( $\alpha=0.05$ ) between adults and children in the monotherapy setting. However the number of children in this analysis was small, n=12 on drug (Figure 2).
- 3) Plasma MHD concentrations were compared in adults and children following monotherapy at different doses (Figure 3). It appears that the average MHD trough concentrations in adults are slightly higher than those observed in children at a given dose (on a mg/kg basis) during monotherapy. Please refer to the Clinical Pharmacology section of this review for additional plots evaluating the effects of age and body weight on plasma MHD steady-state concentrations. A dosing regimen for monotherapy in pediatrics will be selected based on this data (subject of a future review after the applicant responds to our comments from this review).

Figure 1 (PK-PD analysis using repeated measures)

Figure 2 (PK-PD analysis using single PD measure)

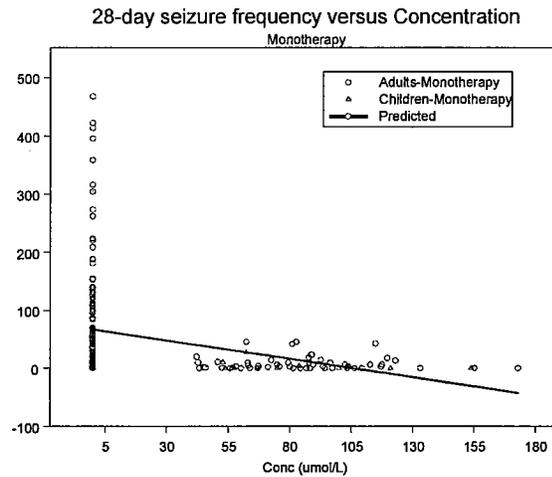
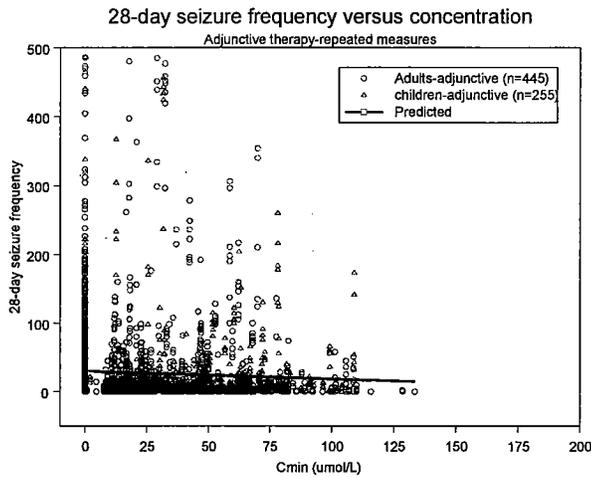
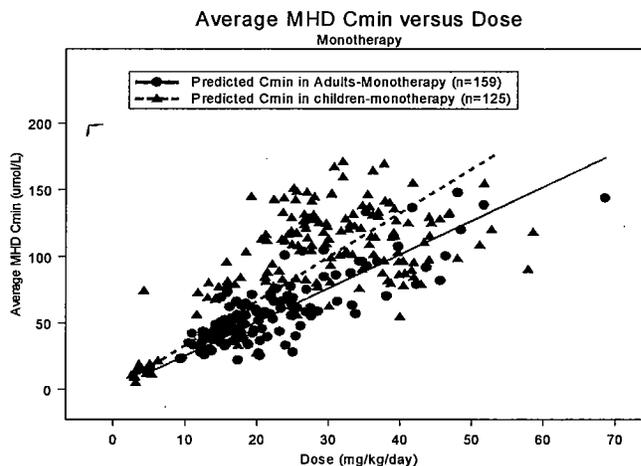


Figure 3



**RECOMMENDATION AND COMMENTS TO APPLICANT**

The Clinical Pharmacology review of the data provided in this supplement is adequate to support approvability of Trileptal as monotherapy in children 4-16 years of age, provided that the following comments are addressed by the applicant.

The following comments should be forwarded to the applicant:

1. Although our analysis of the placebo-response and concentration-response relationship for patients on adjunctive and monotherapy suggests that these relationships are not statistically different between adults and children, this is not the same as stating that there is "pharmacodynamic (PD) equivalence" between the two populations. We request that you submit to us a compelling argument to support PD equivalence between adult and pediatric populations and provide a justification as to what difference observed between children and adults from these analyses should not be considered clinically relevant.
2. Based on review of the applicant's response to (1), if it is concluded that the PK-PD relationship is sufficiently similar between children and adults, a dosing regimen in which these (adult) exposure levels could be reliably achieved when Trileptal is given to pediatric patients as true monotherapy should be determined.

## **INTRODUCTION AND BACKGROUND**

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The anticonvulsant properties of OXC and MHD are possibly mediated by blocking voltage dependant sodium channels, decreasing high voltage activated calcium channels and interaction with potassium channels. The blockade of voltage dependant sodium channels in the brain has been proposed as the most plausible mechanism of action. This is based on results from: 1) in-vitro studies in which OXC and MHD limited sustained high frequency repetitive firing of sodium-dependant action potentials of cultured mouse neurons, and 2) in-vivo study (maximal electroshock) which evaluates the ability of drugs to prevent electrically induced tonic hind limb extension seizures in rodents. Efficacy in the maximal electroshock model has been shown to correlate with the ability to prevent partial and generalized tonic-clonic seizures in humans; also drugs that are active in this test (e.g. carbamazepine, phenytoin) often interact with voltage dependant sodium channels.

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### **ANALYTICAL METHODS**

The bioanalytical methods used to quantify MHD in plasma in the studies submitted to this supplement were reviewed as part of the original NDA for Trileptal and found to be acceptable.

### **FORMULATION**

The formulation that was used in the clinical trials was Trileptal tablets 150, 300 and 600 mg.

## CLINICAL PHARMACOLOGY

### *Is the placebo-response similar between adults and children?*

The placebo response in children and adults was compared from two adjunctive therapy trials, OTPE1 and 011. A description of the study designs is attached as part of the Appendix 1. The placebo data from these trials were analyzed using the Kolmogorov-Smirnov (K-S) goodness-of-fit test to compare the distribution of placebo response in adults and children during adjunctive therapy. The results from this analysis suggest that the distribution of the placebo response is not different in children and adults during adjunctive therapy (Figures 4 and 5),  $p=0.6029$ .

Figure 4

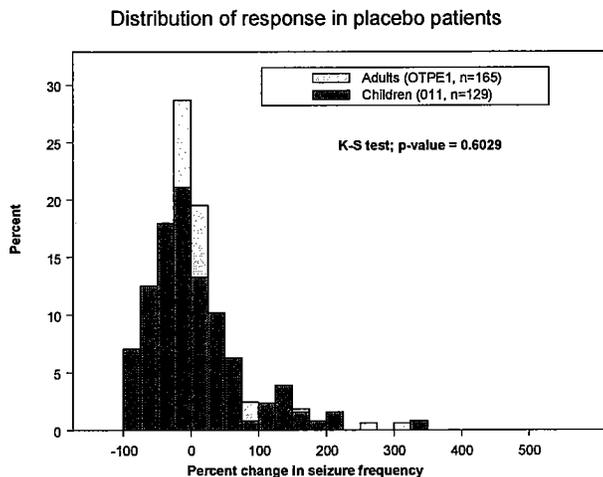
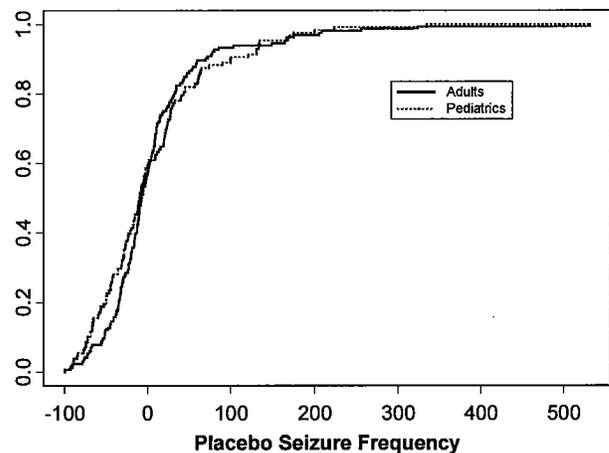


Figure 5



### *Is the relationship between plasma concentrations of MHD (PK) and the clinical (PD) endpoint (reduction in 28-day seizure frequency) similar between adults and children?*

In order to answer this question, the PK-PD relationship was compared in children and in adults in the adjunctive therapy setting. Data from 2 Phase 3 clinical trials (OTPE1 and 011) were used. A description of the study designs is attached as part of the Appendix 1.

The concentration-response relationship in the adjunctive therapy setting was examined for adults using the data from clinical trial OTPE1 and for children from trials OTPE1 and 011. The PD end point that was used in the analysis was the reduction in 28-day seizure frequency. This was also an efficacy endpoint for the adjunctive clinical trials. The 28-day seizure frequency was calculated as the number of seizures that occurred during a 28-day period during the baseline and double blind phase of the studies (See Appendix 1 for details). Two approaches were used to assess the PK-PD relationship in the adjunctive setting:

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(In the monotherapy setting, only approach (1) were used since data was unavailable to use approach (2) because of the study designs and conduct.)

The parameter that was used to summarize the pharmacokinetics of MHD was  $C_{min}$  or trough concentrations of MHD. Trough concentrations were either actual observed concentrations or predicted by the applicant using a one compartment pharmacokinetic model with first order absorption and elimination. For details regarding this PK model, please refer to the Pharmacometrics review (Appendix 2).

PK-PD relationships in adults and children during adjunctive Trileptal therapy using the two approaches were modeled using non-linear mixed effects modeling approaches. The results from the PK-PD modeling in adjunctive therapy is summarized below. For additional details, please refer to the Pharmacometrics review (Appendix 2):

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- 4) The relationship between plasma MHD concentrations and the reduction in 28-day seizure frequency are not statistically different ( $\alpha=0.05$ ) between adults and children in the adjunctive therapy setting (Figures 6a and 6b). (statistical test that was used was the Log-likelihood ratio test). Additional plots of percent change of seizure frequency from baseline versus concentration (in adjunctive therapy) are included in Appendix 3.
- 5) As stated in (2), the study designs for adjunctive therapy were different in adults (OTPE1) and children (011). OTPE1 was designed as a fixed dose study, while 011 was designed as a flexible dose study. However, OTPE1 also had a small number ( $n=18$ ) children included. PK-PD analysis was performed to determine whether the children within Study OTPE1 had a different concentration-response relationship compared to adults from the same study. This analysis suggested that the relationship between plasma MHD concentrations and the reduction in 28-day seizure frequency are not statistically different ( $\alpha=0.05$ ) between adults and children within Study OTPE1.
- 6) Based on (4) and (5), we assumed that the relationship between plasma concentrations of MHD and the 28-day seizure frequency in the monotherapy setting are not significantly different. This assumption was also supported by our analysis of the observed data for monotherapy. The monotherapy studies used in this analysis were studies 004, 006, 025. A brief description of the study designs is attached as part of the Appendix 1. The results suggest that the relationship between plasma concentrations of MHD and the PD endpoint

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Figure 6a

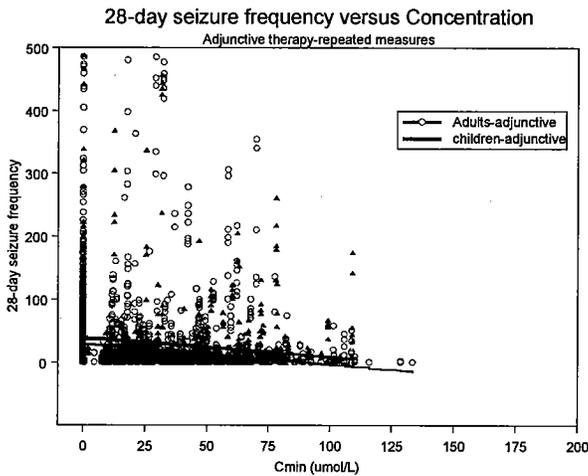


Figure 6b

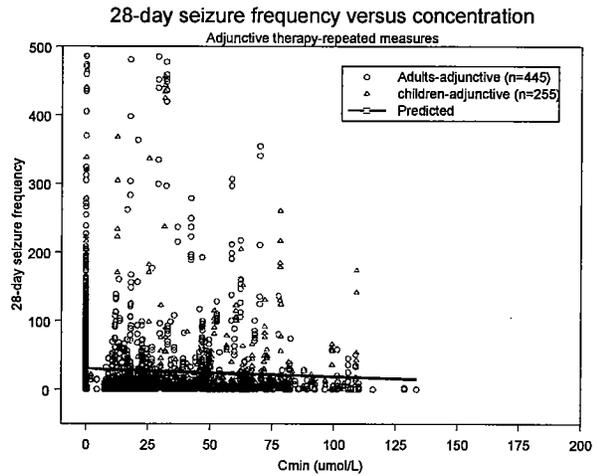


Figure 7a

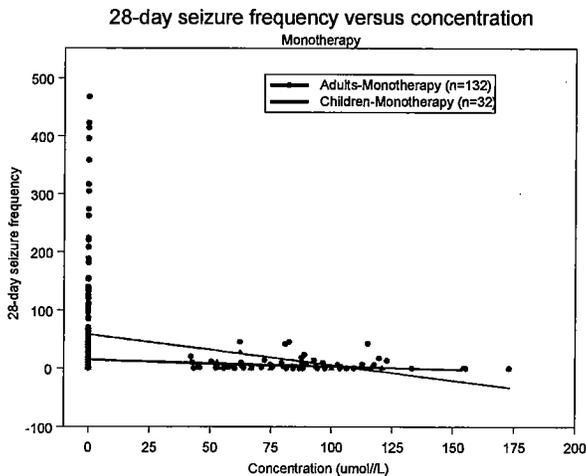
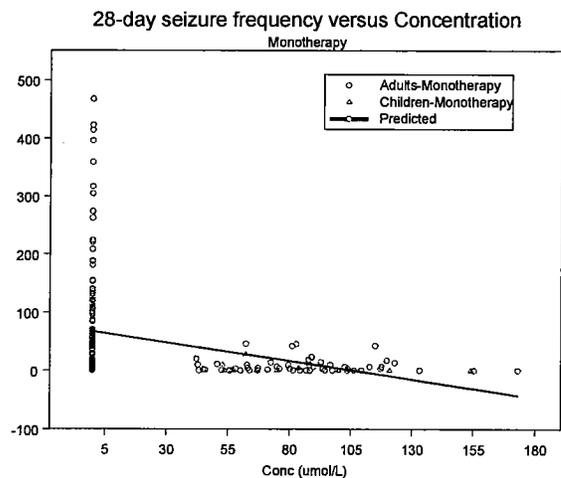


Figure 7b

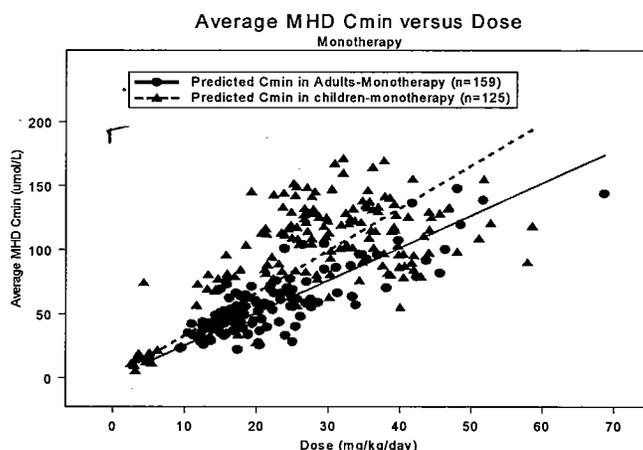


**Are the concentrations of plasma MHD comparable in adults and children following monotherapy?**

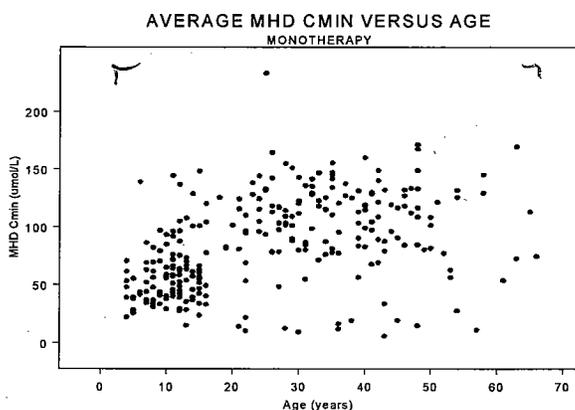
Plasma MHD trough concentrations were compared in adults and children following monotherapy at different doses. Plasma concentrations of MHD were obtained in the following monotherapy trials in adults (n=159) and/or children (n=125 of which 16 were <8 years old): 004, 006, 025, 026, 028, 30, 33, OTE26, OTF02, OTF04, OTF11. Concentrations were measured at different times relative to drug administration in the different studies. In cases where trough MHD concentrations were not measured, the C<sub>min</sub> was predicted using the pharmacokinetic model developed by the applicant using data from 011. For details regarding this PK model, please refer to the Pharmacometrics review (Appendix 2).

It appears that the average MHD trough concentrations in adults are slightly higher than those observed in children at a given dose (on a mg/kg basis) during monotherapy (Figure 8). Plots evaluating the effects of age and body weight on plasma MHD steady-state concentrations are shown in Figures 9-10. Figure 9 suggests that the MHD concentrations at steady state are independent of age.

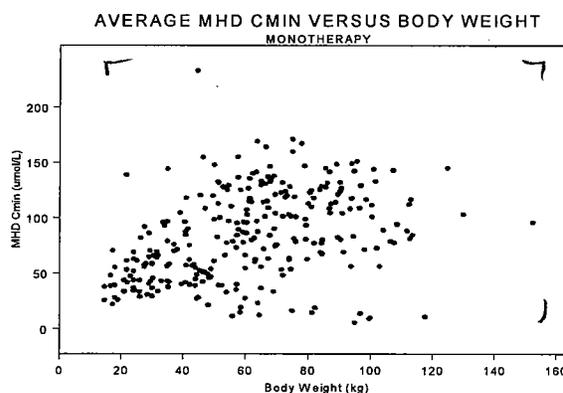
**Figure 8**



**Figure 9**



**Figure 10**



**LABELING COMMENTS**

No labeling or dosing recommendations will be made at this time (See recommendations and comments to applicant).

**Appears This Way  
On Original**

Vanitha J. Sekar, Ph.D.  
Reviewer, Neuropharmacological Drug Section, DPE I  
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

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**APPENDIX 1**  
**SUMMARY OF STUDY DESIGNS USED IN PK-PD ANALYSIS**

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## 1. Adjunctive Therapy in children: Study 011

**Study Design:** Protocol 011 was a multicenter, multinational, double-blind, placebo-control, randomized, parallel-group study designed to evaluate the safety and efficacy of oxcarbazepine as adjunctive therapy in pediatric patients with inadequately controlled partial seizures (including the seizure subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures). The study consisted of three phases: an 8-week Baseline Phase, a 16-week Double-blind Phase, and a Long-term Extension Phase. During the Baseline Phase, patients were required to have a minimum of eight seizures, with at least one seizure occurring in each 28-day period, and to remain on stable doses of one to two AEDs. The Double-blind Phase consisted of a 2-week Titration Period and a 14-week Maintenance Period. Patients were randomized to either oxcarbazepine (900-1800 mg/day based upon body weight) or placebo. Treatment in the oxcarbazepine group was initiated at 10 mg/kg/day. Patients who did not achieve their assigned dose levels during the Titration Period were titrated to their maximum tolerated dose. This dose was to remain constant during the 14-week Maintenance Period. There was some flexibility of dose allowed during the Maintenance Period if necessary and approved by a Novartis monitor. The dose of the concomitant AED(s) was to remain constant during the entire Double-blind Phase. Patients who completed the Double-blind Phase were eligible to enter the Long-term Extension Phase or a Tapering Period during which they were withdrawn from study drug.

The trial consisted of a baseline phase, double-blind treatment and an open label extension. The population pharmacokinetic analysis consists of data collected during the double blind treatment phase. The double blind phase consisted of a titration phase (14 days) and a maintenance phase (98 days). The titration scheme is shown below in Table 1. Based on body weight, patients' target randomized trial drug doses were determined on a mg/kg basis as shown below in Table 2.

Table 1

Days	Dose (mg/kg/day) given bid
1 to 2	10
3 to 6	20
7 to 10	30
11 to 14	Randomized dose or maximum tolerated dose (whichever was less)

Table 2

Body weight	Target randomized daily dose (given bid)
20 to 29 kg	900 mg (31 mg/kg to 45 mg/kg)
29.1 to 39 kg	1200 mg (31 mg/kg to 41 mg/kg)
39.1 to 60 kg	1800 mg (30 mg/kg to 46 mg/kg)

Patients with body weight >60 kg were randomized to 1800 mg/day dose.

Plasma concentrations of MHD and concomitant antiepileptic drugs were measured on Study days 42, 56, 84 and 112 during the maintenance period. At least one plasma sample was obtained on each of these days in each of the following time periods: 0800-1100 hrs, 1101-1400 hrs, 1401 to 1800 hrs. MHD was analyzed in plasma using a validated HPLC method (Note: the analytical methods section was reviewed as part of the original NDA for Trileptal tablets).

The patient population for the population pharmacokinetic analysis consisted of 109 patients contributing a total of 376 blood samples. Of the 109 patients, 58 were male and 51 were female; 93 were Caucasian, 7 were Black, 1 was Oriental and the remaining were other races. Patients ranged in age from 3 to 17 years (one patient was aged 3 years). (Note: n=5 at 4 years, n=5 at 5 years, n=7 at age 6 years, n=7 at age 7 years). Baseline demographic characteristics are shown below in Table 3. The frequency of coadministered antiepileptic drugs for patients in the pharmacokinetic analysis is shown below (out of n=109) in Table 4.

Table 3

Demographic	N	Mean	SD	Min	Max
Age (years)	109	11.0	3.9	3	17
BSA (m <sup>2</sup> )	108	1.31	0.39	0.68	2.59
CrCL (ml/min)	108	79	30	30	150
Height (cm)	108	143	21	98	186
Baseline Seizure Freq (per 28 days)	109	50.1	151	3	1470
SGOT (U/L)	109	23.6	15.1	9	160
SGPT (U/L)	109	16.4	9.5	0	58
Weight (kg)	109	43.3	20.7	15.9	134.5

Table 4:

Coadministered antiepileptic drug	Number of patients on the drug
Carbamazepine	58
Diazepam	4
Gabapentin	14
Lamotrigine	17
Phenobarbital	14
Phenytoin	15
Valproic Acid	33

**Selection Criteria:** Participants were selected from male and female patients 4 to 17 years of age, (two 3-year olds were allowed entry in the study), who weighed at least 20 kg. Patients were required to experience at least eight seizures during the Baseline Phase with at least one partial seizure occurring during each 28-day period. Patients were required to remain on stable doses of one to two concomitant AEDs that were approved in the country in which they were participating in the study. All other non-allowed AED medications needed to be discontinued at least 30 days prior to starting the Baseline Phase except felbamate which needed to be discontinued at least 90 days prior to starting the Baseline Phase.

**Efficacy Variables:** The primary efficacy variable was the percentage change (PCH) in partial seizure frequency per 28 days of the Double-blind Phase relative to the Baseline Phase. Patients who provided double-blind seizure diary data over a longer time period than specified in the protocol had their partial seizure frequency per 28 days adjusted to include data from the time period immediately after randomization to the time point where the Double-blind Phase was intended to end as specified in the protocol. This variable was calculated as the number of partial seizures per 28 days in the Double-blind Phase minus the number of partial seizures per 28 days in the Baseline Phase all divided by the number of partial seizures per 28 days in the Baseline Phase, all multiplied by 100. The partial seizure frequency per 28 days for any study phase was calculated as the total number of partial seizures reported during the phase divided by the number of days in the phase. all multiplied by 28. Secondary efficacy variables included the number and percentage of responders to treatment (defined as a 50% or greater reduction in partial seizure frequency per 28 days from baseline) and the percentage change in secondarily generalized seizure frequency per 28 days from baseline.

**Pharmacokinetic Assessments:** Blood samples for the analyses of MHD derivative and DHD levels were obtained at selected visits during the double-blind phase (or when a patient terminated from the study).

## 2. Adjunctive Therapy in adults and children: Study OTPE1

**Study Design:** Protocol OTPE1 was a multicenter, double-blind, placebo-control, randomized parallel-group study designed to evaluate the safety and efficacy of oxcarbazepine as adjunctive therapy in patients with inadequately controlled partial seizures (including the seizure subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures). The study consisted of three phases: an 8-week prospective baseline phase, a 26-week Double-blind Phase and a Long-term Extension Phase. During the 8 weeks prior to and during the prospective Baseline Phase, patients were required to have an average of at least four seizures per month and remain on stable doses of one to three AEDs. The Double-blind phase consisted of a 2-week Titration Period and a 24-week Maintenance Period. During the Double-blind Phase, patients

were randomized to receive 600, 1200 or 2400 mg/day of oxcarbazepine or placebo. Treatment in each oxcarbazepine group was initiated at 600 mg/day (4.3-17.1 mg/kg/day) and titrated up to the randomized dose. The randomized dose was held constant for the Maintenance Period. The dose of the concomitant AED(s) was to remain constant during the entire Double-blind Phase. For patients assigned to 2400 mg/day, a reduction in dose to 1800 mg/day was allowed when necessary (by an amendment). Patients who completed the Double-blind Phase were eligible to enter the Long-term Extension Phase or a Tapering Period during which they were withdrawn from study drug.

**Selection Criteria:** Participants were selected from male and female patients 15 to 65 years of age. Patients were required to experience at least four partial seizures per month during the 56-day period prior to entering the Baseline Phase while receiving treatment with one to three AEDs (felbamate excluded by protocol). Patients were required to have a white blood cell count  $>3 \times 10^9/L$ .

**Efficacy Variables:** The primary and secondary efficacy variables were similar to those in Protocol 011.

**Pharmacokinetic Assessments:** Blood samples for MHD derivative analysis were obtained Prior to the first dose of study medication and as trough samples thereafter before the morning Dose (if possible) of study medication at selected visits during the Double-blind Phase.

### 3. Monotherapy in adults and children: Study 004

**Study Design:** Protocol 004 was a multicenter, double-blind, placebo-control, randomized, parallel-group study designed to assess the safety and efficacy of oxcarbazepine as Monotherapy in patients with inadequately controlled partial seizures (including the seizure subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures). The study consisted of three phases: a 48-hour Baseline Phase, a 10-day Double-blind Phase, and a Long-term Extension Phase. During the Baseline Phase, patients completing an inpatient presurgical evaluation, who had been taken off all AED(s), were required to have two to 10 partial seizures within 48 hours of randomization. The Double-blind Phase consisted of a 1-day Titration Period and a 9-day Maintenance Period. Patients began treatment with a 1-day dose of 1500 mg/day oxcarbazepine or matching placebo and then received 2400 mg/day oxcarbazepine or matching placebo for the 9-day Maintenance Period. Patients completing the entire Double-blind Phase, or meeting one of the exit criteria, were eligible to enter the Long-term Extension Phase.

**Selection Criteria:** Participants were selected from male and female patients, 12 to 65 years of age who weighed at least 45 kilograms. Hospitalized patients were required to have undergone a presurgical evaluation for epilepsy and been tapered off of all previous concomitant AEDs. Tapering off of benzodiazepine therapy was required 15 days prior to presurgical evaluation. Lorazepam was the only medication allowed for seizure control during the Baseline Phase. During the Baseline Phase, patients needed to experience two to 10 partial seizures of which a maximum of two seizures could be partial seizures evolving to secondarily generalized seizures.

**Efficacy Criteria:** The primary efficacy variable was the time to meeting one of the exit criteria. The time to this event was computed from Day 2 at 8 a.m. (the beginning of the Maintenance Period) to the date and time one of the exit criteria was met. When meeting one of these exit criteria, a patient was considered to have completed the Double-blind Phase and was then eligible for the Long-term Extension Phase. The exit criteria were defined as: 1) experience of a fourth partial seizure with or without partial seizures evolving to secondarily generalized seizures (exclusive of seizures occurring during the 24-hour Titration Period); 2) experience of two new-onset partial seizures evolving to secondarily generalized seizures; and 3) experience of serial seizures or status epilepticus deemed by the investigator to require intervention. Any patient who finished the entire Double-blind Phase or prematurely discontinued for any reason was classified as a censored patient for these analyses. Secondary efficacy variable evaluated was the percentage of patients meeting one of the exit criteria.

**Pharmacokinetic Assessments:** Blood samples for the analysis of oxcarbazepine and its

metabolites were collected before the first dose of the study drug and thereafter as trough samples before the morning dose on selected days during the Double-blind Phase (or when a patient complained of adverse experiences or prematurely discontinued).

#### 4. Monotherapy in children: Study 006

**Study Design:** This study was a multinational, multicenter, double-blind, placebo-control, randomized, parallel-group study designed to evaluate the safety and efficacy of oxcarbazepine therapy in newly-diagnosed, untreated pediatric patients with partial seizures (including the seizure subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures). The study consisted of three phases: a 6-month retrospective Baseline Phase, a 112-day Double-blind Phase and a 10-day Tapering Phase. During the Baseline Phase, patients needed to have experienced at least two seizures. The Double-blind Phase consisted of a 10-day Titration Period and 102-day Maintenance Period. Patients were randomized to receive either 600-1500 mg (18-37 mg/kg/day) oxcarbazepine based upon body weight, or placebo. The dose achieved at the end of the Titration Period was the dose used in the subsequent Maintenance Period, although some flexibility of dose was allowed during the Maintenance Period. A Double-blind Tapering Phase was included for patients who completed the Double-blind Phase, prematurely discontinued, or met the exit criterion. This study was prematurely terminated because of slow patient enrollment.

**Selection Criteria:** Participants were selected from male and female patients, 15 years of age inclusive or younger, who weighed 17.0-80.0 kg. Patients needed to be currently untreated with recent-onset or newly diagnosed partial seizures with or without secondarily generalized seizures, and must have experienced at least two seizures during the Baseline Phase.

**Efficacy Criteria:** The primary efficacy variable was the time to first partial seizure. The time to the occurrence of this event was computed from the date and time of first dose of double-blind study drug to the date and time of the occurrence of the first partial seizure. Counting towards meeting this efficacy endpoint began as soon as a patient received their first dose of double-blind study drug. A secondary efficacy variable included the percentage of seizure-free patients. Since the study was prematurely terminated due to slow patient recruitment, no formal statistical analyses of the results were actually conducted.

**Pharmacokinetic Assessment:** Blood samples for the analysis of the MHD plasma levels were collected as morning trough levels (or random MHD plasma levels if morning trough levels could not be obtained) at selected Visits during the Double-blind Phase.

#### 5. Monotherapy in adults and children: Study 025

**Study Design:** Protocol 025 was a multicenter, double-blind, placebo-control, randomized, Parallel group study designed to evaluate the safety and efficacy of oxcarbazepine in patients with inadequately controlled partial seizures (including the seizure subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures). The study consisted of three phases: a 56-day Baseline Phase (all or part of which could have been retrospective), a 90-day Double-blind Phase, and a Long-term Extension Phase. During the Baseline Phase, patients were required to experience at least two seizures per month and were not allowed to have received any AED treatment in the previous 3 months. The Double-blind Phase consisted of a 6-day Titration Period and an 84-day Maintenance Period. Patients were randomized to receive either oxcarbazepine 1200 mg/day (titrated over 6 days) or placebo. Patients completing the entire Double-blind Phase or who experienced their first seizure and were allowed to leave the study, were eligible to enter the Long-term Extension Phase.

**Selection Criteria:** Participants were selected from male and female patients, at least 10 years of age, who weighed at least 32 kg. Patients were required to have an onset of partial seizures within 2 years and experience at least two partial seizures per month during the Baseline Phase. In addition, each patient was required to have at least 1 seizure-free year prior to the current onset of partial seizures and could not have received treatment from standard AED(s) within 90 days of randomization.

**Efficacy Criteria:** The primary efficacy variable was the time to first partial seizure. The

time to the occurrence of this event was computed from the date and time of first dose of double-blind study drug to the date and time of the occurrence of the first partial seizure. A secondary efficacy variable evaluated the percentage of seizure-free patients.

**Pharmacokinetic Assessments:** Blood samples for the analysis of oxcarbazepine and the MHD plasma levels were collected as trough levels at one center and according to the following schedule at all other centers: blood collection times at selected visits during the Double-blind Phase distributed over three time slots of 8:00 am to 11 :00 am, 11 :01 am to 2:00 p.m. and 2:01 p.m. to 6:00 p.m..

**APPENDIX 2  
PHARMACOMETRICS REVIEW**

## APPENDIX 2

### Pharmacometrics Review

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<b>NDA :</b>	<b>21-014 (S-005)</b>
<b>Compound:</b>	<b>Trileptal Tablets</b>
<b>Submission Date:</b>	<b>2/9/01</b>
<b>Sponsor:</b>	<b>Novartis Pharmaceuticals</b>
<b>Pharmacometrics Reviewer:</b>	<b>Vanitha J. Sekar</b>
<b>Pharmacometrics Team Leader:</b>	<b>Jogarao Gobburu</b>

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#### **Section I Population Pharmacokinetic-Pharmacodynamic Analysis of Trileptal in the Pediatric Population and adults**

**Objectives:** The objectives of this analysis were to:

1. Compare the placebo response in the adult and pediatric patients,
2. Compare the pharmacokinetic-pharmacodynamic (PK-PD) relationship for Trileptal in adults and pediatrics in the adjunctive therapy setting,
3. Compare the pharmacokinetic-pharmacodynamic (PK-PD) relationship for Trileptal in adults and pediatrics in the monotherapy setting,

#### **Methods:**

##### **Study Design(s), Data and Endpoints:**

***Adjunctive Therapy:*** Pharmacokinetic (PK) and pharmacodynamic (PD) data from 2 Phase 3 clinical trials (OTPE1 and 011) were used. A description of the study designs is attached as part of the Appendix 1. From study OTPE1, a total of 445 adults (n=280 on drug and n=165 on placebo) and 110 children aged 15-17 years (n=11 on drug and n=99 on placebo) were included in the PK-PD analysis. From study 011, a total of 146 children aged 3-17 years (n=37 on placebo and n=109 on drug) were included in the PK-PD analysis.

The PK measure that was used in the analysis was trough concentration (C<sub>min</sub>) of MHD. Trough concentrations were either actual observed concentrations or predicted by the applicant using a one compartment PK model with first order absorption and elimination. For details regarding this PK model, please refer to the Section II of this review.

The PD measure that was used in the analysis was the reduction in 28-day seizure frequency. This was also the efficacy endpoint for the clinical trials. The 28-day seizure frequency was calculated as the number of seizures that occurred during a 28-day period during the baseline and double blind phase of the studies. Two approaches were used to assess the PK-PD relationship in the adjunctive therapy setting:

- 1) PD consisted of a single measurement of the clinical response after the baseline period – the overall double blind 28-day seizure frequency that was used as the clinical end point,
- 2) PD consisted of repeated measurements of seizure frequency by visit during the double blind period of the study (following the baseline period)

***Monotherapy:*** The monotherapy studies used in this analysis were studies 004, 006 and 025. A description of the study designs is attached as part of the Appendix 1. The number of patients from monotherapy trials was small – this analysis was performed only to support our assumption that the relationship between plasma concentrations of MHD and the 28-day seizure frequency in the monotherapy setting would not be significantly different (if the relationships are not significantly different in the adjunctive setting). The number of adults included in the analysis was

132 (n=52 on drug and n=80 on placebo) and the number of children was 32 (n=12 on drug of which 1 was under the age of 8).

The PK measure that was used in the analysis was trough concentration (C<sub>min</sub>) of MHD. Trough concentrations were either actual observed concentrations or predicted by the applicant using a one compartment pharmacokinetic model with first order absorption and elimination. For details regarding this PK model, please refer to the Section II of this review.

The PD measure that was used in the analysis was the 28-day seizure frequency. This was not one of the efficacy endpoints for the monotherapy clinical trials, however these data were collected and recorded during the conduct of the trials. In the monotherapy setting, only approach (1) was used since data was unavailable to use approach (2) because of the study designs and conduct.

**Concentration-Response Relationship for Trileptal:** Initial model explorations suggested that the effects of MHD trough concentrations on the 28-day seizure frequency were described using a linear function. Therefore, PK-PD relationships in adults and children were modeled using a linear function using non-linear mixed effects modeling approaches. All modeling was performed using NONMEM version 5, level 1.1 using the first order conditional estimation method. Data formatting was performed using Microsoft Excel and SAS version 6.12. The model was parameterized in the intercept (INT) and slope (DISP for placebo-treated patients and SLP for drug-treated patients). Covariates that were tested in the model included baseline seizure frequency, age, population (1=children, 0=adults).

**E0=INT(0)+DISP\*TIME; calculates the PD response for placebo patients**

**EFF=E0+SLP\*CONC; calculates PD effect for drug treated patients**

A description of the model building and selection is presented below in Tables 1-3.

Table 1 Model Building: Selection of covariates (using repeated measures of seizure frequency, i.e. by-visit data; adjunctive therapy)

<i>Model</i>	<i>-2 x Log Likelihood</i>
Base model: no covariates. and additive residual error model	36600.224
Base+ Population (Pop) as covariate for SLP	36600.221
Base+ Population (Pop) as covariate for DISP	36599.949
Base+ Baseline seizure frequency as covariate for SLP	36295.783*
Base+ Baseline seizure frequency as covariate for DISP	36600.229
Base+ Age as covariate for SLP	36600.230
Base+ Age as covariate for DISP	36600.224
Base+ Age as covariate for INT	36600.224

\* p < 0.01 in comparison with final model

Table 2 Model Building: Selection of covariates (using single PD measure of seizure frequency; adjunctive therapy)

<i>Model</i>	<i>-2 x Log Likelihood</i>
Base model: no covariates. and additive residual error model	13819.698
Base+ Population (Pop) as covariate for SLP	13820.157
Base+ Population (Pop) as covariate for DISP	13818.976
Base+ Baseline seizure frequency as covariate for SLP	13789.167*
Base+ + Baseline seizure frequency as covariate for DISP= final model	13643.252*
Base + Baseline seizure frequency as covariate for SLP and DISP	13643.253

\* p < 0.01 in comparison with final model

Table 3 Model Building: Selection of covariates (using single PD measure of seizure frequency: monotherapy)

Model	-2 x Log Likelihood
Base model: no covariates. and additive residual error model	3049
Base+ Population (Pop) as covariate for SLP	3057
Base+ Population (Pop) as covariate for DISP	3038*
Base+ Baseline seizure frequency as covariate for SLP	3047
Base+ Baseline seizure frequency as covariate for DISP= final model	2988*
Base + Baseline seizure frequency as covariate for SLP and DISP	3017
Base+ Baseline seizure frequency as covariate for DISP	2987
+ Population as covariate for DISP	2987

\* p < 0.01 in comparison with final model

## Results and Discussion

### Evaluation of Placebo-response in Adults and Children on Adjunctive Therapy

Prior to examining the PK-PD relationship, the placebo response in children and adults was compared from the two trials. The placebo data from these trials were analyzed using the Kolmogorov-Smirnov (K-S) goodness-of-fit test to compare the distribution of placebo response in adults and children during adjunctive therapy. Figures 1-4 describe and compare the distribution of response (% change in 28-day seizure frequency) in adults and children during adjunctive therapy. Visual inspection of the data and statistical results suggest that the distribution of the placebo response is not different in children and adults during adjunctive therapy.

Figure 1

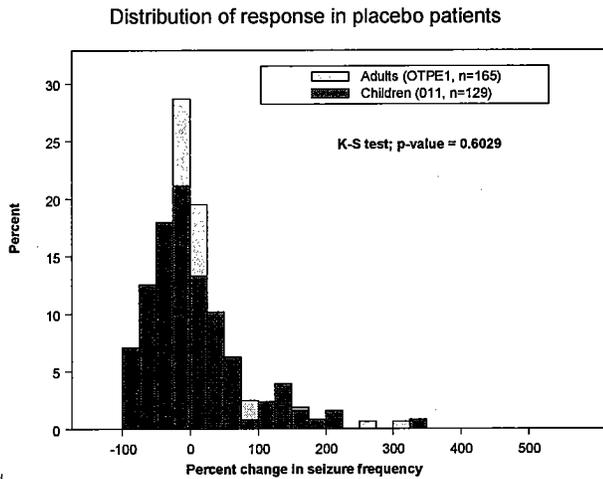


Figure 2

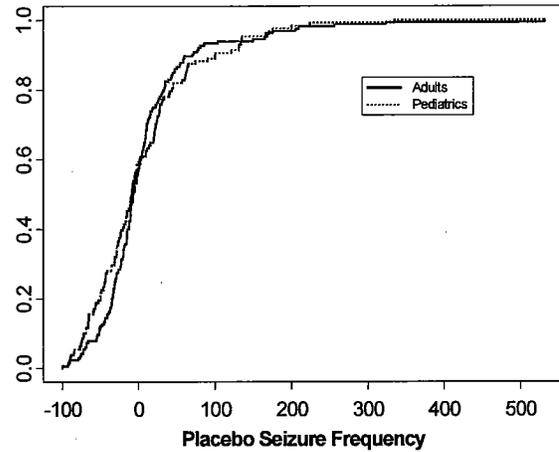


Figure 3

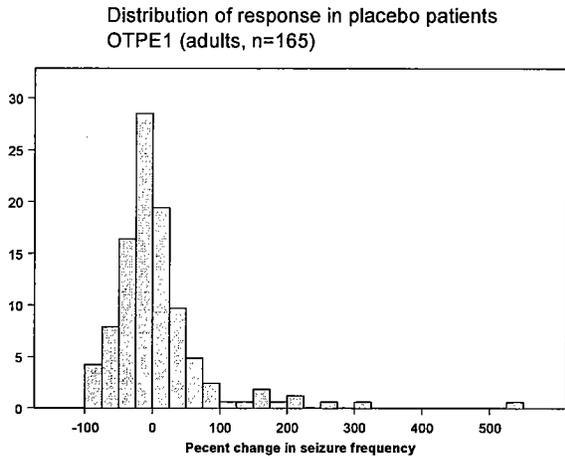
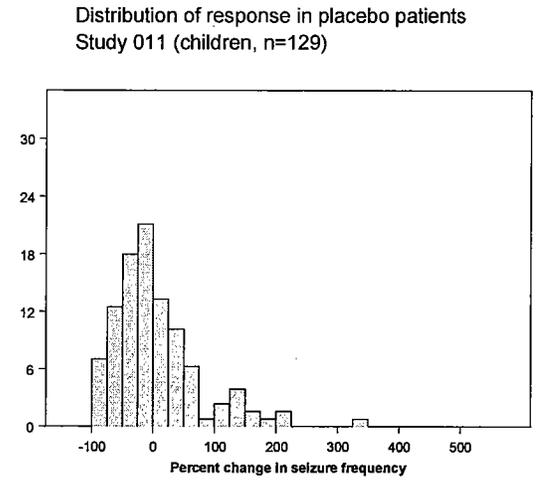


Figure 4



### Concentration-Response Relationship for Trileptal in Adjunctive Therapy

Visual inspection of the plots of 28-day seizure frequency versus MHD concentration suggests that the relationship between PD effect and trough MHD concentrations is not strong (see figures 5-6). However, the data shows a trend for increased effect with increasing MHD concentrations.

Plots illustrating the relationship between the various covariates and the parameters (slopes for placebo and drug-treated patients) in the adjunctive therapy setting using repeated PD measures are shown in Figures 7-9. These (covariate) plots are shown only for the scenario where repeated measures of PD were obtained. For the scenario of the single PD measure, the relationships were similar.

Figure 5 (Repeated PD measures-adjunctive therapy)

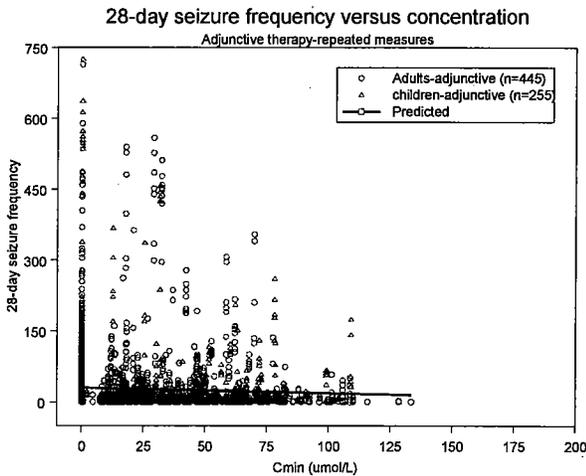


Figure 6 (Single PD measure- adjunctive therapy)

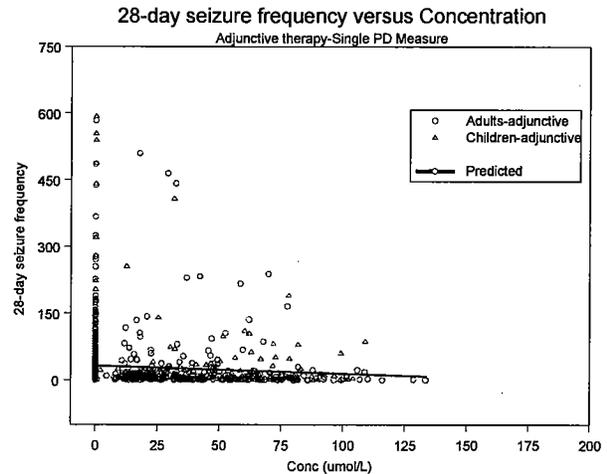


Figure 7a

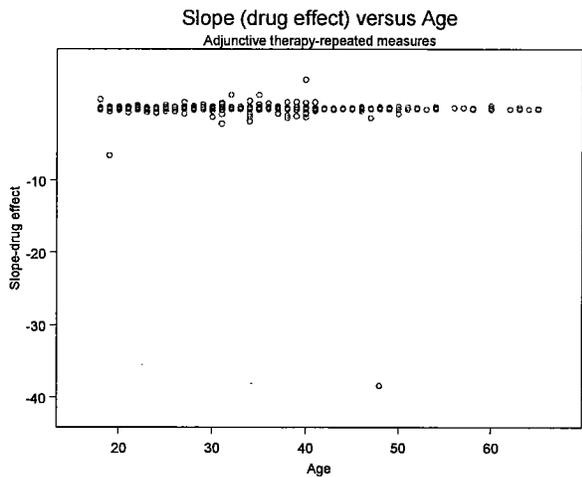


Figure 8a

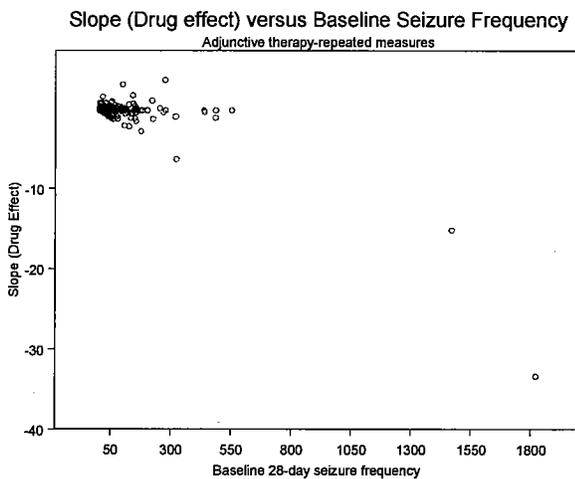


Figure 9a

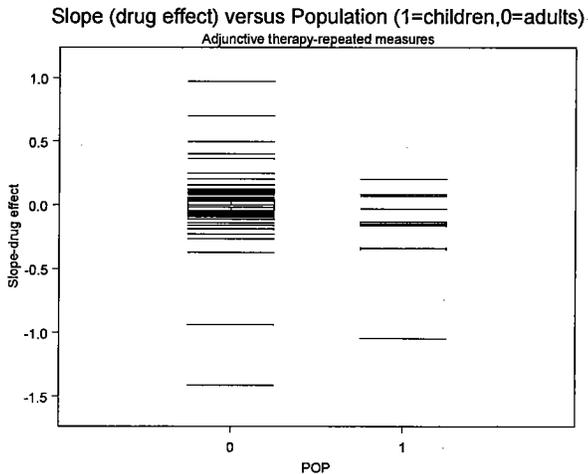


Figure 7b

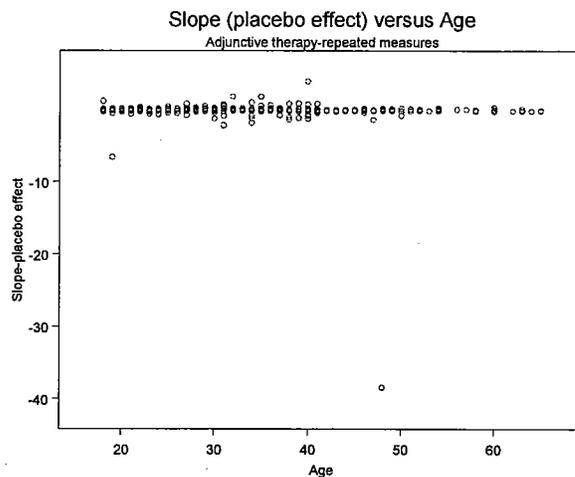


Figure 8b

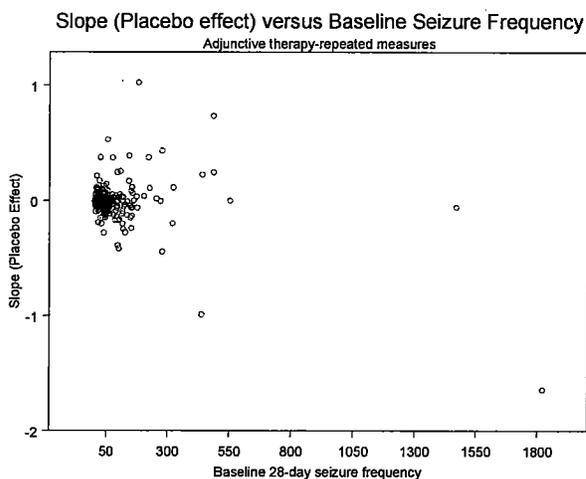
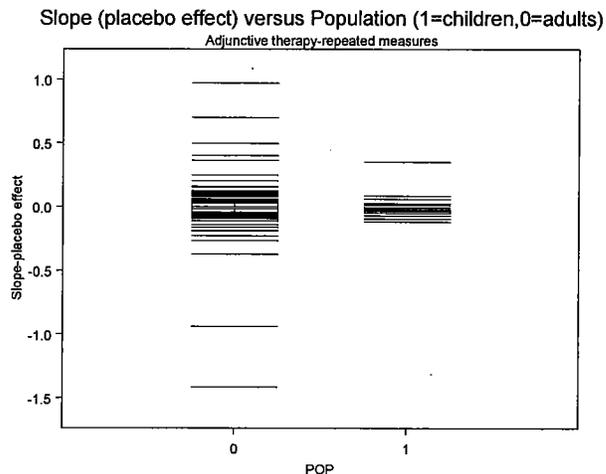


Figure 9 b



Baseline seizure frequency was found to be a significant covariate in the final model (using repeated measures of PD response) that affected the slope of the the drug effect (SLP). Baseline seizure frequency was also found to be a significant covariate in the final model (using a single measurement of PD response) that affected the slope of the placebo and drug response (DISP and SLP). Although the plots of baseline versus the model parameters (Figures 7a and 7b) did not suggest a trend, incorporation of baseline as a covariate in the models resulted in a highly significant decrease (Table 1) in the objective function. However, the model with baseline as a covariate resulted in negative predicted values for seizure frequency. Therefore, the base model was used as the final model in the repeated measures analysis. Representative profiles of 28-day seizure frequency vs time(using repeated PD measures) to illustrate the goodness-of-fit of the final model (using repeated PD measures) are shown in Figure 10a. The plot of observed seizure frequency versus predicted (by the final model using repeated PD measures) is shown in Figure 10b.

Figure 10a

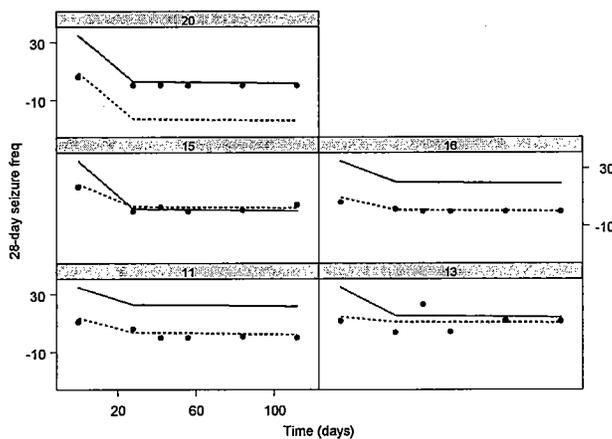
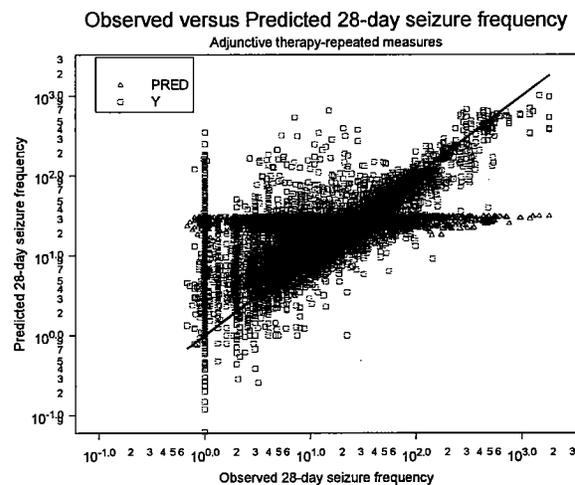


Figure 10b



The relationship between plasma MHD concentrations and the 28-day seizure frequency are not statistically different ( $\alpha=0.05$ ) between adults and children in the adjunctive therapy setting.

Population pharmacodynamic parameter estimates in the adjunctive setting for the final models are shown in the Tables 4-6 below. Since the inter-individual variability is very large, this model can be utilized only to conclude that on the average the PK-PD relationship in children and adults is not significantly different (Table 6), but it cannot be utilized to make any individual predictions. It is important to note that the model does not reflect the mechanism of action of the drug, and is highly empirical. Exploration of physiologically relevant models was limited by the available data.

Table 4: Population parameter estimates (PD model with repeated measures of seizure freq in adjunctive therapy)

	Slope (seizures/days) (placebo effect)	Slope (seizures/ $\mu\text{mol/L}$ ) (drug effect)	Intercept (seizures)
Mean	-0.0137	-0.319	34.7
SE (%)	91.2	56.7	11.7
IIV (% CV)	1400	700	267
SE (%)	35.3	173.1	61.1
Residual Error, seizures	30.3809		

**Table 5: Population parameter estimates comparing children and adults (PD model with repeated measures of seizure freq in adjunctive therapy)**

	Slope (placebo) (seizures/days) Adults	Slope(placebo) (seizures/days) children	Slope (drug) (seizures/umol/L) Adults	Slope (drug) (seizures/umol/L) children	Intercept (seizures) Adults	Intercept (seizures) children
Mean	-0.0115	-0.0187	-0.33	-0.251	30.7	42.1
SE (%)	124.3	320.9	94.8	129.1	16.5	16.6

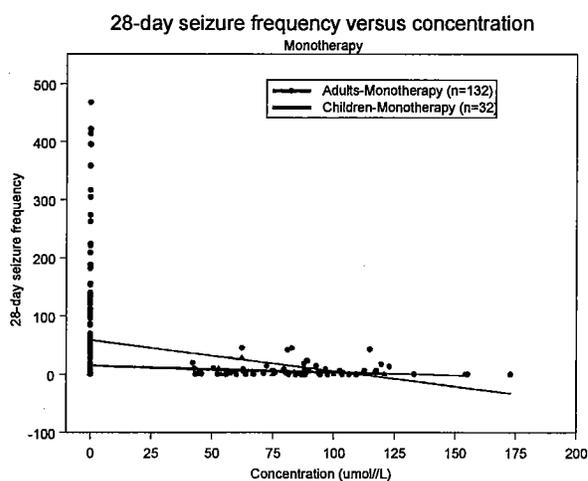
**Table 6: Population parameter estimates (PD model with single measure of seizure freq in adjunctive therapy)**

	Slope (seizures/days) (placebo effect)	Slope (seizures/umol/L) (drug effect)	Intercept (seizures)
Mean	-0.635	-0.167	34.2
SE (%)	63.3	242.5	11.5
Residual Error, seizures	79.68 (additive)		
SE (%)	51.3		

### **Concentration-Response Relationship for Trileptal in Monotherapy**

Based on the finding that the relationship between plasma MHD concentrations and the 28-day seizure frequency are not different between adults and children in the adjunctive therapy setting, we assume that the relationship between plasma concentrations of MHD and the 28-day seizure frequency in the monotherapy setting are also not significantly different. This assumption was also supported by PK-PD analysis of the observed monotherapy PK and PD data (Figure 11). The results suggest that the relationship between plasma concentrations of MHD and the PD endpoint (28-day seizure frequency) are not statistically different ( $\alpha=0.05$ ) between adults and children in the monotherapy setting. However the number of children in this analysis was small, n=12 on drug of which 1 was under the age of 8.

**Figure 11 (Monotherapy-Single PD Measure)**



Population pharmacodynamic parameter estimates in the monotherapy setting for the final models are shown in the Table 7 below. The inter-individual variability in the monotherapy setting is also very large; this model can be utilized only to conclude that on the average the PK-PD relationship in children and adults is not significantly different, but it cannot be utilized to make any individual predictions.

Note: The monotherapy studies were not designed to measure the reduction in 28-day seizure frequency as an efficacy endpoint; these data were derived retrospectively. Also, the sample size in this analysis was small compared to that in the adjunctive therapy setting. Therefore, these results from this analysis are only supportive in nature.

**Table 7: Population parameter estimates (PD model with single measure of seizure freq in monotherapy)**

	Slope (placebo effect)	Slope (drug effect)	Intercept
<b>Mean</b>	<b>-0.113</b>	<b>-0.764</b>	<b>37.7</b>
<b>SE (%)</b>	<b>268</b>	<b>16</b>	<b>8.5</b>
<b>Residual Error</b>	<b>61.07</b>		
<b>SE (%)</b>	<b>(additive) 19.0</b>		

**Reviewer’s Comments and Conclusions**

Our analysis of the concentration-response relationship for patients on adjunctive and monotherapy suggests that this relationship is not statistically different between adults and children. However, this is not the same as stating that there is “pharmacodynamic equivalence” between the two populations. The applicant will be requested to submit a justification regarding the clinical relevance of this difference. Based on review of the applicant’s response, if it is concluded that the PK-PD relationship is sufficiently similar between children and adults, a dosing regimen in which these exposure levels could be reliably achieved when Trileptal is given to pediatric patients as true monotherapy should be determined.

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## **Section II Assessment of predictability of applicant's population pharmacokinetic model**

### **Objective**

The objective was to assess the predictive ability (to provide reasonable individual predictions) of the population pharmacokinetic (PK) model developed by the applicant to describe the PK of MHD.

### **Methods**

#### ***Study Design and Pharmacokinetic Data***

The study (O11) design is described in detail in Appendix 1.

#### ***Population Pharmacokinetic Model***

The base structural model was a one compartment model with first order absorption and elimination with a time lag. Covariates excluding concomitantly administered antiepileptic drugs were first considered for inclusion in order to account for interpatient differences in apparent oral clearance (CL/F) and apparent Volume of distribution (V/F). The covariates that were tested are listed in table 7; in addition gender and race were also tested as covariates in the model. The Study day (or visit number) was also included as a covariate to test for visit-to-visit differences in pharmacokinetics of MHD. Based on this covariate analysis, BSA was found to be the only covariate significantly affecting CL/F and height for V/F. Therefore, these two covariates were included the pharmacokinetic model. Following this, the seven coadministered antiepileptic drugs (AEDs) were then added simultaneously to the model affecting CL/F. Three of the seven coadministered drugs (carbamazepine, phenobarbital and phenytoin) were found to be significant covariates affecting CL/F for MHD. The residual error model was a combined constant and proportional error model. The final population pharmacokinetic model contained a combined residual error model and two random effects, CL/F and V/F. Body surface area and three coadministered AEDs (carbamazepine, phenobarbital and phenytoin) were the covariates affecting CL/F; height was the covariate affecting V/F (see below). The addition of other covariates in to the final model were not significant.

$$\begin{aligned} CL1 &= BSA/1.3^{**}THETA(7) \\ CL2 &= THETA(8)^{**}CRBA * THETA(9)^{**}PHNO \\ CL3 &= THETA(10)^{**}PHNY \\ TVCL &= THETA(1)*CL1*CL2*CL3 \\ CL &= TVCL*EXP(ETA(1)) \\ V1 &= HT/145^{**}THETA(12) \\ TVV &= THETA(2)*V1 \\ V &= TVV*EXP(ETA(2)) \end{aligned}$$

The final model was analyzed for appropriateness using goodness-of-fit tests which are described below in the Results section.

### **Results and Discussion**

A description of the model building and selection is presented below in Tables 7-9.

**Table 7 Model Building: Selection of covariates**

Model	-2 x Log Likelihood
Stage 0 Model	
Naive model: $\Omega=0$ , no covariates. and combined residual error model	2879.1
Stage 1 Model	
Correlated intersubject random effects for CLf and V/f, no covariates and combined residual error	2591.7***
Stage 2 Models=Stage 1 + one covariate	
Stage 1 + Age as covariate for CLf	2529.2***
Stage 1 + Body Surface Area as covariate for CLf	2494.5***
Stage 1 + Creatinine Clearance as covariate for CLf	2519.8 ***
Stage 1 + Gender as covariate for CLf	2577.4***
Stage 1 + Height as covariate for CLf	25052 ***
Stage 1 + Race as covariate for CLf	2588.2
Stage 1 + Seizure frequency as covariate for CLf	2591.4
Stage 1 + SGOT as covariate for CLf	2568.4***
Stage 1 + SGPT as covariate for CLf	2591.7
Stage 1 + Visit as covariate for CLf	2589.7
Stage 1 + Weight as covariate for CLf	2498.8***
Stage 1 + Age as covariate for V/f	2586.1*
Stage 1 + Body Surface Area as covariate for V/f	2584.3**
Stage 1 + Height as covariate for V/f	2583.6**
Stage 1 + Weight as covariate for V/f	2585.1**
Stage 2 models: Stage 1 + Body Surface Area (BSA) for CL/f + one new covariate	
Stage 1 + BSA for CLf + Age as covariate for CLf	2493.6
Stage 1 + BSA for CLf + Creatinine Clearance as covariate for CLf	2494.5
Stage 1 + BSA for CLf + Gender as covariates for CLf	2492.1
Stage 1 ...BSA for CLf + Height as covariate for CLf	2493.2
Stage 1 + BSA for CLf + Race as covariate for CLf	2489.9*
Stage 1 + BSA for CLf + Seizure frequency as covariate for CLf	2493.5
Stage 1 + BSA for CLf + SGOT as covariate for CLf	2486.7*
Stage 1 + BSA for CLf + SGPT as covariate for CLf	2494.1
Stage 1 + BSA for CLf + Visit as covariate for CLf	2493.0
Stage 1 + BSA for CLf + Weight as covariate for CLf	2493.2
Stage 1 + BSA for CLf + Age as covariate for V/f	2486.1*
Stage 1 + BSA for CLf + BSA as covariate for V/f	2484.0**
Stage 1 + BSA for CLf + Height as covariate for V/f	2483.6**
Stage 1 + BSA for CLf + Weight as covariate for V/f	2484.6**
Stage 2 models: Stage 1 + BSA for CL/f + Height as covariate for V/f + AEDs as covariate for CL/f	
Stage 1 + BSA for CLf + Height as covariate for V/f	
+ 7 AEDs as covariates for CLf = Full Model	2426.7
Stage 1 + BSA for CLf + Height as covariate for V/f +	
<u>3 AEDs as covariates for CL/f = Final Model</u>	<u>2433.2</u>

\* p < 0.05 in forward selection conditional on model from previous step

\*\* p < 0.01 in forward selection conditional on model from previous step

\*\*\* p<0.001 in forward selection conditional on model from previous step

Table 8 Final Model Assessment: comparisons to expanded or restricted models

Model	-2 x Log Likelihood
Stage 1 + BSA for CLf + Height as covariate for V/f + 7 AEDs as covariates for CLf = Full Model	2426.7
Stage 1 + BSA for CLf + Height as covariate for V/f + 3 AEDs as covariates for CLf = Final Model	2433.2
Full Model + Two-way interactions of AEDs	2422.2
Final Model + one new covariate	
Final Model + Age as covariate for CLf	2433.1
Final Model + Creatinine clearance as covariate for CLf	2433.1
Final Model + Dose as covariate for CLf	2430.1
Final Model + Gender as covariate for CLf	2432.3
Final Model + Height as covariate for CLf	2432.4
Final Model + Race as covariate for CLf	2430.8
Final Model + Seizure frequency as covariate for CLf	2433.2
Final Model + SGOT as covariate for CLf	2427.6*
Final Model + SGPT as covariate for CLf	2432.9
Final Model + Visit as covariate for CLf	2431.8
Final Model + Weight as covariate for CLf	2432.4
Final Model + Age as covariate for V/f	2433.0
Final Model + Body surface area as covariate for V/f	2433.1
Final Model + Weight as covariate for V/f	2433.1
Final model expanded in other ways	
Final Model + full covariance structure for CLf, V/f, and KA	2430.4
Final Model + absorption time lag (ALAG 1) not set to zero	2433.1
Restricted models	
Final Model without Body surface area as covariate for CLf	2547.4***
Final Model without Height as covariate for V/f	2440.5**
Final Model without AEDs as covariates for CLf	2483.6***
Final Model with proportional residual error model (i.e., THETA5=0)	2433.2
Final Model with constant residual error model (i.e., THETA6=0)	2490.1***
Final Model without random effect for CLf	2518.8***
Final Model without random effect for V/f	2477.2***
*p < 0.05 in comparison with final model	
** p < 0.01 in comparison with final model	
*** p < 0.001 in comparison with final model	

Table 9 Parameter estimates (and their standard errors) from the full population-pharmacokinetic model with seven AEDs and the final model with three selected AEDs

	Full Model with 7 AEDs	Final Model with 3 AEDs
THETA1 (L/h)	2.39 (0.159)	2.33 (0.110)
THETA2 (L)	89 (67.2)	177 (60.5)
THETA3 =KA (h-1)	0.632 (0.272)	0.598 (0.248)
THETA4 =ALAG1	0.0 (by constraint)	0.0 (by constraint)
Exponent for BSA as covariate for CLf	0.866 (0.0687)	0.902 (0.0736)
Exponent for Height as Covariate for V/f	3.40 (1.10)	3.54 (1.14)
Ratio for carbamazepine	1.29 (0.077)	1.31 (0.0679)
Ratio for diazepam	0.938 (0.0382)	1.0 (by constraint)
Ratio for gabapentin	0.852 (0.0658)	1.0 (by constraint)
Ratio for lamotrigine	0.967 (0.0522)	1.0 (by constraint)
Ratio for phenobarbital	1.29 (0.114)	1.33 (0.112)
Ratio for phenytoin	1.36 (0.107)	1.35 (0.104)
Ratio for valproic acid	1.05 (0.0518)	1.0 (by constraint)
Intersubject variance for random effect for CLf	0.0376 (0.00832)	0.0409 (0.00926)
Intersubject variance for random effect for V/f	9.52 (7.31)	8.49 (6.29)
Intersubject covariance for CLf / V/f random effects	0.303 (0.163)	0.293 (0.166)
THETA5	0.395 (16.7)	0.787 (14.6)
THETA6	0.0295 (0.00844)	0.0298 (0.00778)
-2 log likelihood	2426.7	2433.2

Figure 8: MHD plasma concentrations versus time post-dose. Solid line is the prediction from the final model and dotted line is prediction for the full model.

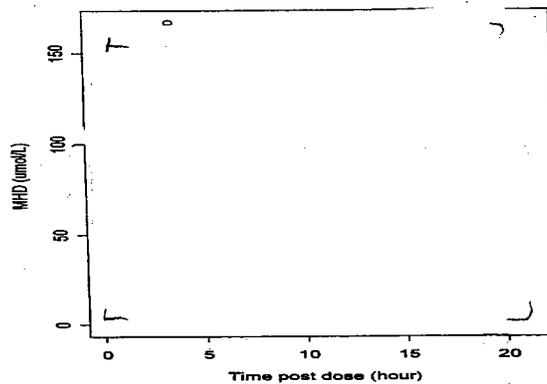
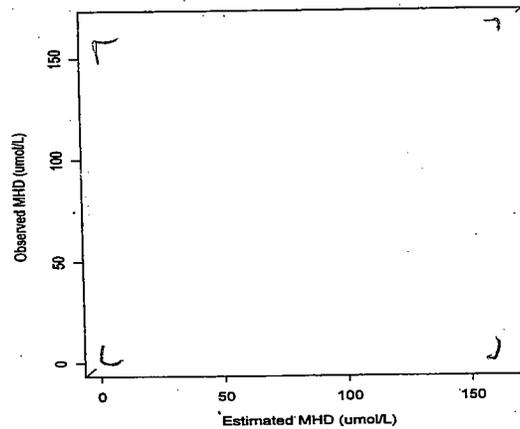
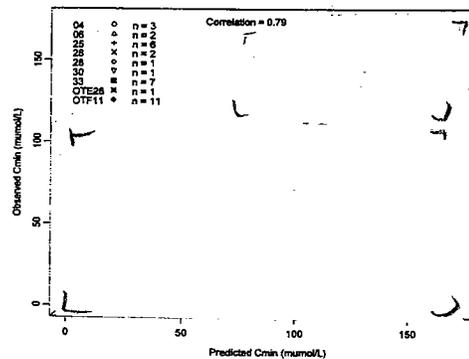


Figure 9: Observed versus Predicted Concentrations (during adjunctive therapy) from the Final PK model



**Application of the PK model:** The applicant has used the above described population PK (which was developed in the setting of pediatric adjunctive therapy) model to predict MHD trough concentrations (Cmin) in adults and children during adjunctive as well as monotherapy. Figure 10 shows a plot of the observed Cmin versus predicted Cmin for patients on monotherapy.

Figure 10 Observed versus Predicted Concentrations (during monotherapy)



**Reviewer's Comments and Conclusions:** The population PK model developed by the applicant reasonably predicts MHD concentrations (trough) in adjunctive and monotherapy setting.

Vanitha J. Sekar, Ph.D.  
Reviewer, Neuropharmacological Drug Section, DPE I  
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

Jogarao Gobburu, Ph.D.  
Team Leader, Pharmacometrics Group,  
DPE I, OCPB

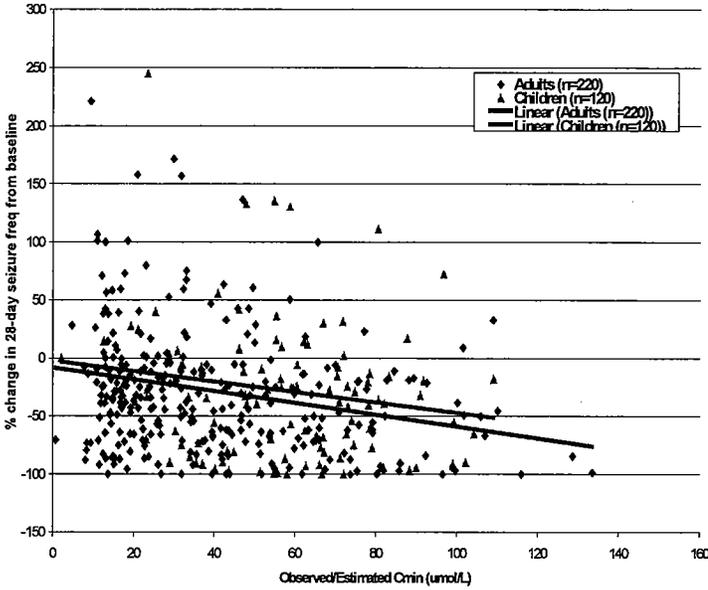
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	HFD-860	/DD DPE1/M. Mehta

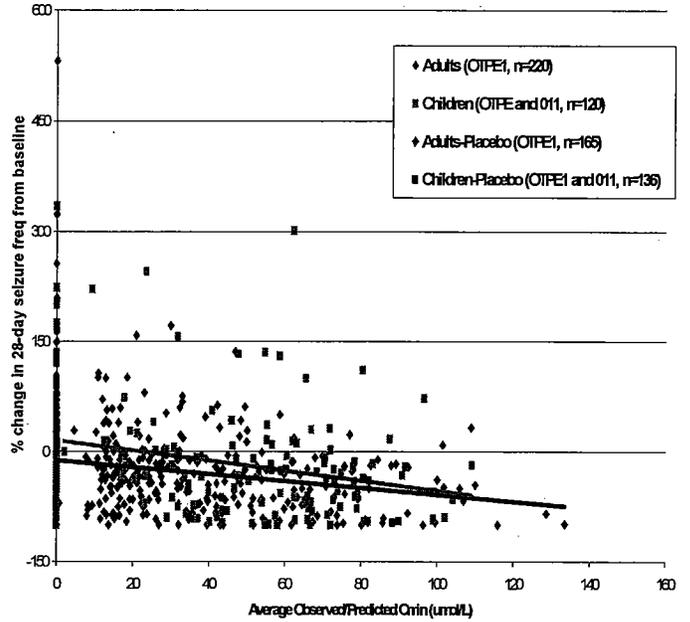
**APPENDIX 3**  
**PLOTS- %CHANGE FROM BASELINE VERSUS MHD CONC**

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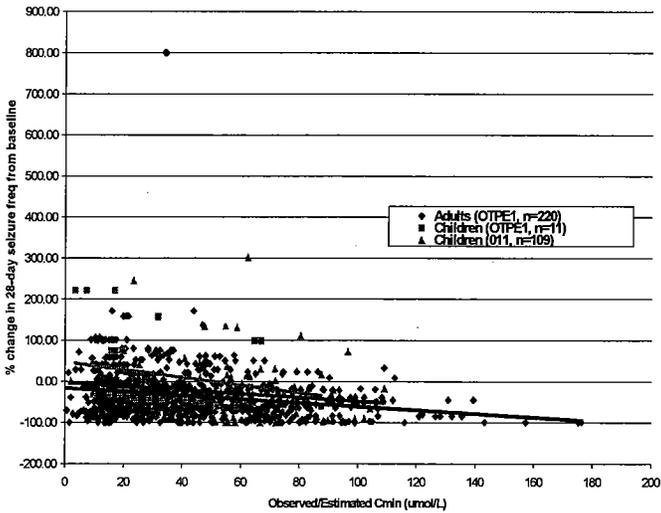
Percent change in 28-day seizure freq from baseline versus Crin (OTPE1, 011)  
(without placebo data)



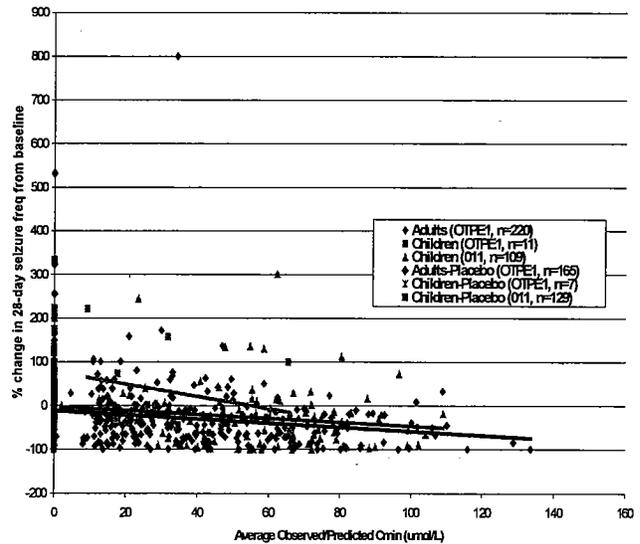
Percent change in 28-day seizure freq from baseline versus Crin (OTPE1, 011)  
with placebo



Percent change in 28-day seizure freq from baseline versus Crin (OTPE1, 011)  
(without placebo data)



Percent change in 28-day seizure freq from baseline versus Crin (OTPE1, 011)  
with placebo



**APPENDIX 4**  
**OCPB NDA FILING AND REVIEW FORM**

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**Office of Clinical Pharmacology and Biopharmaceutics  
New Drug Application Filing and Review Form**

**General Information About the Submission**

	Information		Information
NDA Number	21-014 S-005	Brand Name	Trileptal
OCPB Division (I, II, III)	I	Generic Name	Oxcarbazepine
Medical Division	Neuropharm	Drug Class	Anti-epileptics
OCPB Reviewer	Vanitha J. Sekar	Indication(s)	Partial seizures
OCPB Team Leader	Ramana Uppoor Jogarao Gobburu	Dosage Form	Tablets
		Dosing Regimen	Dosing recommendation in adults : 600-2400 mg/day, as bid dosing Dosing recommendation in children 4-16 years of age (adjunctive) : 8-51 mg/kg/day, as bid dosing
Date of Submission	2/9/01	Route of Administration	Oral
Estimated Due Date of OCPB Review	11/30/01	Sponsor	Novartis
PDUFA Due Date	12/11/01	Priority Classification	Standard
Division Due Date			

**Clin. Pharm. and Biopharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<b>Healthy Volunteers-</b>				
<b>single dose:</b>				
<b>multiple dose:</b>				
<b>Patients-</b>				
<b>single dose:</b>				
<b>multiple dose:</b>	X			
Dose proportionality -				
<b>fasting / non-fasting single dose:</b>				
<b>fasting / non-fasting multiple dose:</b>				
Drug-drug interaction studies -				
<b>In-vivo effects on primary drug:</b>				
<b>In-vivo effects of primary drug:</b>				
<b>In-vitro:</b>				
Subpopulation studies -				
<b>ethnicity:</b>				
<b>gender:</b>				
<b>pediatrics:</b>	X			
<b>geriatrics:</b>				
<b>renal impairment:</b>				
<b>hepatic impairment:</b>				
PD:				
<b>Phase 2:</b>				
<b>Phase 3:</b>				
PK/PD:				

<b>Phase 1 and/or 2, proof of concept:</b>				
<b>Phase 3 clinical trial:</b>				
Population Analyses -				
<b>Data rich:</b>	X			
<b>Data sparse:</b>	X			
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
<b>solution as reference:</b>				
<b>alternate formulation as reference:</b>				
Bioequivalence studies -				
<b>traditional design; single / multi dose:</b>				
<b>replicate design; single / multi dose:</b>				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
Filability and QBR comments				
	"X" if yes	Comments to be sent to firm		
<b>Application filable ?</b>	X			
<b>Comments sent to firm ?</b>				
QBR questions (key issues to be considered)	No new studies have been submitted, however, reanalysis of studies from the original NDA has been submitted. The appropriateness of the sponsor's PK-bridging approach (using population pharmacokinetic analysis) as well as the proposed dosing regimen for this indication will be evaluated.			
Other comments or information not included above				
Primary reviewer Signature and Date	Vanitha Sekar, PhD			
Secondary reviewer(s) Signature and Date	Ramana Uppoor, PhD Jogarao Gobburu, PhD			

CC: NDA 21-014, HFD-850(Lee), HFD-120(Fanari), HFD-860(Sekar, Uppoor, Gobburu, Mehta, Sahajwalla), CDR (B. Murphy)

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this page is the manifestation of the electronic signature.**  
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/s/

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Vanitha Sekar  
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Venkata Ramana Uppoor  
12/7/01 05:12:10 PM  
BIOPHARMACEUTICS

Jogarao Gobburu  
12/10/01 09:41:46 AM  
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