

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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

**STATISTICAL REVIEW(S)**

## **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

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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:

1. Justification of the PK/Efficacy analysis
2. Equivalence of PK/Efficacy relationships in adults and pediatric patients
3. Methods of determining effective concentrations and doses
4. 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

1. 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:

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

The empirical model for pediatric patients was

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

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,  $\epsilon_A$ ,  $\epsilon_P$ , 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

## 2. 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.

### 2.1 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.

## 2.2 – 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.

## 2.3 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:

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

This is the same as:

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

The sponsor used the available data and estimated the 95% confidence interval of the ratio  $\hat{\beta}_{P,1}/\hat{\beta}_{A,1}$ . 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):

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

which reduces to

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

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.**

## 2.4 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.

## 2.5 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

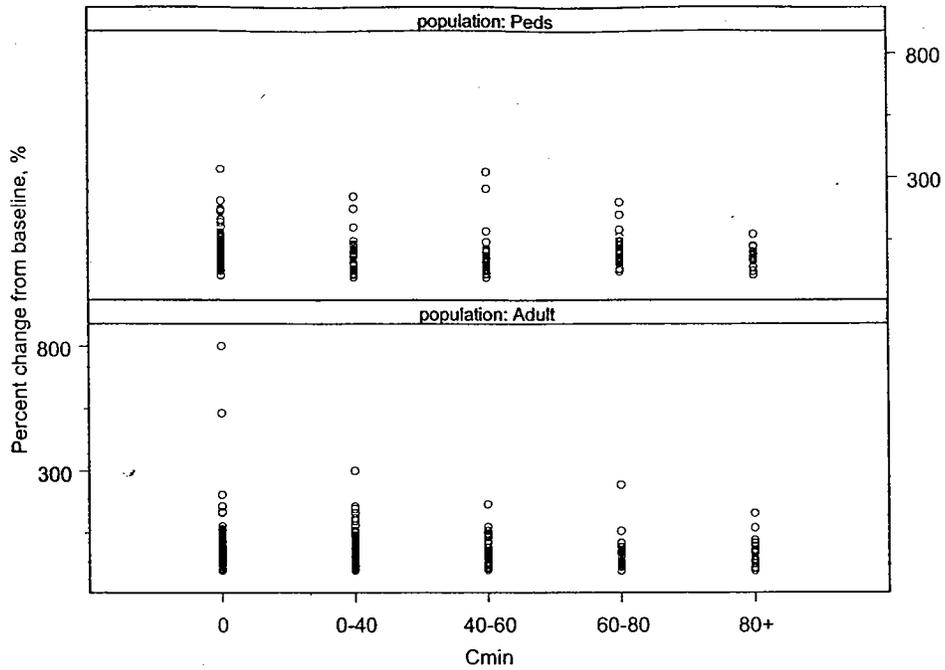
### 1. The PK/Efficacy models

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.

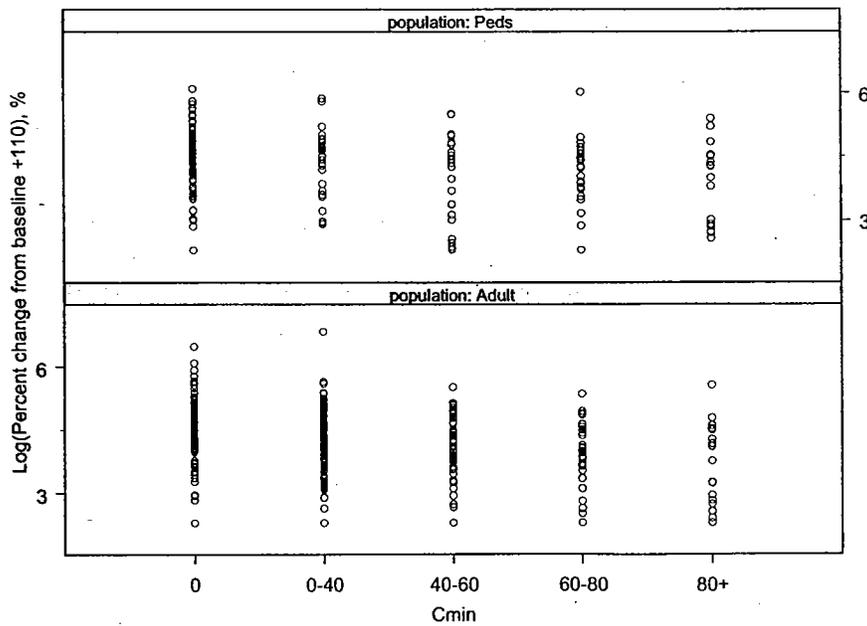
When developing models for different populations, one would generally use the same model form (eg, linear,  $e_{max}$ ) for each one. We consider it would have been better practice to have used model (1) for the pediatric population, where the interaction term between baseline frequency and  $C_{min}$  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  $\log(\text{PCB}+110)$  values for pediatric and adult patients. The average response to treatment for pediatric patients is less steep than that for adults.

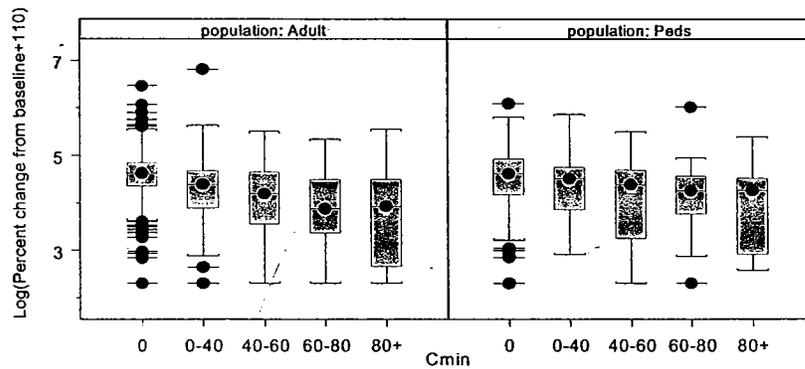
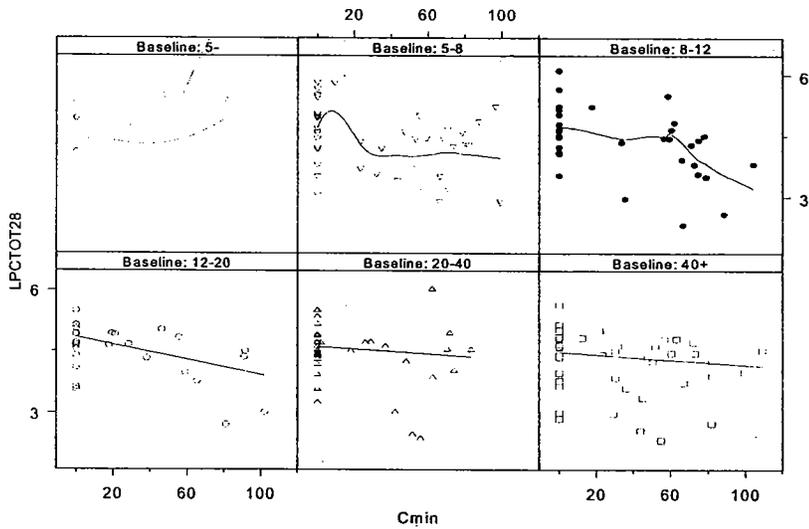
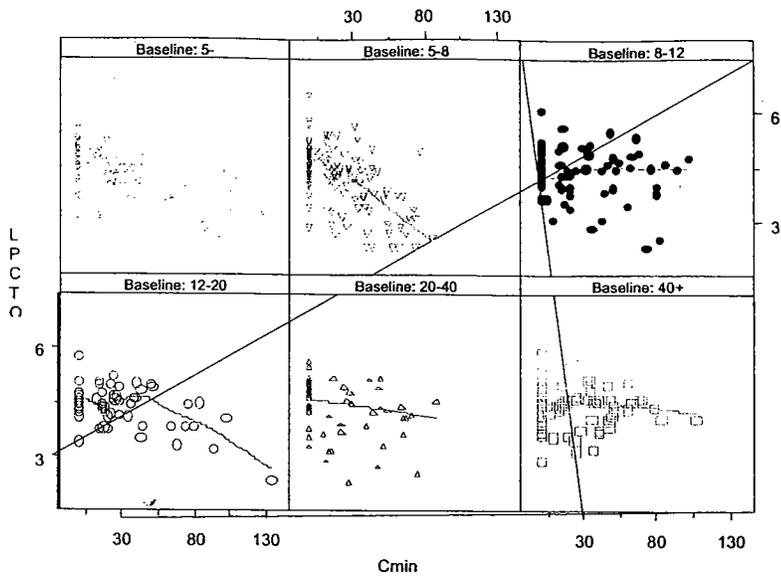


Figure 2 Box plots of  $\log(\text{PCB}+110)$  versus categorized Cmin for adult and pediatric patients

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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.

## 2. 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		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

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?

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.

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?

To demonstrate similarity of PK/efficacy, one needs to establish that the predicted efficacy responses in the two populations are closely similar, for each Cmin 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 Cmin in the range 40.8 to 112. The 95% confidence intervals for these percentages were broad: for Cmin = 40.8, the interval was 51% to 119% and for Cmin = 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 Cmin=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 Cmin 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 Cmin=40.8; the width of the confidence intervals is greater/narrower for Cmin values less than/greater than 40.8. For Cmin 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  $\beta_0^i = \beta_0 + z_0(\text{s.e.}(\beta_0))$  and  $\beta_1^i = \beta_1 + z_1(\text{s.e.}(\beta_1))$ , 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  $110 * \exp(\beta_0^i + \beta_1^i * C_{min} + z_2(\sigma))$ , 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.

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