OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	20505 (S042), 20844 (S036)
Submission Date	June 16, 2010
Brand Name	Topamax
Generic Name	Topiramate
Dosage Form	Tablets and Sprinkle Capsules
Dosage Strengths	Tablets: 25, 50, 100 and 200 mg Sprinkle Capsules: 15 and 25 mg
Sponsor	Johnson & Johnson
Proposed Indication	Initial monotherapy in patients 2 -9 years of age with partial onset or primary generalized tonic-clonic seizures
Sponsor's Proposed Dosing regimen	(b) (4)
Pharmacometrics Reviewer	Anshu Marathe, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Clinical Pharmacology Team Leader	Angela Men, M.D., Ph.D
OCP Division	Pharmacometrics, DCP I
OND Division	DNP

1 EXECUTIVE SUMMARY

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed supplemental NDA 20505 (S042)/20844 (S036) and finds the sNDA acceptable provided an agreement regarding the label language and dosing regimen can be reached between the sponsor and the Agency. OCP recommends the following body weight based dose for pediatrics of 2 to <10 years of age based on matching drug exposures in pediatrics to exposures observed in adults and pediatrics of the age 6 to 9 years in clinical trial (TOPMAT-EPMN-106):

Table 1**: Monotherapy Target Total Daily Maintenance Dosing for Patients 2 to <10 years**

Weight (kg)	**Total Daily Dose (mg/day)*** **Lower Limit**	**Total Daily Dose (mg/day)*** **Upper Limit**
Up to 11	150	250
12 - 22	200	300
23 - 31	200	350
32 - 38	250	350
greater than 38	250	400

**** Administered in two equally divided doses***

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

Topiramate is approved as initial monotherapy for treatment of partial onset seizures (POS) and primary generalized tonic-clonic seizures (PGTCS) in adults and children of age 10 years and above based on Phase 3 trial (study TOPMAT-EPMN-106). Topiramate is also approved as adjunctive therapy in adults and in children of age 2 years and above based on Phase 3 trials (studies YP, YTC and YTCE). In this application a pharmacometric bridging approach is used to gain approval for topiramate as initial monotherapy in children 2 to < 10 years of age with epilepsy, in order to meet the PREA requirements set forth in the June 29, 2005 approval letter for monotherapy treatment in adults and children of age 10 years and above. On September 29, 2006, the sponsor and FDA discussed and agreed on the pharmacometric bridging approach to address the

PREA commitment. This approach was successfully used previously in the approval of Trileptal (NDA21014-S-003) as monotherapy in pediatric subjects with epilepsy.

The current US label recommends a daily dose of 400 mg in two divided doses for adults and pediatrics (≥ 10 years of age) in monotherapy. This dose is to be achieved by weekly dose titration. In this application, the sponsor is proposing a daily dose of (b) (4) mg/kg divided as two doses for pediatrics 2 to <10 years of age. This dose is to be achieved by an upward titration of a starting dose of (b) (4)

(b) (4)

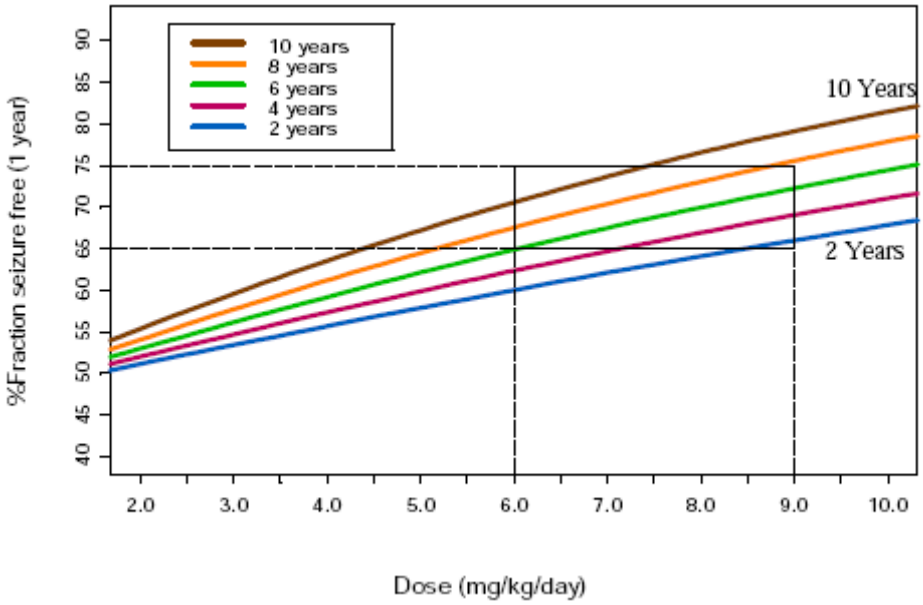

Figure 1: Relationship between topiramate dosing regimen and expected proportion of patients seizure free following daily administration divided in two doses in pediatrics of age 2-10 years. The dashed line represents the target for seizure freedom after one year, 65-75%. Source: Sponsor's Pharmacokinetic Bridging Analysis Report, Figure 8, pg 38

Thus an alternative dosing regimen is proposed by the reviewer which utilizes matching topiramate exposure in pediatrics with the exposure observed in adults in montherapy setting which was shown to be effective. The population PK model predicted steady state

trough concentrations (C_{MIN}) in adults and pediatrics in TOPMAT-EPMN-106 in the 400 mg dose group is shown in Figure 2. As expected, drug concentrations achieved in pediatrics upon administration of fixed dose of 400 mg is higher in pediatrics than adults because of lower total clearance (L/hr) in pediatrics compared to adults. The median C_{MIN} in adults is 8.4 µg/ml, which is lower than the median C_{MIN} in pediatrics of age 6-9 years that is 13.3 µg/ml (Table 2). Thus, the adult and pediatric (6-9 years) C_{MIN} of 8.4 and 13.3 µg/ml establish the lower and upper bounds of the target concentrations that need to be achieved by pediatrics (2-9 years) because: 1) the monotherapy studies suggested an exposure response relationship (increase in exposure is likely to increase response) and 2) the medical officer determined that the upper bound target concentration (13.3 µg/ml) was safe in pediatric patients.

To achieve the median adult C_{MIN} of 8.4 µg/ml, a daily dose of 179 to 227 mg/day (14 to 7 mg/kg/day) in two divided doses is required for pediatrics of the age 2 to 9 years. To achieve the median pediatric (6-9 years) C_{MIN} of 13.3 µg/ml, a daily dose of 284 to 360 mg/day (23 to 11 mg/kg/day) in two divided doses is required. For easy comparison with Figure 1, the dose range was converted to mg/kg/day and shown in Figure 3 for different weights corresponding to the approximate median weights of different age groups.

A dosing table was derived by matching the target exposures for various body weights ranging from 10 to 50 kg. Based on the available tablet strengths of Topiramate, the actual unit dose for a BID regimen was rounded off to the nearest multiple of 25 (i.e. the lowest tablet strength). The dosing recommendation is provided in Table 3. The mg/kg/day dose in the table is shown here only for comparison with the sponsor's proposed dose.

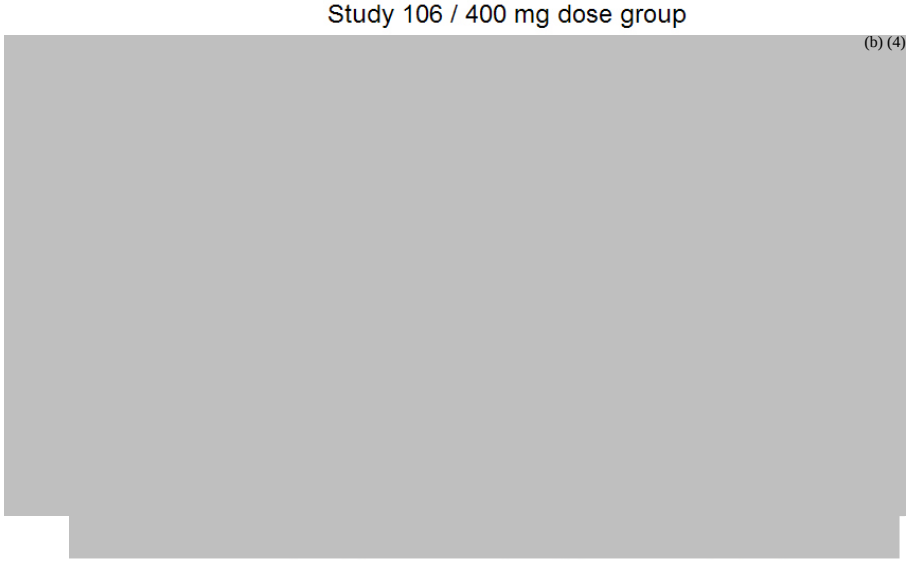

Figure 2: Steady state trough concentrations (C_{MIN}) of topiramate in adults and pediatrics in TOPMAT-EPMN-106 (monotherapy). The dashed lines show the median Cmin in adults and pediatrics (6-9 years)

Table 2: C_{MIN} of topiramate in adults and pediatrics in TOPMAT-EPMN-106

Group	N	Median Cmin (µg/ml)
Adults (>=16 yrs)	138	8.4
Pediatrics (10-15 yrs)	56	10.6
Pediatrics (6-9 yrs)	19	13.3

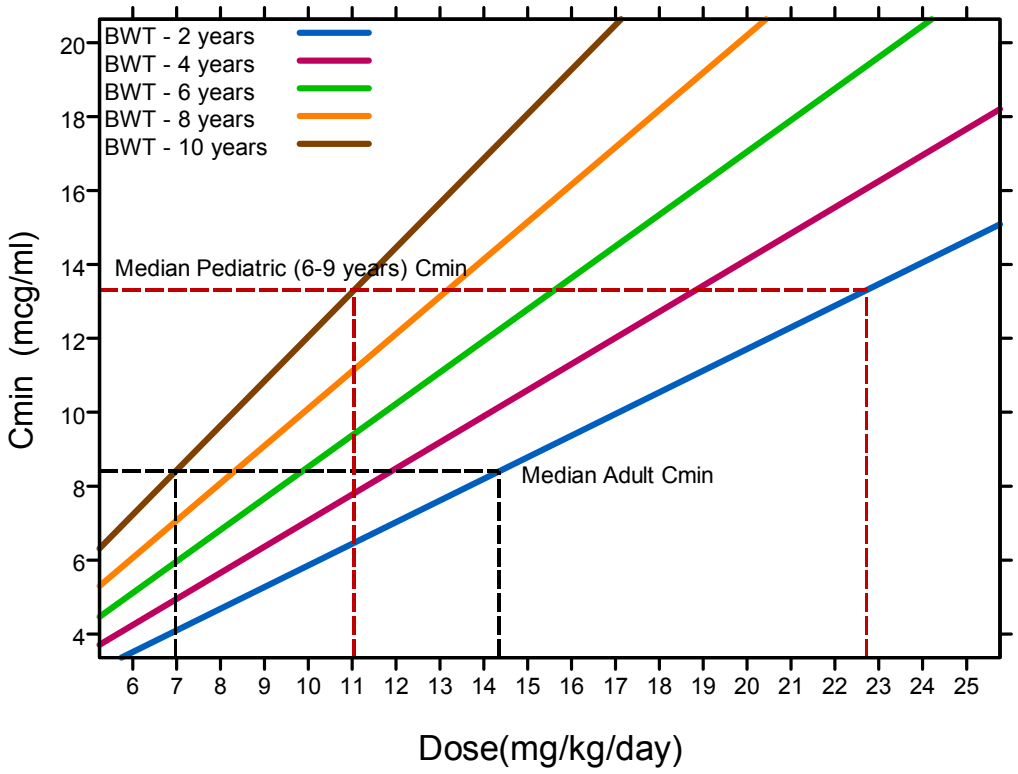

Figure 3: Relationship between topiramate dosing regimen and steady state trough concentrations (C_{MIN}) of topiramate in pediatrics. The solid lines (blue, purple, green, orange and brown) show the relationship for different body weights (BWT) representing approximate median weights (12.5, 16, 20.5, 25.7 and 32.6 Kg) of 2, 4, 6, 8 and 10 years old pediatrics. The horizontal dashed black line represents the median C_{MIN} in adults. The horizontal dashed purple line represents the median C_{MIN} in pediatrics (6-9 years).

Table 3: Monotherapy Target Total Daily Maintenance Dosing for Patients 2 to <10 years

Weight (kg)	Total Daily Dose (mg/day)* Lower Limit	Total Daily Dose (mg/day)* Upper Limit	Total Daily Dose (mg/kg/day)* Lower Limit	Total Daily Dose (mg/kg/day)* Upper Limit
Up to 11	150	250	≥ 14	≥ 23
12 - 22	200	300	17-9	25-14
23 - 31	200	350	9-6	15-11
32 - 38	250	350	8-7	11-9
greater than 38	250	400	≤ 7	≤ 11

**** Administered in two equally divided doses***

2 QUESTION BASED REVIEW

2.1 Key Review Questions

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

2.1.1 Is the exposure-response relationship similar between adults and pediatrics in monotherapy?

Yes, the exposure response relationship is similar between adults (16 years and above) and pediatrics (6-15 years) in monotherapy. A Cox proportional hazard model was used to link the steady state trough drug concentrations to the time-to-first-seizure after randomization in montherapy trials. This analysis utilized data from 842 subjects from monotherapy trials (TOPMAT-106,-105 and -104) with baseline seizure frequency of 2 or less. Subjects with baseline seizure frequency of 2 or less were selected to reflect the patient population in the pivotal trial TOPMAT-106 that was used for the approval of Topiramate in monotherapy setting for adults and pediatrics of age 10 years and old. Baseline seizure frequency and steady state trough exposure (C_{MIN}) were found to be significant predictors for hazard (Table 4). Age did not show a statistically significant effect on the baseline hazard rate or the slope of the exposure-response relationship.

Table 4: Cox model parameter estimates

Predictor	Slope estimate	Std. error on estimate	p-value
Cmin per 1 μg/mL	-0.121	0.023	<.0001
Baseline seizure frequency	0.527	0.120	<.0001
Age on baseline hazard (pediatics versus adults)	-0.227	0.204	0.265
Age on slope of exposure-response	-0.004	0.04	0.922

(Source code: CPH_Model.R. See section 7 for details)

Despite the non-significance of age effect on baseline hazard and exposure-response relationship, the full model (Table 4) was used as a conservative way to simulate the impact of age on hazard ratio between adults and pediatrics by taking into account the estimation uncertainty of the parameter estimates. 10,000 simulations were conducted using the Cox proportional hazard model described above and the ratio of the absolute hazard for pediatrics (6-15 years old) to adults was calculated for different C_{MIN} values. Table 5 shows the median hazard ratio and the 95% confidence interval of the ratio. The 95% confidence interval of the ratio includes 1 suggesting no significant difference in the hazard for seizure between pediatrics and adults. The median hazard

ratio of pediatrics to adults varied from 0.75 to 0.80 across various concentrations of topiramte. The deviation of the median hazard ratio from 1 is due to the non-significant age effect on the intercept of the Cox model, suggesting a numerically lower risk for seizure in pediatrics than in adults under a placebo treatment. Table 6 shows the median hazard ratio and the 95% confidence interval of the ratio after correcting for placebo response. The median placebo-corrected hazard ratio of pediatrics to adults varied from 0.94 to 1 across various concentrations of topiramte. The 95% confidence interval of the ratio includes 1 suggesting no significant difference in the placebo-corrected relative hazard for seizure between pediatrics and adults.

Table 5: Hazard Ratio between Pediatrics (<16 years) and Adults for Time-to-First-Seizure after Randomization

Cmin (µg/mL)	Hazard Ratio	2.5% CI	97.5 % CI
0	0.80	0.54	1.18
1	0.80	0.57	1.12
2	0.79	0.58	1.07
3	0.79	0.59	1.04
4	0.78	0.59	1.03
5	0.78	0.58	1.05
6	0.78	0.56	1.07
7	0.77	0.53	1.12
8	0.77	0.50	1.17
9	0.77	0.47	1.24
10	0.76	0.44	1.32
11	0.76	0.40	1.41
12	0.76	0.38	1.50
13	0.76	0.35	1.60
14	0.75	0.32	1.72
15	0.75	0.30	1.84

(Source code: CPH_Model.R. See section 7 for details)

Table 6: Hazard Ratio between Pediatrics (<16 years) and Adults for Time-to-First-Seizure after Randomization Corrected for Placebo Response

Cmin (µg/mL)	Hazard Ratio	2.5% CI	97.5 % CI
1	1.00	0.92	1.07
2	0.99	0.85	1.15
3	0.99	0.78	1.24
4	0.98	0.72	1.33
5	0.98	0.67	1.43
6	0.98	0.61	1.54
7	0.97	0.57	1.65
8	0.97	0.52	1.77
9	0.96	0.48	1.91
10	0.96	0.44	2.05
11	0.96	0.41	2.20
12	0.95	0.38	2.36
13	0.95	0.35	2.54
14	0.94	0.32	2.73
15	0.94	0.30	2.93

(Source code: CPH_Model.R. See section 7 for details)

Since data was not available in pediatrics of age 2- 5 years from monotherapy trials, additional analysis was conducted by the sponsor using data from adjunctive setting as these studies included pediatrics of ages 2 years and above. Similar relationship between exposure (steady state C_{MIN}) and log-transformed percent reduction in seizure frequency (primary endpoint) in adjunctive therapy is observed in Figure 4. A linear regression model was fitted to the observed data. The parameters of the final model representing the baseline seizure frequency (β_0) and the slope of the exposure-response relationship (β_1) are shown in Table 7. Similar baseline seizure frequency and slope estimates are obtained in pediatrics (2-15 years) and adults (>15 years) suggesting similar exposure response relationship in these populations. The effect of age as both continuous and discrete on the final model was evaluated. Table 17 shows that there was no effect of age on the exposure-response relationship as inclusion of age as a covariate in the model did not reduce the objective function significantly

In order to confirm the similarity of the PK-efficacy relationships in adults and pediatrics for different C_{MIN} values, 10,000 simulations were conducted for each age group and the ratio of median effect (% percent change of seizure from baseline) for pediatrics to median effect for adults was calculated. The 90% confidence interval of the ratio was also calculated and shown in Table 8. The results show that the efficacy in pediatrics is approximately 88%-96% of that in adults across various concentrations of topiramte with 90% confidence intervals including 100%.

Overall, similar exposure-response relationship is observed in pediatrics and adults in monotherapy which is further supported by data from adjunctive therapy.

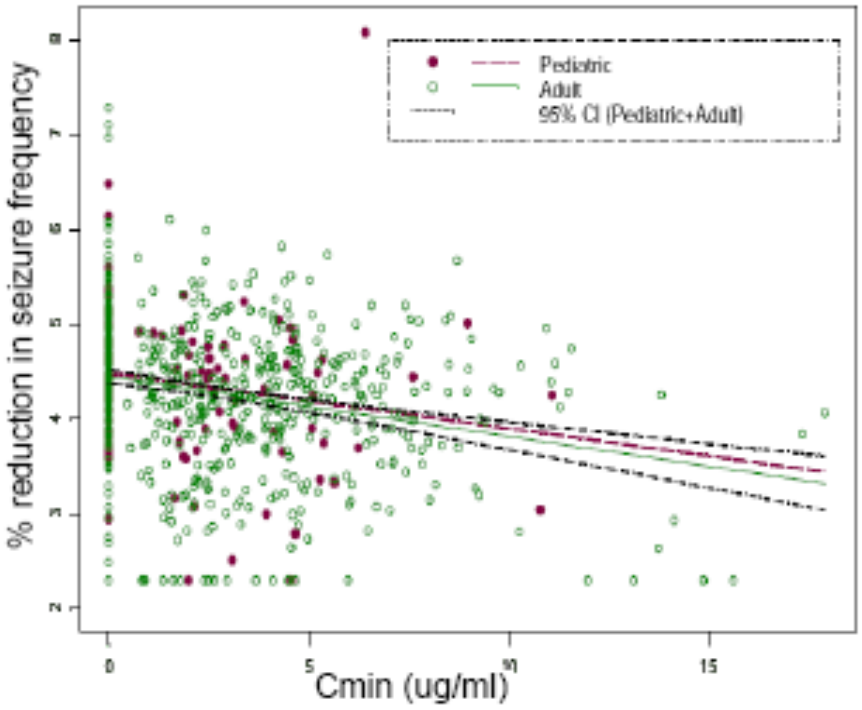

Figure 4: Percent reduction in seizure frequency vs. C_{MIN} in pediatrics and adults in adjunctive therapy. The solid green line and the dashed red line represent the fit of the regression model in adults and pediatrics. The dashed black lines represent the confidence intervals of the model fit combining adult and pediatric populations. Source: Sponsor's Pharmacokinetic Bridging Analysis Report, Figure 11, pg 44.

Table 7: Parameters Estimates of the Final Model for Percent Reduction in Seizure Frequency for Topiramate in Adjunctive Therapy Trials

Parameter	Estimate ± SE		
	Adults (n=663)	**Pediatrics (n=115)**	**Combined**
β_0	4.4469 ± 0.0313	4.4830 ± 0.0916	4.4538 ± 0.0361
β_1	-0.0627 ± 0.0097	-0.0579 ± 0.0305	-0.0628 ± 0.0092

(Source: Sponsor's Pharmacokinetic Bridging Analysis Report, Table 9, pg 45)

Table 8: Ratio of Effect (% Reduction in Seizure Frequency from Baseline) Between Pediatrics and Adults

C_{MIN} (ug/ml)	% Percent change of seizure from baseline (median)		Ratio	5%	95%
	Peds	Adults			
0	-21.58	-24.61	0.88	0.13	1.70
5	-44.01	-47.57	0.93	0.51	1.27
10	-60.58	-64.37	0.94	0.38	1.31
15	-73.06	-76.63	0.95	0.30	1.28
20	-82.40	-85.59	0.96	0.25	1.24

(Source: Sponsor's Pharmacokinetic Bridging Analysis Report, Table 10, pg 47)

2.1.2 Is the proposed dose of (b) (4) adequate for pediatrics of age 2 to <10 years?

(b) (4)

65% of the pediatrics of 2 years of age are predicted to be seizure free at 1 year which is lower than the observed rate of 71% in adults in TOPMAT-EPMN-106 (Figure 5). Reviewer's analysis utilized matching exposures in pediatrics with the exposures observed in adults and pediatrics of the age 6 to 9 years in clinical trial (TOPMAT-EPMN-106) to derive the dose for pediatrics.

(b) (4)

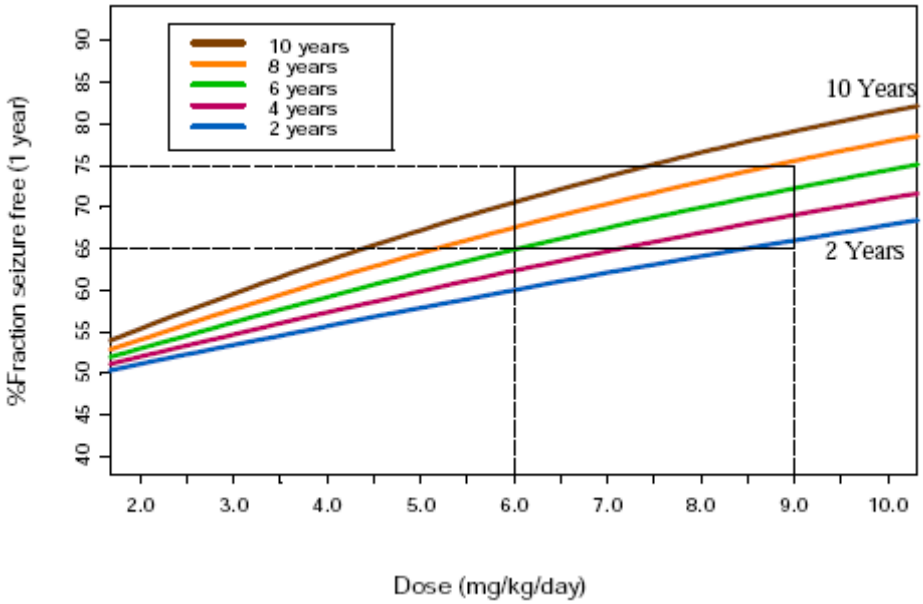

Figure 5: Relationship between topiramate dosing regimen and expected proportion of patients seizure free following daily administration divided in two doses in pediatrics of age 2-10 years. The dashed line represents the target for seizure freedom after one year, 65-75%. Source: Sponsor's Pharmacokinetic Bridging Analysis Report, Figure 8, pg 38

Reviewer's analysis shows that the population PK model predicted steady state trough concentrations (C_{MIN}) in adults and pediatrics in TOPMAT-EPMN-106 in the 400 mg dose group is shown in Figure 6. As expected, drug concentrations achieved in pediatrics upon administration of fixed dose of 400 mg is higher in pediatrics than adults because of lower total clearance (L/hr) in pediatrics compared to adults. The median C_{MIN} in adults is 8.4 µg/ml, which is lower than the median C_{MIN} in pediatrics of age 6-9 years that is 13.3 µg/ml (Table 9). Thus, the adult and pediatric (6-9 years) C_{MIN} of 8.4 and 13.3 µg/ml establish the lower and upper bounds of the target concentrations that need to be achieved by pediatrics (2-9 years) because: 1) the monotherapy studies suggested an exposure response relationship (increase in exposure is likely to increase response) and 2) the medical officer determined that the upper bound target concentration (13.3 µg/ml) was safe in pediatric patients.

To achieve the median adult C_{MIN} of 8.4 µg/ml, a daily dose of 179 to 227 mg/day (14 to 7 mg/kg/day) in two divided doses is required for pediatrics of the age 2 to 9 years. To achieve the median pediatric (6-9 years) C_{MIN} of 13.3 µg/ml, a daily dose of 284 to 360 mg/day (23 to 11 mg/kg/day) in two divided doses is required. For easy comparison with Figure 1, the dose range was converted to mg/kg/day and shown in Figure 3 for different weights corresponding to the approximate median weights of different age groups.

A dosing table was derived by matching the target exposures for various body weights ranging from 10 to 50 kg. Based on the available tablet strengths of Topiramate, the actual unit dose for a BID regimen was rounded off to the nearest multiple of 25 (i.e. the lowest tablet strength). The dosing recommendation is provided in Table 10. The

mg/kg/day dose in the table is shown here only for comparison with the sponsor's proposed dose.

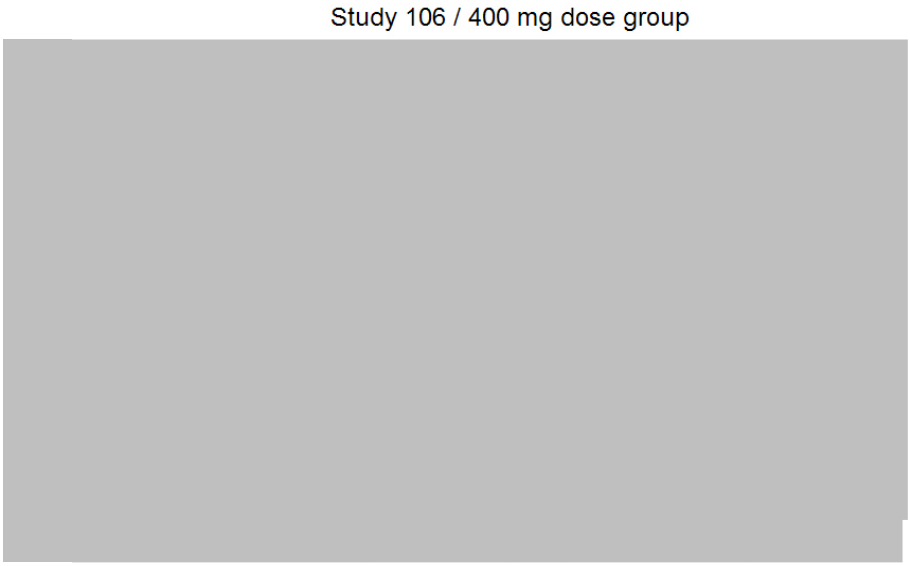

Figure 6: Steady state trough concentrations (C_{MIN}) of topiramate in adults and pediatrics in TOPMAT-EPMN-106 (monotherapy). The dashed lines show the median Cmin in adults and pediatrics (6-9 years) (Source code: indv-cmin-mono-pkonlyavgdose.SSC. See section 7 for details)

Table 9: C_{MIN} of topiramate in adults and pediatrics in TOPMAT-EPMN-106

Group	N	Median Cmin (µg/ml)
Adults (>=16 yrs)	138	8.4
Pediatrics (10-15 yrs)	56	10.6
Pediatrics (6-9 yrs)	19	13.3

** Only subjects who were in the population PK dataset were included in the analysis*

(Source code: indv-cmin-mono-pkonlyavgdose.SSC. See section 7 for details)

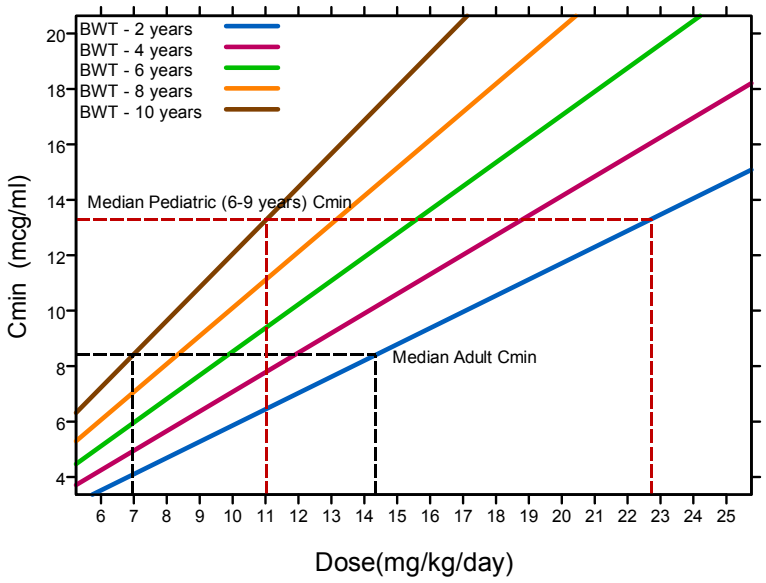

Figure 7: Relationship between topiramate dosing regimen and steady state trough concentrations (C_{MIN}) of topiramate in pediatrics. The solid lines (blue, purple, green, orange and brown) show the relationship for different body weights (BWT) representing approximate median weights (12.5, 16, 20.5, 25.7 and 32.6 Kg) of 2, 4, 6, 8 and 10 years old pediatrics The horizontal dashed black line represents the median C_{MIN} in adults. The horizontal dashed purple line represents the median C_{MIN} in pediatrics (6-9 years). (Source code: dosecminwt-final.SSC. See section 7 for details)

Table 10: Monotherapy Target Total Daily Maintenance Dosing for Patients 2 to <10 years

Weight (kg)	Total Daily Dose (mg/day)* Lower Limit	Total Daily Dose (mg/day)* Upper Limit	Total Daily Dose (mg/kg/day)* Lower Limit	Total Daily Dose (mg/kg/day)* Upper Limit
Up to 11	150	250	≥ 14	≥ 23
12 - 22	200	300	17-9	25-14
23 - 31	200	350	9-6	15-11
32 - 38	250	350	8-7	11-9
greater than 38	250	400	≤ 7	≤ 11

**** Administered in two equally divided doses***

(Source code: dosecminwt-final.SSC. See section 7 for details)

3 PRELIMINARY LABELING RECOMMENDATIONS

The following are the labeling recommendations relevant to clinical pharmacology for NDA 22468. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

2 Dosage and Administration

(b) (4)

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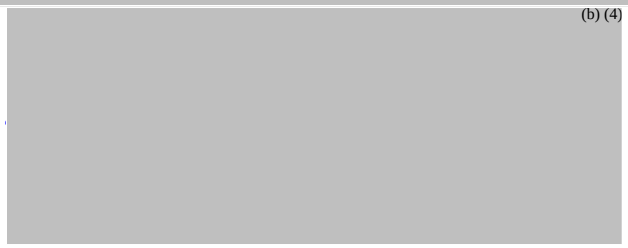
(b) (4)


(b) (4)


(b) (4)


(b) (4)

14.1 Monotherapy Epilepsy Controlled Trial

(b) (4)

4 PERTINENT REGULATORY BACKGROUND

Topiramate is approved as adjunctive therapy in the treatment of partial onset seizures (POS) and primary generalized tonic-clonic seizures (PGTCS) in adults and in children of age 2 years and above. In the U.S., topiramate is also approved as initial monotherapy in adults and children of age 10 years and above. In this application a pharmacometric bridging approach is used to gain approval for topiramate as initial monotherapy in children 2 to < 10 years of age with epilepsy, in order to meet the PREA requirements set forth in the June 29, 2005 approval letter for monotherapy treatment in adults. On September 29, 2006, the sponsor and FDA discussed the pharmacometric bridging approach to address the PREA commitment. This approach was successfully used previously in the approval of Trileptal (NDA21014-S-003) as monotherapy in pediatric subjects with epilepsy.

5 RESULTS OF SPONSOR'S ANALYSIS

5.1 Population PK Analysis

Sponsor performed population PK modeling utilizing data from 11 studies (8-adjunctive, 3-monotherapy trials) that included adults and pediatrics with partial-onset seizures or partial generalized tonic clonic seizures. Primary objective of the population PK analysis was to relate topiramate dosing regimen to steady state plasma concentrations (C_{MIN}) after accounting for covariates such as body weight, age and use of concomitant medication. C_{MIN} was further used for exposure-response analysis.

5.1.1 Methods

PK data from a total of 1217 subjects (4640 observations) including 258 pediatric subjects of ages 2-25 years with 751 observations was used for the analysis. Description of the studies with other relevant information is provided in Table 11.

Table 11: Studies Used for the Population PK Model

Indication/Study	Active doses (mg/day)	Total number of subjects with measured topiramate plasma concentrations	Number of measured topiramate plasma concentrations
Adjunctive therapy			
Y1	400	20	101
Y2	600	20	132
Y3	800	28	207
YD	200,400,600	125	902
YE	600,800,1000	135	1179
YP	125,175,225,400	40	206
YTC	175,225,400	39	151
YTCE	175,225,400	33	137
Monotherapy			
TOPMAT-EPMN-104	50,500*	202	613
TOPMAT-EPMN-105	100,200	145	145
TOPMAT-EPMN-106	50,400	430	867
Total			
		1217	4640

*(25/200 if ≤50 kg)

(Source: Sponsor's Pharmacokinetic Bridging Analysis Report, Appendix1, Table 1, pg 61)

PK data were then fitted using Nonmem Version V Level 1.1 (GloboMax LLC, Hanover MD). All modeling work was done using the first order conditional method (FOCE) with interaction option.

5.1.2 Results

The population PK for topiramate was described by a two compartment linear model with first order absorption. The model included the effects of weight, age, use of concomitant medications on oral clearance. In addition the model took into consideration the apparent difference in baseline clearance of topiramate for subjects who were treatment naive versus those previously treated with other concomitant anti-epileptic drug (AEDs). The model also included the effect of weight on the central volume of distribution. The sponsor's final model is described below:

$$CLST = \theta_1 \bullet (1 + ADJ \bullet \theta_2)$$

$$FCWT = \left(\frac{Weight}{69.9}\right)^{\theta_3}$$

$$FCAGE = Exp(\theta_4 \bullet (Age - 31.4))$$

$$FCIN = \theta_5^{INMD}$$

$$FCVP = \theta_6^{VPA}$$

$$FCNE = \theta_7^{NEMD}$$

$$TVCL = CLST \bullet FCWT \bullet FCAGE \bullet FCIN \bullet FCVP \bullet FCNE$$

$$\frac{CL}{F} = TVCL \bullet Exp(\eta_1)$$

$$VST = \theta_8$$

$$FVWT = \left(\frac{Weight}{69.9}\right)^{\theta_9}$$

$$\frac{S2}{F} = VST \bullet FVWT \bullet Exp(\eta_2)$$

$$Ka = \theta_{10} \bullet Exp(\eta_3)$$

$$K23 = \theta_{11}$$

$$K32 = \theta_{12}$$

Where, ADJ is an indicator for adjunct treatment that captures the difference in baseline oral clearance of topiramate seen in monotherapy versus adjunctive therapy, INMD contains cytochrome P450 inducing agents, VPA captures valproates and NEMD contains all other no effect medications and those that are not known to be either inducer or inhibitor of P450 enzymes. CL/F is the apparent oral clearance of topiramate, S2/F (or V2/F) is the apparent volume of distribution of the central compartment, Ka is the first order absorption rate constant, and K23 and K32 are the first order transfer rate constants between the central and peripheral compartments, respectively. The parameters of the sponsor's final model are provided in Table 12.

Table 12: Parameter Values from the Sponsor's Final Population PK Model

Parameter (Units)	Typical Value	Inter-Individual Variability
Clearance (L/h)		
CLSTM (baseline clearance monotherapy) (θ1)	1.21	27.28
CLSTA (effect of adjuvant) (θ2)	0.479	
FCWT (effect of weight) (θ3)	0.453	
FCAGE (effect of age) (θ4)	-0.00306	
FCIN (effect of INMD) (θ5)	1.94	
FCVP (effect of valproate) (θ6)	0.686	
FCNE (effect of NEMD) (θ7)	0.635	
Central Volume of Distribution (L)		
VST (θ8)	4.61	116.2
FVWT (effect of weight) (θ9)	1.14	
Ka (h-1) (θ10)	0.105	22.34
K23 (h-1) (θ11)	0.577	NE
K32 (h-1) (θ12)	0.0586	NE
CCV residual error (%CV)	25.46	
Additive residual error (mg/L)	0.1797	

NE – Not Evaluated

(Source: Sponsor's Pharmacokinetic Bridging Analysis Report, Appendix1, Table 6, pg 80)

Reviewer's comments on Sponsor's Population PK Analysis:

- *Sponsor's population PK analysis is generally adequate.*
- *The exponential coefficient of the effect of age on clearance was negative, suggesting an older pediatric patient will have smaller clearance (L/hr) given the same weight, which is physiologically not possible for a drug primarily eliminated by kidney. Reviewer's independent analysis showed that while inclusion of age was statistically significant as evidenced by the change in the objective function, it resulted in very small change in the inter-individual variability on clearance (from 27.4% to 27%).*
- *The parameters of the above model without age as a covariate on clearance were re-estimated (see Table 19). The diagnostic plots, observed versus individual predicted stratified by age groups (adults, pediatrics) are shown in Figure 11 in reviewer's analysis in section 6.3.1. No systematic bias is observed.*

5.2 Exposure-Response Analysis for Effectiveness

The primary objectives for conducting exposure-response analysis were to answer the following key questions:

1. Are placebo responses in adults (≥16 years) and pediatrics (<16 years) subjects similar?
2. Are exposure-response relationships of topiramate similar between adults and pediatrics in monotherapy and adjunctive therapy?

The first key question was answered by utilizing data from adjunctive therapy trials because the monotherapy trials did not have any placebo data and evaluated only active topiramate doses. The second key question was answered primarily with data from monotherapy trials. Since no data in pediatrics of the age of 2-5 years is available from monotherapy trials, data from adjunctive trials were used as supportive evidence as these trials included subjects in the 2-5 years age group.

5.2.1 Data

Summary of monotherapy and adjunctive trials used for exposure-response analysis is provided in Table 13.

Table 13: Summary of Objective Response Rate

Indication Study (age range)	Topiramate target dose (mg/day)	Number of subjects Total	(adults/pediatrics*)
Adjunctive:			
Y1 (15-63 years)	0	24	(23/1)
	400	23	(23/0)
Y2 (16-65 years)	0	30	(30/0)
	600	30	(30/0)
Y3 (19-63 years)	0	28	(28/0)
	800	28	(28/0)
YD (19-68 years)	0	45	(45/0)
	200	45	(45/0)
	400	45	(45/0)
	600	46	(46/0)
YE (18-68 years)	0	47	(47/0)
	600	48	(48/0)
	800	48	(48/0)
	1000	47	(47/0)
YP (2-16 years)	0	45	(1/44)
	125	15	(0/15)
	175	8	(0/8)
	225	9	(0/9)
	400	9	(1/8)
YTC (3-59 years)	0	40	(29/11)
	175	5	(0/5)
	225	1	(0/1)
	400	33	(31/2)
YTCE (7-52 years)	0	40	(38/2)
	175	4	(0/4)
	225	2	(0/2)
	400	33	(30/3)
Monotherapy:			
TOPMAT-EPMN-104 (6-85 years)	25	20	(4/16)
	50	105	(100/5)
	200	14	(3/11)
	500	113	(110/3)
TOPMAT-EPMN-105 (6-84 years)	100	201	(171/30)
	200	195	(166/29)
TOPMAT-EPMN-106 (6-83 years)	50	234	(160/74)
	400	236	(159/77)
Total:		1896	(1536/360)

*Pediatrics defined as 2 -15 yrs

(Source: Sponsor's Pharmacokinetic Bridging Analysis Report, Table 1, pg 16)

5.2.2 Method and Results

Placebo-response between adults and pediatrics in adjunctive studies for Topiramate: Similar placebo-response in adults and pediatrics is shown by the distribution plots in Figure 8 . Further, Kolmogorov-Smirnov goodness-of-fit test suggested that the distributions of the placebo response are not different in pediatrics and adults during adjunctive therapy (p=0.532 and p=0.632 in 2-15 years and 2-9 years old children, respectively), as shown in Figure 9.

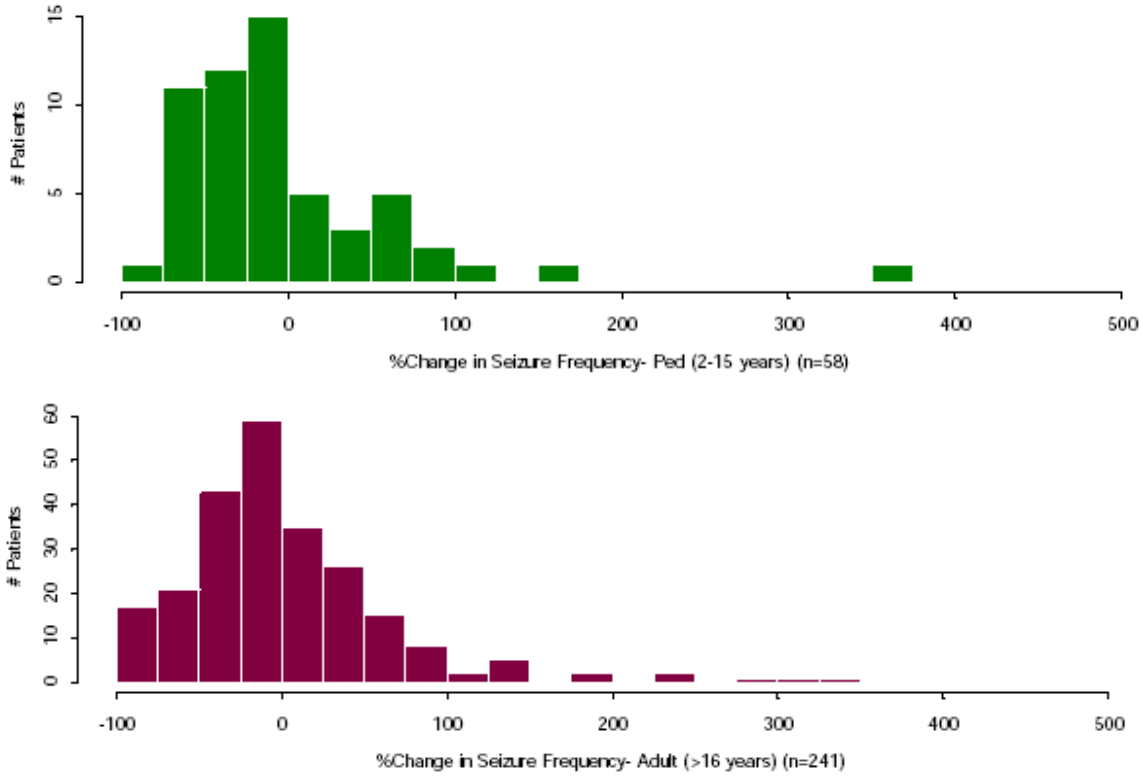


Figure 8: Distribution of placebo response in adjunctive therapy in pediatrics (2-15 years) and adults (>16 years). (Source: Sponsor's Pharmacokinetic Bridging Analysis Report, Figure 10, pg 43)

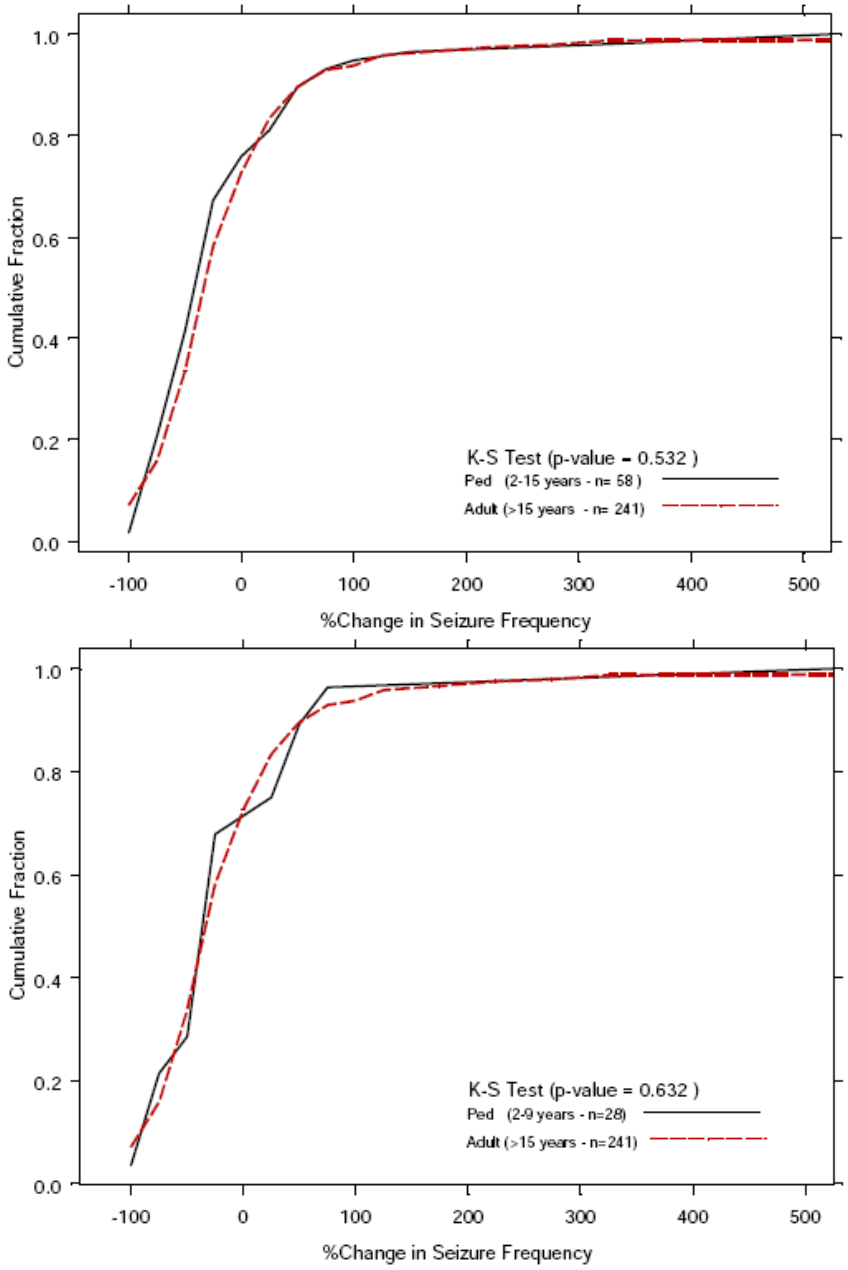


Figure 9: Distribution of placebo response in adjunctive therapy. (Source: Sponsor's Pharmacokinetic Bridging Analysis Report, Figure 9, pg 42)

Reviewer's comments:

- *The sponsor's conclusion that the placebo-response is similar between adults and pediatrics is adequate. A similar approach was used for Trileptal and the results reported here are consistent with the findings for Trileptal.*

Exposure-response relationship for adults and pediatrics in monotherapy for Topiramate: A parametric hazard model was developed to relate the steady state trough plasma concentration of Topiramate (C_{MIN}) given the average daily dose for each subject during the blinded treatment phase to the time-to-first seizure after randomization. C_{MIN} was predicted from the population PK model. Model development was performed by stepwise inclusion of candidate explanatory variables. Baseline hazard(λ_0), exposure (C_{MIN}), time since randomization (t), and baseline seizure frequency ($BS_{3\text{-}10}$ and $BS_{>10}$) were found to be significant predictors of hazard. According to the sponsor's Splus code hazard in the i^{th} subject is described as follows:

$$\log\left(\frac{\lambda_i}{1-\lambda_i}\right) = \lambda_0 + \lambda_t \cdot t + \lambda_{C_{MIN}} \cdot C_{MIN,i} + \lambda_{BS3-10} \cdot BS_{3-10,i} + \lambda_{BS>10} \cdot BS_{>10,i} \qquad \text{(Eq.2)}$$

$BS_{3\text{-}10}$,i is an indicator value (0 or 1) reflecting whether the i^{th} subject had up to 3 to 10 seizures during the 3 month run-in period (BS3-10,i=1) or not (BS3-10,i=0). BS>10 is a similar indicator reflecting whether the ith subject had more than 10 seizures during the 3 month run-in period (BS>10, i=1) or not (BS>10, i = 0). λ_0, λ_{CMIN}, λ_t, $\lambda_{BS3\text{-}10}$ and $\lambda_{BS>10}$ are the parameters that link the respective predictors to hazard. The parameter estimates of the final model are shown in Table 14. The final model was not a log transformation of hazard as mentioned in sponsor's study report but a logit transformation of hazard. See reviewer's comments on the implications of logit transformation on the results.

Table 14: Parameters Estimates of the Parametric Hazard Model for Time-to-First-Seizure After Randomization for Topiramate in Monotherapy

Parameter	Estimate ± SE	(p-value)
λ_0	-3.130± 0.0919	-
λ_t	-0.051 ± 0.0036	<0.0001
λ_{CMIN}	-0.112 ± 0.0151	<0.0001
$\lambda_{BS3\text{-}10}$	1.048 ± 0.1046	<0.0001
$\lambda_{BS>10}$	2.411 ± 0.1356	<0.0001

(Source: Sponsor's Pharmacokinetic Bridging Analysis Report, Table 3, pg 23)

The effect of age as both continuous and discrete on the final model was evaluated. There was no effect of age on the exposure-response relationship as inclusion of age as a covariate in the model did not reduce the objective function significantly (data not shown). Additional analysis using the Cox-proportional hazard model showed that exposure (C_{MIN}) is a predictor of hazard while age did not have a significant effect on hazard (data not shown).

A subgroup analysis was further performed on the final model for different age groups of subjects. Similar slope of the exposure response relationship (λ_{CMIN}) was

observed for pediatrics of age 6-9 years (-0.081) and adults (-0.106) as shown in Table 15. The baseline hazard (λ_0) was also similar between the two groups.

Table 15: Subgroup Analysis of the Final Parametric Hazard Model for Various Age Groups

Parameter	Estimate ± SE			
	6-9 years	**10-15 years**	**6-15 years**	**16 years and older**
λ_0	-2.914 ± 0.350	-3.652 ± 0.247	-3.414 ± 0.198	-3.067 ± 0.104
λ_{CMIN}	-0.081 ± 0.048	-0.165 ± 0.041	-0.128 ± 0.031	-0.106 ± 0.017
	p=0.015	p<0.001	p<0.001	p<0.001
λ_t	-0.064 ± 0.015	-0.023 ± 0.008	-0.036 ± 0.007	-0.054 ± 0.004
	p<0.001	p<0.001	p<0.001	p<0.001
λ_{BS3-10}	1.025 ± 0.536	1.323 ± 0.305	1.144 ± 0.260	1.004 ± 0.115
	p=0.094	p<0.001	p<0.001	p<0.001
$\lambda_{BS>10}$	1.097 ± 0.761	1.723 ± 0.489	1.422 ± 0.407	2.571 ± 0.149
	p=0.207	p=0.004	p=0.003	p<0.001
remove λ_{CMIN}	p=0.096	p<0.001	p<0.001	p<0.001

(Source: Sponsor's Pharmacokinetic Bridging Analysis Report, Table 5, pg 29)

The model predicts that the ratio of the mean hazard ratio for pediatrics of the age <16 years and subjects of age ≥ 16 years is 0.82 and the confidence interval includes 1 which suggests similar hazard between these age groups (Table 16).

Table 16: Model Predicted Hazard ratio of Effect on Time-to-First-Seizure after Randomization between Two Age Groups

	Mean hazard ratio (90% CI)
<10 years versus ≥ 10 years	0.93 (0.61-1.34)
<16 years versus ≥ 16 years	0.82 (0.63-1.04)

(Source: Sponsor's Pharmacokinetic Bridging Analysis Report, Table 6, pg 30)

Reviewer's Comment:

- *The sponsor's parametric hazard model is a logistic model with C_{MIN}, time (week) and baseline seizure frequency as the predictors. The sponsor inserted non-event data (0) for each patient before the event (seizure) time or censoring time on a weekly time scale so that at a given week, patients will have 0 (no seizure) or 1 (seizure) for efficacy endpoint. Patients with seizure or censored status at a certain time will not contribute to the data for later time points. The logit of hazard at a certain week was assumed to be linearly related to time. A sensitivity analysis showed this assumption was not justified (**Error! Reference source not found.**). However, the slope for Cmin was not influenced by the violation of this assumption. In addition, the selection of non-event data is arbitrary. Adding more non-event data at smaller time interval led to different parameter estimates.*
- *Sponsor's overall conclusion that the exposure response relationship is similar between adults and pediatrics in monotherapy was confirmed by an independent analysis performed by the reviewer using a Cox proportional hazard model (see section 2.1.1 for details).*

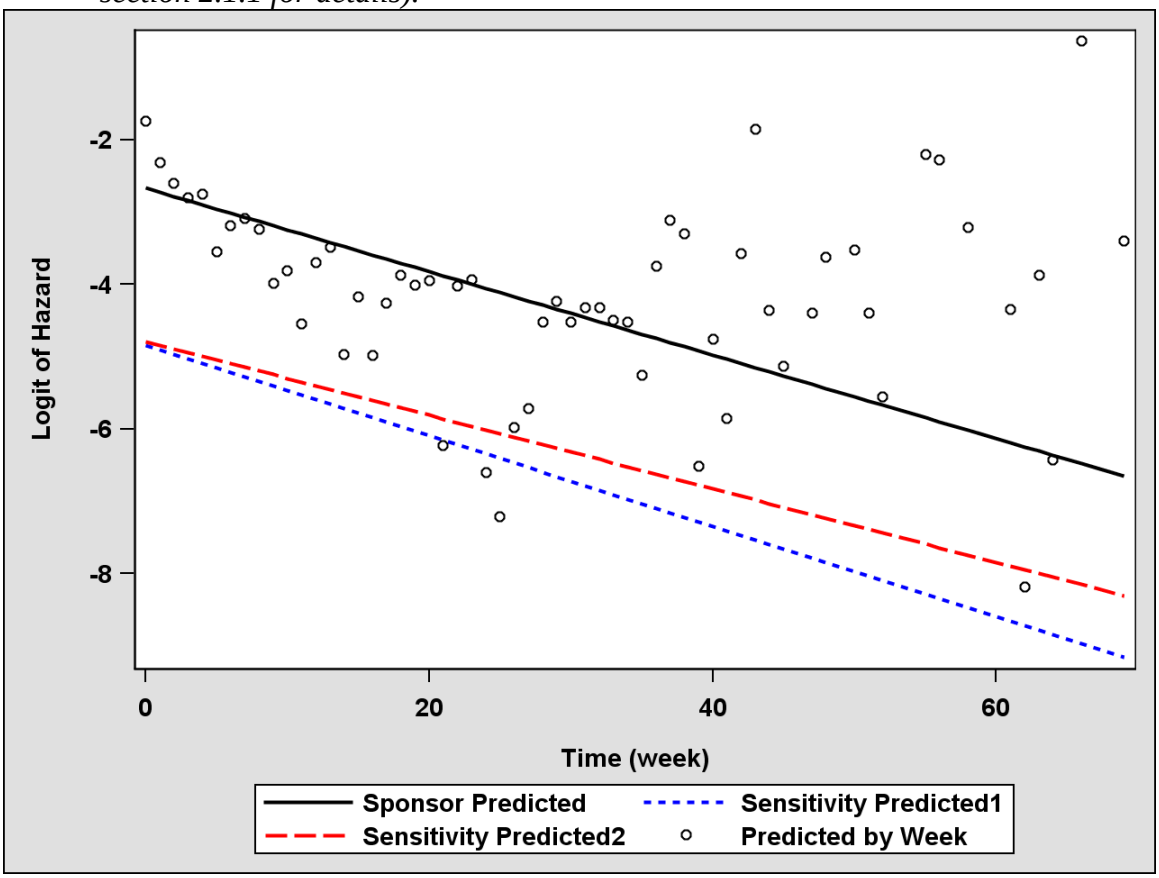


Figure 10: Comparison of logit of hazard when C_{MIN}=0 under various conditions showing the assumed linear relationship (lines) between logit hazard and time is not supported by the data (circles) (Sponsor Predicted: sponsor's model; Sensitivity Predicted1: sponsor's model with 9 more non-event data records for each patient; Sensitivity Predicted2: sponsor's model with daily non-event data records for each patient; Predicted by Week: logistic model at each week with one outlier (-22 at week 54) removed)

Exposure-response relationship for adults and pediatrics in adjunctive therapy for Topiramate: Exposure-response relationship for adults and pediatrics in adjunctive therapy for Topiramate was evaluated because these trials included pediatrics in the age group of 2-5 years that were not present in the monotherapy trials.

Similar relationship between exposure (steady state C_{MIN}) and log-transformed percent reduction in seizure frequency (response) in adjunctive therapy is observed in Figure 4. A linear regression model was fitted to the observed data. The parameters of the final model representing the baseline seizure frequency (β_0) and the slope of the exposure-response relationship (β_1) are shown in Table 7. Similar baseline seizure frequency and slope estimates are obtained in pediatrics (2-15 years) and adults (>15 years) suggesting similar exposure response relationship in these populations.

The effect of age as both continuous and discrete on the final model was evaluated. Table 17 shows that there was no effect of age on the exposure-response relationship as inclusion of age as a covariate in the model did not reduce the objective function significantly.

In order to confirm the similarity of the PK-efficacy relationships in adults and pediatrics for different C_{MIN} values, 10,000 simulations were conducted for each age group and the ratio of median effect (% percent change of seizure from baseline) for pediatrics to median effect for adults was calculated. The 90% confidence interval of the ratio was also calculated and shown in Table 8. The results show that the efficacy in pediatrics is approximately 90% that of the adults across various concentrations of topiramte. The 90% confidence interval of the ratios include 1, suggesting no difference in the response between pediatrics and adults.

Reviewer's comments:

- *The sponsor's conclusion that the exposure-response relationship is similar between adults and pediatrics in adjunctive setting is adequate. A similar approach was used for Trileptal and the efficacy in pediatrics was approximately 82%-88% that of the adults across various concentrations of trileptal.*

Table 17: Evaluation of Age Effect on Percent Reduction in Seizure Frequency for Topiramate in Adjunctive Therapy Trials

Model	Description	MOF[a]	Δdf[b]	ΔMOF[c]
Final	As MVal1, but remove baseline seizure frequency term, Equation 4	447.952	+1	+1.478
AVal 1	As Final + age term	446.557	-1	
AVal 2	As AVal 1 + interaction term C_{MIN} *age	446.552	-1	-0.0048
AVal 3	As Final + age<10 term	447.831	-1	+1.279
AVal 4	As Aval 3 + interaction term C_{MIN} *age<10	446.598	-1	-1.233
AVal 5	As Final + age<16 term	447.752	-1	+1.154
AVal 6	As Aval 5 + interaction term C_{MIN} *age<16	447.738	-1	-0.014

[a] Minimum value of the objective function obtained from S-PLUS

[b] difference in the number of degrees of freedom relative to the referred model

[c] ΔMOF follows approximately a chi-squared distribution whereby a value of 3.84 or more is associated with a p-value of <0.05 for a model with Δdf =+1

(Source: Sponsor's Pharmacokinetic Bridging Analysis Report, Table 9, pg 45)

Dose selection in monotherapy for pediatrics of age 2 to < 10 years: The sponsor used (b) (4)

Reviewer's Comment:

- (b) (4)

6 RESULTS OF REVIEWER'S ANALYSIS

6.1 Objectives

The reviewer's analysis objectives are:

1. To determine if the exposure-response relationship is the same between pediatrics and adults in monotherapy.
2. To determine the optimum dose for pediatrics of the age 2 to <10 years in monotherapy.

In order to accomplish the above objectives, the adequacy of the sponsor's population PK model was assessed because predicted steady state trough concentrations of the drug (C_{MIN}) from the model was used for the exposure-response analysis and for dose selection.

6.2 Methods

6.2.1 Data Sets

Data sets used are summarized in

Table 18.

Table 18: Analysis Data Sets.

Study Number	Name	Link to EDR
See Table 11 for studies included	data11-csv.xpt	\\Cdsesub1\evsprod\NDA020505\0099\m5\datasets\pharm-bridging-anal-rpt\poppk-pd\1-poppk\final-model-control-33-24m\data11-csv.xpt
Monotherapy trials (TOPMAT-EPMN-106,-105, -104.	szm-csv.xpt	\\Cdsesub1\evsprod\NDA020505\0099\m5\datasets\pharm-bridging-anal-rpt\poppk-pd\2-cmin-poppk-mono\szm-csv.xpt
See Table 11 for studies included	out-model33-24m-csv.xpt	\\Cdsesub1\evsprod\NDA020505\0099\m5\datasets\pharm-bridging-anal-rpt\poppk-pd\2-cmin-poppk-mono\out-model33-24m-csv.xpt
Monotherapy trials (TOPMAT-EPMN-106,-105, -104.	szmcmin-csv.xpt	\\Cdsesub1\evsprod\NDA020505\0099\m5\datasets\pharm-bridging-anal-rpt\poppk-pd\2-cmin-poppk-mono\szmcmin-csv.xpt
Monotherapy trials (TOPMAT-EPMN-106,-105, -104.	kdemog.xpt	\\Cdsesub1\evsprod\NDA020505\0099\m5\datasets\iss\tabulations\iss-monotherapy\kdemog.xpt

6.2.2 Software

SAS, R, S-PLUS, NONMEM were used for the reviewer's analyses.

6.3 Results

6.3.1 Population Pharmacokinetic Analysis

The parameters of the sponsor's model were re-estimated without including age as a covariate on clearance because the exponential coefficient of the effect of age on clearance was negative, suggesting an older pediatric patient will have smaller clearance (L/hr) given the same weight, which is physiologically not possible for a drug primarily eliminated by kidney. Overall, the results were consistent as reported by the sponsor (Table 19 versus Table 12). The observed versus individual predicted for different age groups (<10, 10-15, >15 years) in Figure 11 show no systematic bias and suggests reasonable prediction of individual concentrations from the population PK model without age as a covariate on clearance. The C_{MIN} predicted from this model was used to determine the target concentrations and dose for pediatrics (2-9 years).

Table 19: Parameter Values from the Reviewer's Final Population PK Model

Parameter (Units)	Typical Value	Inter-Individual Variability
Clearance (L/hr)		
CLSTM (baseline clearance monotherapy) (θ_1)	1.2	27.4
CLSTA (effect of adjuvant) (θ_2)	0.46	
FCWT (effect of weight) (θ_3)	0.383	
FCIN (effect of INMD) (θ_4)	1.95	
FCVP (effect of valproate) (θ_5)	0.696	
FCNE (effect of NEMD) (θ_6)	0.649	
Central Volume of Distribution (L)		
VST (θ_7)	5.13	101
FVWT (effect of weight) (θ_8)	1.09	
Ka (h^{-1}) (θ_9)	0.121	18.5
K_{23} (h^{-1}) (θ_{10})	0.61	NE
K_{32} (h^{-1}) (θ_{11})	0.068	
Residual Error		
CCV residual error (%CV)	25.6	
Additive residual error (μg/ml)	0.0319	

NE-Not Evaluated

(Source code: run4.mod. See section 7 for details)

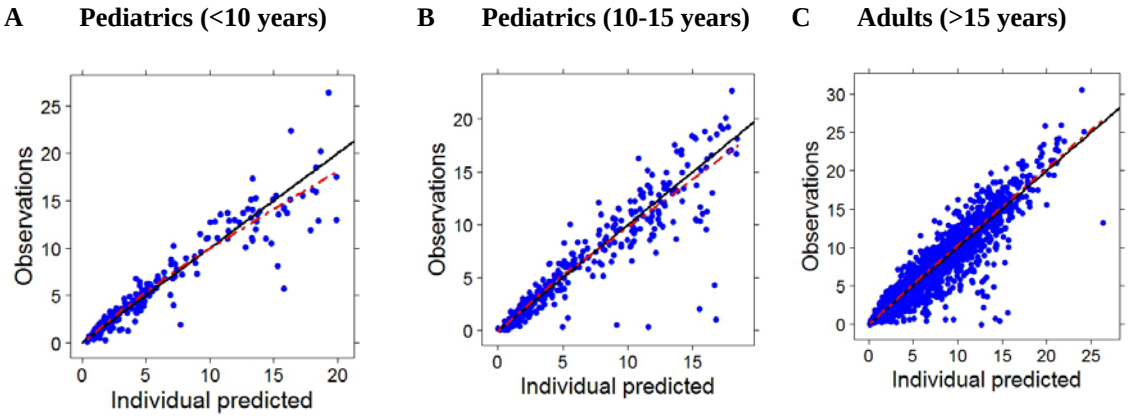


Figure 11: Observed versus individual predicted concentrations in different age groups.
(Source code: run4.R. See section 7 for details)

6.3.2 Exposure-Response Analysis

A Cox proportional hazard model was used to link the steady state trough drug concentrations to the time-to-first-seizure after randomization in montherapy trials. Baseline seizure frequency and steady state trough exposure (C_{MIN}) were found to be significant predictors for hazard (Table 4). Age did not show a statistically significant effect on the baseline hazard rate or the slope of the exposure-response relationship. Despite the non-significance of age effect on baseline hazard and exposure-response relationship, the full model (Table 4) was used as a conservative way to simulate the impact of age on hazard ratio between adults and pediatrics by taking into account the estimation uncertainty of the parameter estimates. 10,000 simulations were conducted using the Cox proportional hazard model described above and the hazard ratio for pediatrics (6-15 years old) to adults was calculated for different C_{MIN} values. Table 5 shows the median hazard ratio and the 95% confidence interval of the ratio. For details see section 2.1.1. The 95% confidence interval of the ratio includes 1 suggesting no significant difference in the hazard for seizure between pediatrics and adults. The median hazard ratio of pediatrics to adults varied from 0.75 to 0.80 across various concentrations of topiramte. Similar results were obtained when a non-parametric bootstrap was conducted (data not shown). The deviation of the median hazard ratio from 1 is due to the non-significant age effect on the intercept of the Cox model, suggesting a numerically lower risk for seizure in pediatrics than in adults under a placebo treatment. Table 6 shows the median hazard ratio and the 95% confidence interval of the ratio after correcting for placebo response. The median placebo-corrected hazard ratio of pediatrics to adults varied from 0.94 to 1 across various concentrations of topiramte. The 95% confidence interval of the ratio includes 1 suggesting no significant difference in the placebo-corrected relative hazard for seizure between pediatrics and adults.

6.3.3 Dose Selection

Reviewer's dose selection for pediatrics less than 10 years of age in monotherapy was based on matching exposures (C_{MIN}) in pediatrics to exposures observed in adults and exposures observed in pediatrics (6-9 years) in the pivotal monotherapy trial, TOPMAT_EPMN_106. This rationale is based on the established similar exposure-response relationship between pediatrics and adults. Table 10 shows the recommended pediatric dose based on body weight. For details see section 2.1.2.

7 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
Exposure-Response Analysis		
CPH_Model.R Output-CPH-Table4.doc out-parametricbootstrap-Table5.csv out-parametricbootstrap-Table6.csv	Program file for Cox-proportional-hazard (CPH) model for monotherapy. Parametric and non-parametric bootstrap is also conducted. Output from CPH_Model.R. It contains the parameter estimates of the CPH model as described in Table 4 of the PM review. Output from CPH_Model.R. It contains the hazard ratio (CI) of pediatrics compared to adults for different C_{min} values as described in Table 5 and Table 6 of the PM review	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Topiramate_NDA020505_S042_AM\ER Analyses\Efficacy Model\Reviewer CPH Model Monotherapy
Population PK Analysis		
run4.mod run4.lst sdtab4 patab4 cotab4 catab4	Reviewer's final population PK model. Code generates Table 19 of the PM review Output from run4.mod.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Topiramate_NDA020505_S042_AM\ PPK Analyses\Reviewer Final Model\
run4.R DVIPRE_Ped_Less10y_Fig 7A_run4.jpg DVIPRE_Ped_10to16y_Fig 7B._run4jpg DVIPRE_Ped_10to16y_Fig 7B_run4.jpg	Code to generate diagnostic plot DV versus IPRED stratified by age Output from run4.R (Figure 11 of PM review)	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Topiramate_NDA020505_S042_AM\PPK Analyses\PK programs \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Topiramate_NDA020505_S042_AM\PPK Analyses\Final Graphs

File Name	Description	Location in \\cdsnas\pharmacometrics\
Analysis for Dose Selection by Matching Exposures		
indv-cmin-mono-pkonlyavgdose.SSC	Code to predict Cmin in monotherapy, generate box-plots of C_{min} versus age groups and calculate median Cmin values in various age groups.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Topiramate_NDA020505_S042_AM\ \Dosing Rationale
Plot_TargetCmin.jpg Output_Target.csv	Output from indv-cmin-mono-pkonlyavgdose.SSC (Figure 6 and Table 9 of PM review)	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Topiramate_NDA020505_S042_AM\ \Dosing Rationale\Final Output
dosecminwt-final.SSC	Code to calculate the pediatric dose that matches target cmin.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Topiramate_NDA020505_S042_AM\ \Dosing Rationale
Output_Dose.csv Plot_Dose.jpg	Outputs from dose-cmin-mgkg-wtbased-final.SSC (Table 10 and Figure 7 of PM review)	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Topiramate_NDA020505_S042_AM\ \Dosing Rationale\Final Output

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