Clinical Pharmacology Review

NDA	20844 (S031)
Submission Date(s)	April 25, 2008
PDUFA Due Date	January 25, 2009
Brand Name	Topamax
Generic Name	Topiramate
Dosage Form	Tablets and Sprinkle Capsules
Dosage Regimen	200 to 400 mg/day divided in two doses for adults and 5-9 mg/kg/day for pediatric patients 2-16 yrs
Pharmacometrics Reviewer	Nitin Mehrotra, Ph.D.
Pharmacometrics Secondary Reviewer	Hao Zhu, Ph.D.
Clinical Pharmacology Reviewer	Jagan Mohan Parepally, Ph.D.
Clinical Pharmacology Team Leader	Ramana Uppoor, Ph.D.
Submission Type	Pediatric supplement in response to written request
Proposed indication	Partial onset seizures in pediatric patients 1 month - 2 years of age

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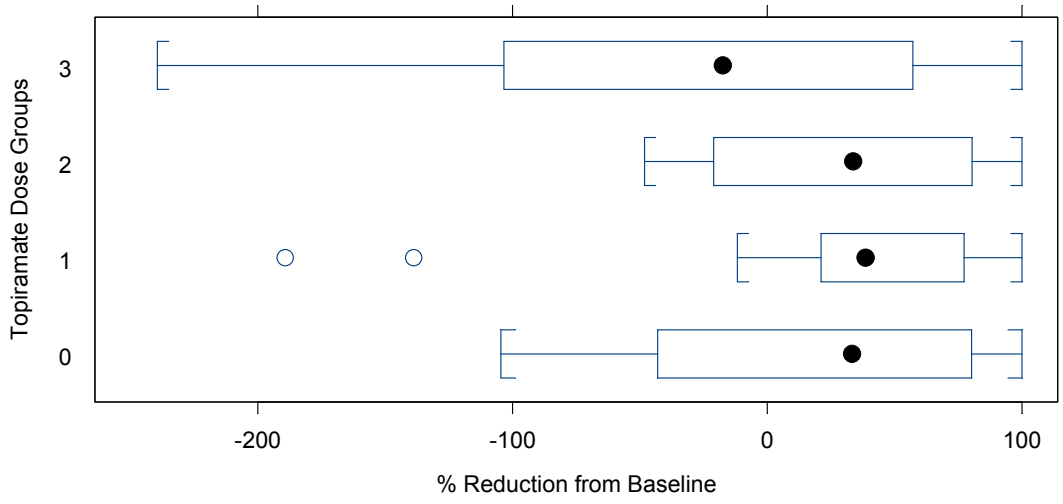
Executive Summary

Recommendation

The Office of Clinical Pharmacology (OCP) reviewed the information submitted under supplemental new drug application NDA 20844 SE5-031, which was submitted in response to the pediatric written request. This submission includes three clinical pharmacology studies (Study TOPMAT-PEP-1001, TOPMAT-PEP-1002, and TOPMAT-PEP-1004) and one population pharmacokinetic study (population-pk-report). TOPMAT-PEP-3001 is the pivotal efficacy trial conducted by the sponsor in 1 month-2 year pediatric patients with partial onset seizures (POS). We found that:

- Topiramate does not appear to be effective in treating pediatric patients 1 month – 2 year of age with partial onset of seizures. This conclusion is based on:
    - The sponsor's primary efficacy analysis and other secondary subgroup analysis failed to demonstrate significant topiramate treatment effect compared to placebo.
    - Our exploratory analysis using the primary efficacy variable (percentage seizure reduction from baseline) in subgroup of patients with at least 48 hour of vEEG observations at end point and no less than one episode of baseline seizure also failed to demonstrate treatment benefit of topiramate as compared to placebo across all dose groups, ranging from 1-5 fold of adult body weight adjusted dose (Figure 1).

Figure 1: Percentage reduction of partial onset of seizures is not improved as dose increases.



Percentage reduction in partial onset seizure (POS) rate from baseline for patients ≥ 48 h vEEG at end point after excluding those with zero seizure rate at baseline (0: Placebo, 1: 5 mg/kg/day, 2: 15 mg/kg/day, 3: 25 mg/kg/day).

Phase IV commitment

None

Summary of clinical pharmacology findings

In addition to the findings summarized previously in the executive summary, we also found:

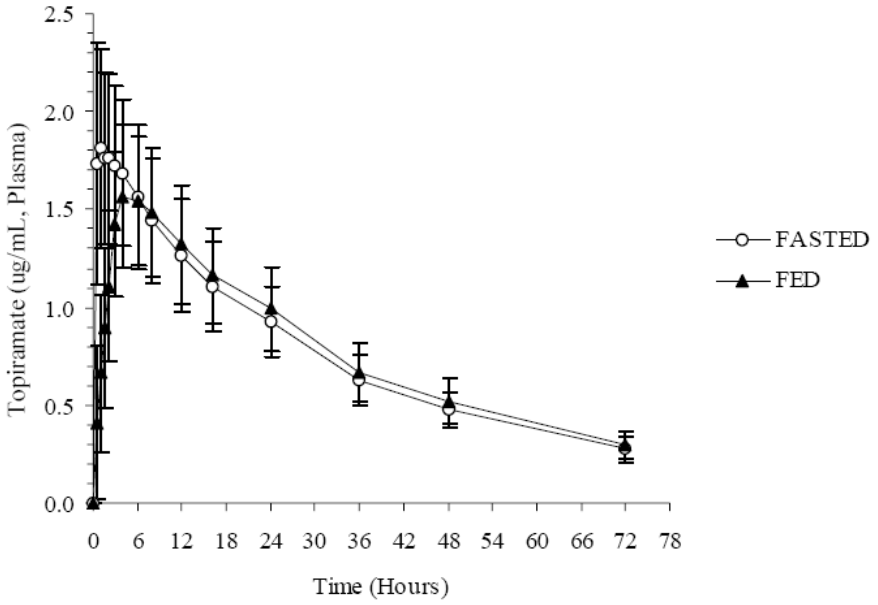
- An adequate link has been established between the commercial formulation and the clinical trial formulation used in the clinical development for pediatric studies. Topiramate oral solution was developed for the pediatric clinical trial. This formulation has been shown to be bioequivalent with the sprinkle capsule, an approved commercial formulation (Table 1).

Table 1: Topiramate oral solution (clinical trial formulation) is bioequivalent with the sprinkle capsule (approved commercial formulation).

Parameter	Geometric Mean			90% confidence limits	
	Topiramate Liquid (test) n=40	Topiramate Sprinkle Capsule (Reference), n=40	Ratio (%)	Lower limit (%)	Upper limit (%)
C_{max} (μg/mL)	1.67	1.75	95.62	91.78	99.63
AUC_{last} (μg.h/mL)	60.78	61.27	99.20	96.47	102.01
AUC_{∞} (μg.h/mL)	72.85	72.75	100.14	97.27	103.09

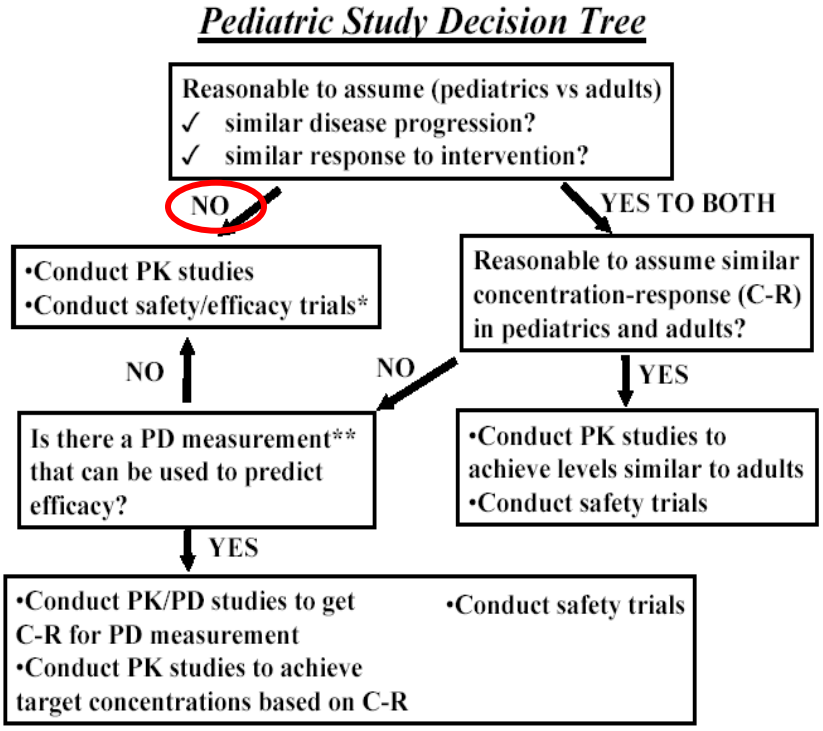
- Mean plasma topiramate concentration profiles are similar when topiramate oral solution was given under fasted or fed condition. C_{max} and AUC are comparable, except a delay of 5 hours on t_{max} observed when topiramate oral solution was administered after a high-fat, high-calorie meal (**Figure 2**)

Figure 2: Mean plasma topiramate concentration profiles are similar when topiramate oral solution was administered with or without food.



- Topiramate exhibits linear pharmacokinetics in the dose range 3 mg/kg/day to 15 mg/kg/day.
    - A traditional PK study in patients 1 month – 2 years of age showed no dose dependence (3 mg/kg/day to 15 mg/kg/day) on clearance along with the historical evidence which shows that PK of topiramate is linear in adults (200 mg to 800 mg) and pediatrics (4-17 years, 1-9 mg/kg/day)
    - Even though, population PK analysis indicated a significant dose effect on clearance in patients 1 month – 2 years, the dose effect appears to be shallow, with 1.7 fold increase in clearance over 5 fold increase in dose.

Pediatric decision tree



Indication: Topiramate is indicated as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures. It is also indicated for patients 2 years and older as an adjunct monotherapy in partial onset seizures. In the current submission, (b) (4)

Is it reasonable to assume that pediatric patients are similar to adults with regard to disease progression?

- No. There is no adequate reason to assume that pediatric patients with partial onset seizure are similar to adults on disease progression. In addition, seizure measurements are performed using vEEG in pediatric patients and in adults the seizure episodes are recorded.

Is it reasonable to assume that pediatric patients are similar to adults with regard to response to intervention?

- No. Pediatric patients can be more refractory than adults with regard to response to drug intervention. Drugs shown to be effective in older pediatric patients (> 2yrs) were not found to be efficacious in younger pediatric patients.

Because two "No" to the two questions in Box 1, the Pediatric Study Decision Tree suggests:

- Conducting PK studies

- Conducting safety and efficacy trials

These studies were performed by the Sponsor.

Question Based Review

A General Attributes of the Drug

(a) What is the proposed therapeutic indication?

Topiramate is indicated as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures. It is also indicated for patients 2 years and older as an adjunct therapy in partial onset seizures. Since the pivotal pediatric trial (TOPMAT-PEP-3001) was not successful, sponsor does not seek any indication in this age range for treating POS.

(b) What is the proposed dosage and route of administration?

Topiramate is approved in adults and pediatrics (greater than 2 years) as tablet or sprinkle capsules for treating POS. The recommended dose for topiramate monotherapy in adults and pediatric patients 10 years of age and older is 400 mg/day in two divided doses. The recommended total daily dose of TOPAMAX® as adjunctive therapy in adults with partial onset seizures is 200 to 400 mg/day in two divided doses, and 400 mg/day in two divided doses as adjunctive therapy in adults with primary generalized tonic-clonic seizures. It is recommended that therapy be initiated at 25 to 50 mg/day followed by titration to an effective dose in increments of 25 to 50 mg/day every week. The recommended total daily dose of TOPAMAX® (topiramate) as adjunctive therapy for pediatric patients with partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome is approximately 5 to 9 mg/kg/day in two divided doses. The sponsor tested a wide range of doses 5mg/kg/day to 25 mg/kg/day in the pediatric clinical trial (TOPMAT-PEP-3001) in 1-24 month pediatrics. But since the trial was unsuccessful, no dosage regimen for pediatrics less than 2 years is proposed. Please refer to Topamax label for complete details.

(c) What efficacy and safety information contribute to the assessment of clinical pharmacology and biopharmaceutics study data?

Study TOPMAT-PEP_1002 designed to assess the PK, safety and tolerability and pivotal pediatric trial (TOPMAT-PEP_3001) conducted to assess the efficacy, safety and tolerability in infants with POS contribute towards assessing clinical pharmacology and biopharmaceutics data.

B General Clinical Pharmacology

(a) What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

Percentage change in seizure rate from baseline is the widely used clinical endpoint to assess POS. It has been shown that reliable differential diagnosis classifying seizures is very difficult in the absence of ictal EEG recordings or brain imaging data. The vEEG methodology has been chosen over clinical observations because it will provide a quantitative and reliable measure of seizure frequency over a very short period of time, and has been shown to be a more sensitive instrument than subject take-home records for detecting and classifying seizures in this age range.
A 48-hour vEEG was recorded during screening and at Visit 4 (Days 19 to 20 or at early visit). The vEEG was also deemed preferable to parent/caregiver-reported data, since infantile seizures may occur in clusters, may constitute brief movements or behavioral changes without persistent sequelae, and may occur at night. Thus, they would be difficult for parents/caregivers to diagnose and count.

(b) Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

A validated LC/MS/MS method was employed for the determination of topiramate in human plasma samples.

(c) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

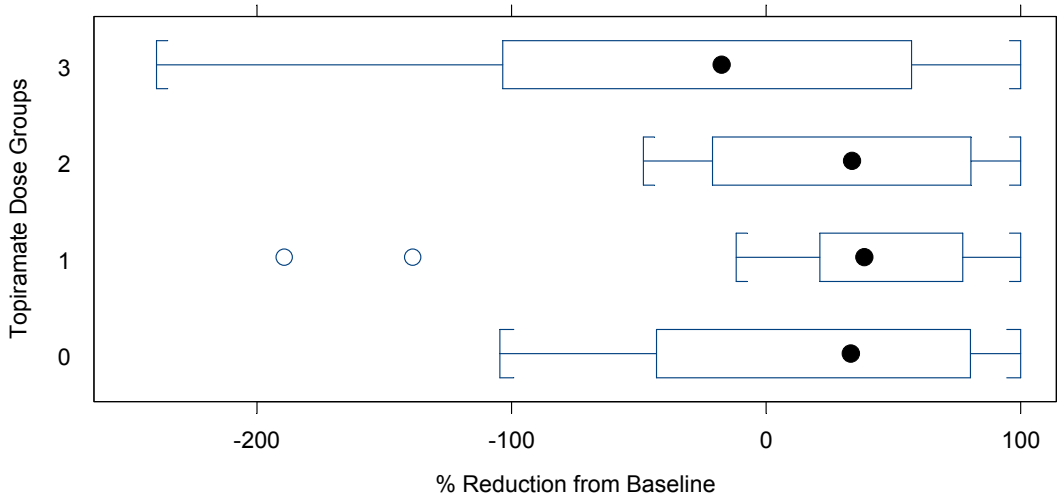
The exposures were not available for the double blind phase of the pivotal efficacy trial, thus exposure response analysis could not be performed. However, since sponsor tested three dose levels in this trial, evidence for effectiveness and dose-safety relationship was explored.

(i) Is there an evidence for effectiveness of topiramate in pediatrics 1 month to 2 years?

There seems to be no topiramate treatment effect as compared to placebo (
Figure **3**). This was based upon the following two analyses: First, the primary efficacy analysis conducted by the sponsor showed no treatment effect. Second, the modified analysis performed by the reviewer after discussions with the medical officer also showed lack of any treatment effect. It is to note that in the primary efficacy analysis, the average seizure counts were imputed for 38 % of patients with less than 48 hour of vEEG observations at the endpoint bearing the assumption the seizure rates are constant over time. In addition, the patients with zero baseline seizure observations were also included in the analysis. In the reviewer's analysis, however, only patients with at least 48 h of vEEG data at endpoint were included as imputation of the primary efficacy endpoint may create some bias. Also, patients with zero baseline seizure rates are irrelevant as there is

no scope for the drug to be superior than placebo. Therefore, patients with at least 48 h of vEEG were selected after removal of those patients with zero baseline seizure rates. The results are shown in
Figure **3**. No treatment benefit can be identified as compared to placebo across all dose groups.

Figure 3: % Reduction in POS from baseline for patients ≥ 48 h vEEG after excluding patients with zero seizure rate at baseline.

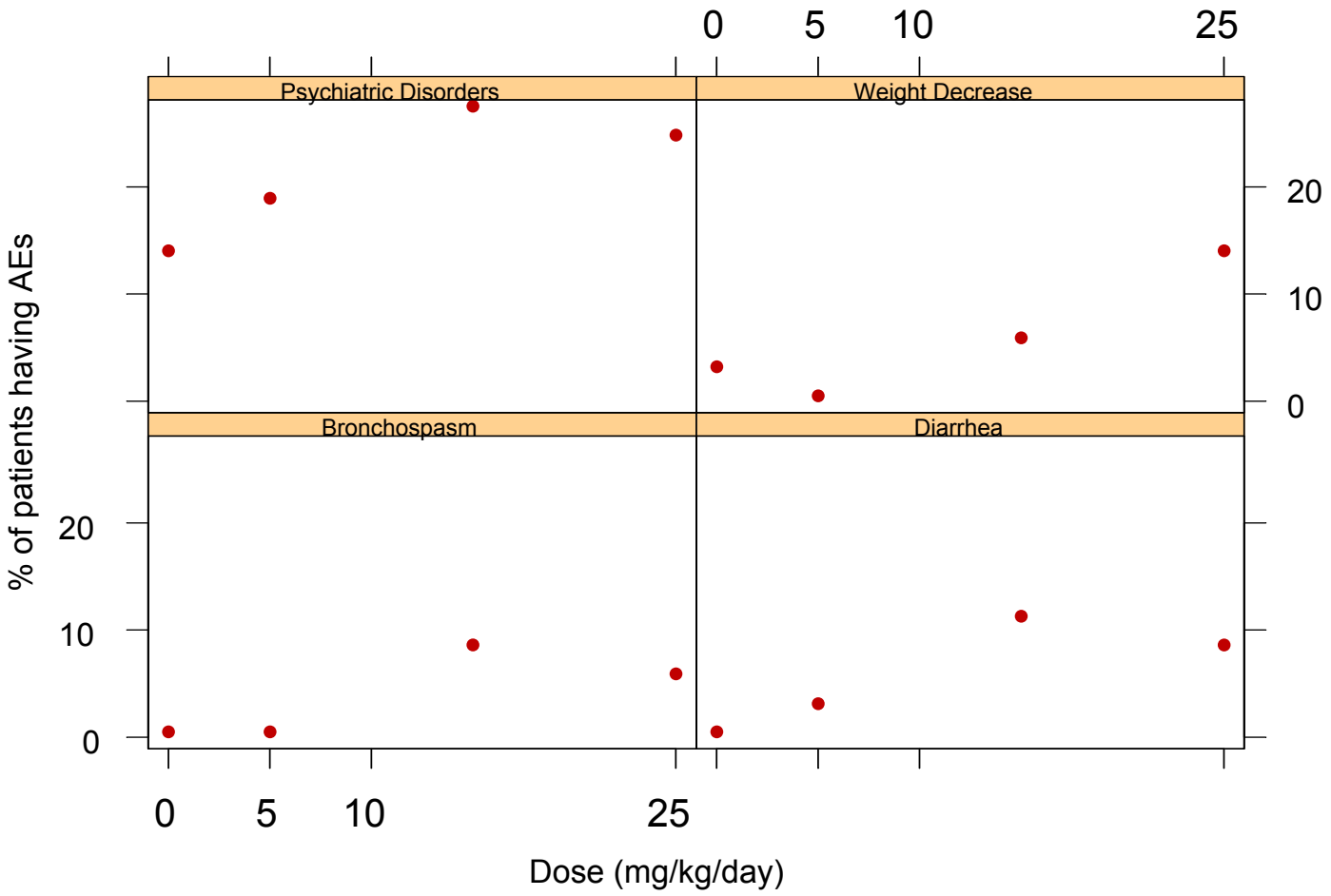


0: Placebo, 1: 5 mg/kg/day, 2: 15 mg/kg/day, 3: 25 mg/kg/day.

(ii) Is there a Dose-Safety relationship for topiramate in pediatrics 1 month- 2 years of age?

There seems to be dose related increase in adverse events like psychiatric disorders (nervousness, anorexia, somnolence), weight decrease, diarrhea and bronchospasm. However, it should be noted that majority of these adverse events were mild to moderate in nature. Furthermore, the incidence of these adverse events is relatively low at the approved adult dose (2.9 -5.8 mg/kg/day for an average 70 kg adult). Higher incidences of adverse events are mainly seen at doses higher than the approved adult dose.

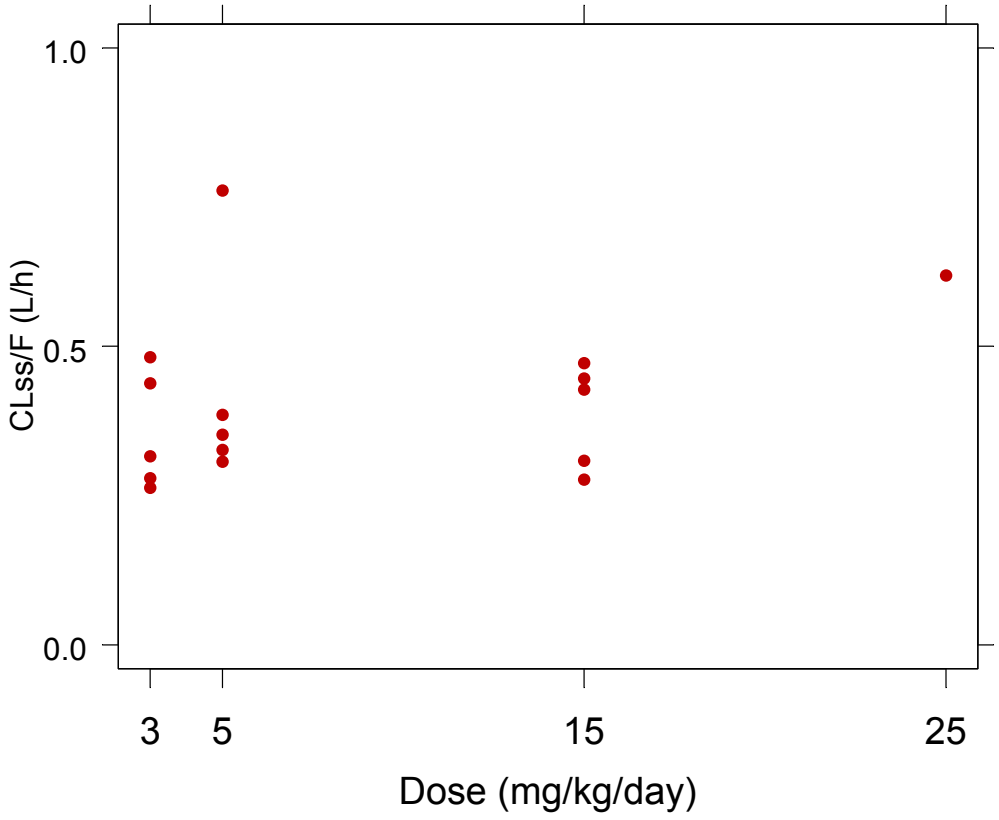
Figure 4: % of treatment emergent adverse events for placebo and the three dose groups in the pivotal efficacy trial TOPMAT-PEP-3001. Number of patients in 0 (placebo), 5, 15 and 25 mg/kg/day dose groups are 37, 38, 37 and 37 respectively.



(d) Does Topiramate exhibit non linear pharmacokinetics with increasing dose in patients less than two years?

No, the PK of topiramate seems to be linear over the range of doses study based on pharmacokinetic study TOPMAT PEP 1002 in 1 month to 24 month pediatric patients with intensive samples (average 5 samples/subject). Figure 5 shows the similar clearance over 3 to 15 mg/kg/day dose range.

Figure 5: Steady state oral clearance in different dose groups from the study TOPMAT-PEP-1002 in patients who were not on concomitant inducers or inhibitors.



Even though the population PK analysis demonstrated a significant dose-clearance relationship in pediatric patients 1 month to 2 years of age, the relationship appears to be shallow. When the sponsor evaluated the relationship between interindividual variability in clearance and average dose from the original population PK model, a clear trend was seen only for 1 month to 2 yr pediatrics. Thus, they included dose as a covariate on Cl in their final model. However, inclusion of dose effect on clearance only explained 6% of the interindividual variability on clearance. This contradicts the results for study TOPMAT-PEP-1002 (< 2 year pediatric population) which concluded that there was no effect of dose on clearance. Considering that significant amount of data for less than two year pediatrics in the model comes from open label phase of the trial which was uncontrolled in nature, it is quite possible that this Dose~Cl relationship is confounded by some unknown variable. The Dose-Cl relationship was shallow with a modest 1.7 fold increase in oral Cl over 5 fold increase in dose which should not be clinically significant given the high interindividual variability in clearance (35%). Furthemore, PK of topiramate is shown to be linear in adults (200-800 mg/day) and pediatrics (4-17 years, 1-9 mg/kg/day). These reasons along with the results of the standalone PK study show that topiramate (TOPMAT-PEP-1002) did not exhibit any clinically meaningful dose dependent increase in clearance.

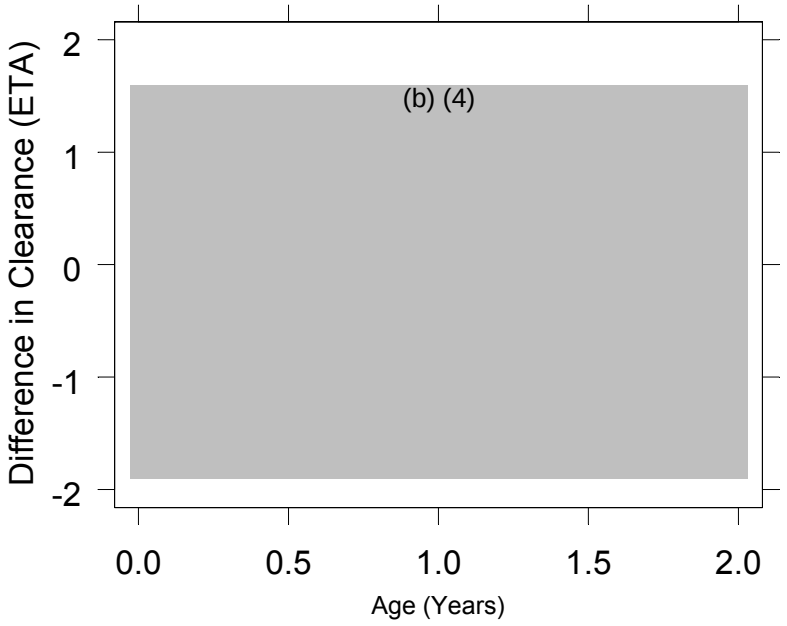
C Intrinsic Factors

For details of all relevant intrinsic factors, refer to Topamax label, the key question relevant to the present submission was:

(a) Is there an effect of age on pharmacokinetics of topiramate in 1 month to 2 years pediatrics?

After the introduction of weight as a covariate on clearance into the model, further inclusion of age neither explained the interindividual variability in clearance, nor caused a significant drop in objective function. The y-axis in Figure 6 depicts the interindividual variability in clearance after accounting for all factors except age. It has been seen consistently for drugs like topiramate which are primarily excreted by kidney and have good bioavailability that age has an effect on clearance even after adjusting for weight. However, given the current data and model, the effect of age on clearance was not observed.

Figure 6: No effect of age once clearance is adjusted for body weight.

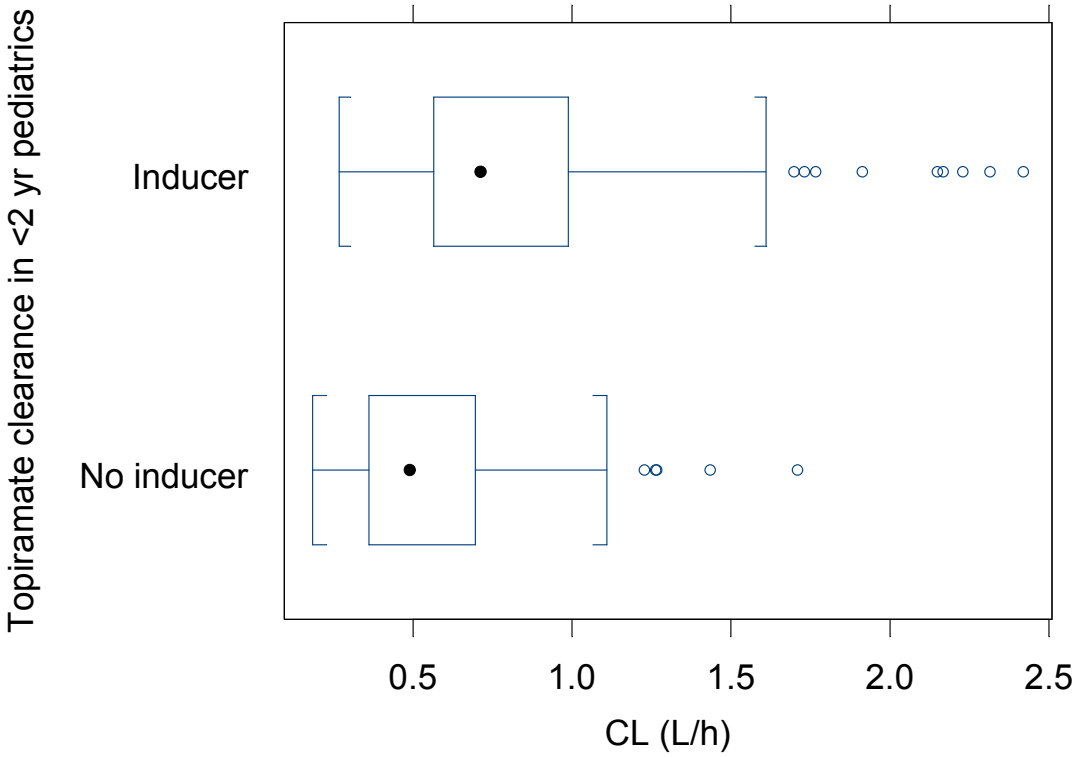


D Extrinsic Factors

(a) Is there an effect of administration of inducers on pharmacokinetics of topiramate in pediatric patients < 2 years?

Yes, the apparent clearance increased by 60% fold in the presence of inducers, however the variability is high. This is similar to 40-48% decrease in exposure with concurrent administration of phenytoin and carbamazepine reported in Topamax label. There are no recommendations for dose adjustment as the proposed indication will not be granted for pediatrics 1 month-2 years.

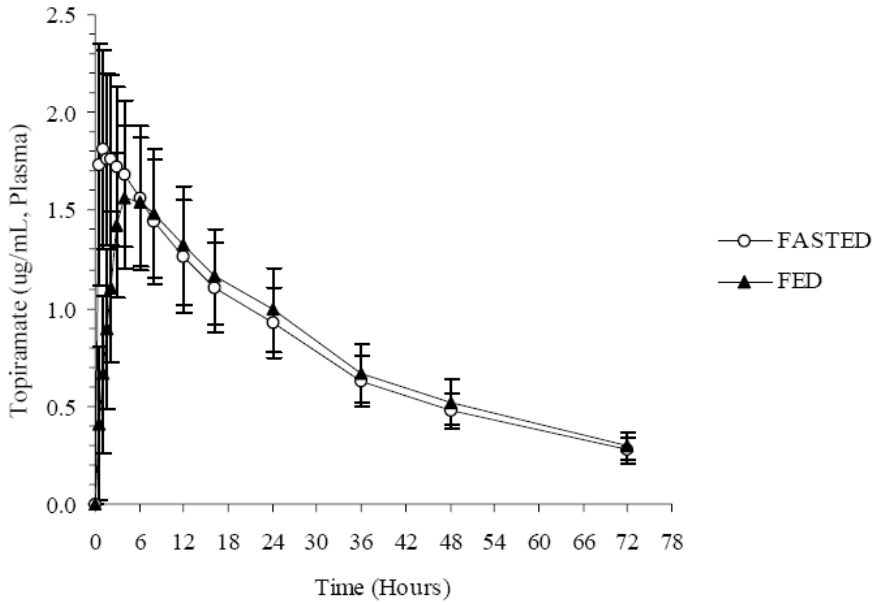
Figure 7: Difference in clearance among pediatric patients with and without co-administration of inducers.



(b) Is there an effect of food on topiramate pharmacokinetics?

There is no effect of food on PK of topiramate. The effect of food on the pharmacokinetics of a 100-mg dose of an oral liquid formulation of topiramate was determined in study TOPMAT-PEP-1004. Administration of oral liquid formulation with food did not affect C_{max} or AUC. However, t_{max} was delayed by 5 hours between the fed and fasted treatment groups (**Figure 8**).

Figure 8: Mean Plasma Concentration versus Time Profiles of topiramate in fasted and fed condition.



For complete details for extrinsic factors affecting topiramate PK, refer to Topamax label.

E General Biopharmaceutics

TOPAMAX® (topiramate capsules) Sprinkle Capsules contain topiramate coated beads in a hard gelatin capsule. The inactive ingredients are: sugar spheres (sucrose and starch), povidone, cellulose acetate, gelatin, silicone dioxide, sodium lauryl sulfate, titanium dioxide, and black pharmaceutical ink.

The oral liquid formulation of topiramate was provided (b) (4) .

(a) Is there adequate link established between the clinically evaluated formulation and the commercial formulation?

Yes, an adequate link has been established between the clinically evaluated formulation (oral solution) and the commercial formulation (sprinkle capsule). The relative bioavailability (F_{rel} [%]) for the oral liquid to the sprinkle capsule formulation was 100% and the oral liquid was shown to be bioequivalent to the sprinkle capsule formulation in a

pivotal bioequivalence study (TOPMAT-PEP-1001). Following table indicates mean ratios and 90% confidence intervals calculated for C_{max} and AUC.

Table 2: Pharmacokinetic parameters for the two formulations.

Parameter	Geometric Mean			90% confidence limits	
	Topiramate Liquid (test) n=40	Topiramate Sprinkle Capsule (Reference), n=40	Ratio (%)	Lower limit (%)	Upper limit (%)
C_{max} (µg/mL)	1.67	1.75	95.62	91.78	99.63
AUC_{last} (µg.h/mL)	60.78	61.27	99.20	96.47	102.01
AUC_{∞} (µg.h/mL)	72.85	72.75	100.14	97.27	103.09

F Analytical Method

Plasma samples from TOPMAT-PEP-1002 and open label phase TOPMAT-PEP-3001\1002 were analyzed for topiramate concentrations employing a (b) (4) liquid chromatography mass spectrometry (LC-MS/MS) method. The internal standard was a (b) (4) The nominal mass transitions (± 0.5 mass units) of *m/z* 338.20 to 77.90 and *m/z* 338.32 to 95.95 were monitored for topiramate and internal standard, respectively.

Table 3: Details of the bioanalytical method.

Assay Type	LC-MS/MS (b) (4) Mobile phase ((b) (4)
Compound	Topiramate
Matrix	Human plasma
Standard	(b) (4)
Standard curve range	0.01 µg/mL to 10 µg/mL ($r^2 \geq 0.999$)
Accuracy (%) ***Inter-assay***	% Nominal: (b) (4) %
Precision (% CV) ***Inter-assay***	% CV ≤11.8
Specificity:	No interferences at the retention times of topiramate, or (b) (4) (internal standard) were observed in human plasma (heparin).
Sensitivity (LOQ)	0.01 µg/mL
Stability	Long-term storage stability was demonstrated for topiramate in human plasma (heparin) for a period of 598 days at -20°C
Conclusion	**The analytical method validation is acceptable**

Labeling Recommendations

This was a PLR conversion of the label from the old format, there are some changes from clinical pharmacology perspective (See Appendix for the proposed label with changes highlighted in red). Below are the changes proposed by the sponsor in the current topamax label in reference to the efficacy trial TOPMAT PEP 3001 (blue text represents addition of new information in (b) (4)):

(b) (4)

Signatures:

Nitin Mehrotra, Ph.D.
Pharmacometrics Reviewer
Office of Clinical Pharmacology

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Appendix

(Individual Study Review: TOPMAT-PEP-1002: Pharmacokinetic safety and tolerability study)

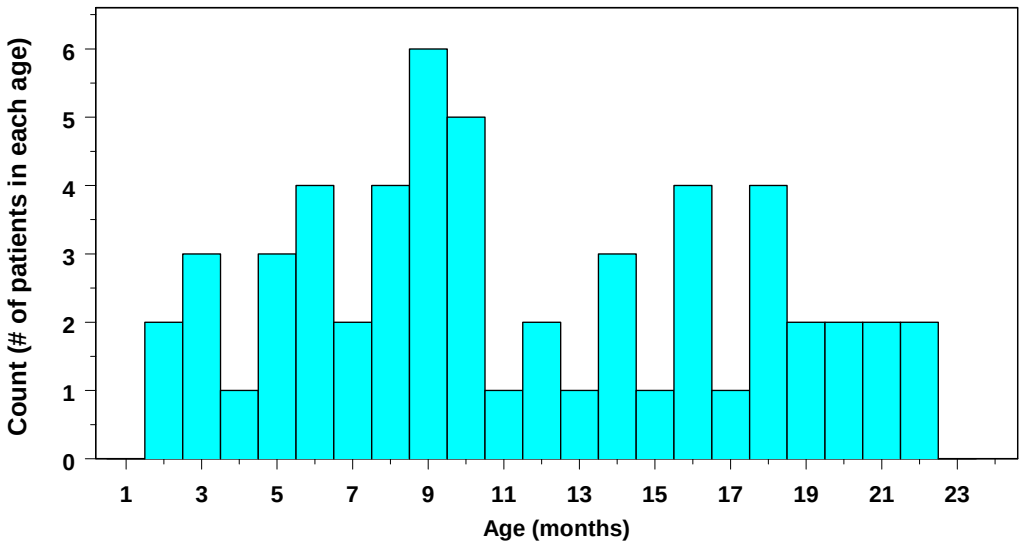
Study Title	A Randomized, Open-Label, Multicenter Study With Open-Label Extension of the Pharmacokinetics and Safety of Topiramate Administered as the Oral Liquid and Sprinkle Formulations as an Adjunct to Concurrent Anticonvulsant Therapy in Infants (Aged 1 to 24 Months, Inclusive) With Refractory Partial-Onset Seizures: Results From the Open-Label Treatment (Core) Phase
Study number	TOPMAT-PEP-1002
Study Period	15 June 2006 – 29 January 2007
Study Director	Vinay Puri, M.D.
Objective	The objectives of this study were to describe the concentration-time profile for topiramate using a sparse sampling scheme in infants aged 1 to 24 months, inclusive, with refractory POS, taking at least 1 concomitant antiepileptic drug (AED) and to evaluate the safety and tolerability of topiramate as adjunctive therapy.

Study Population: N= 60
Age: Infants between 1-24 months
Gender: Male and Female
Weight: Between 3.5 and 15.5 Kg

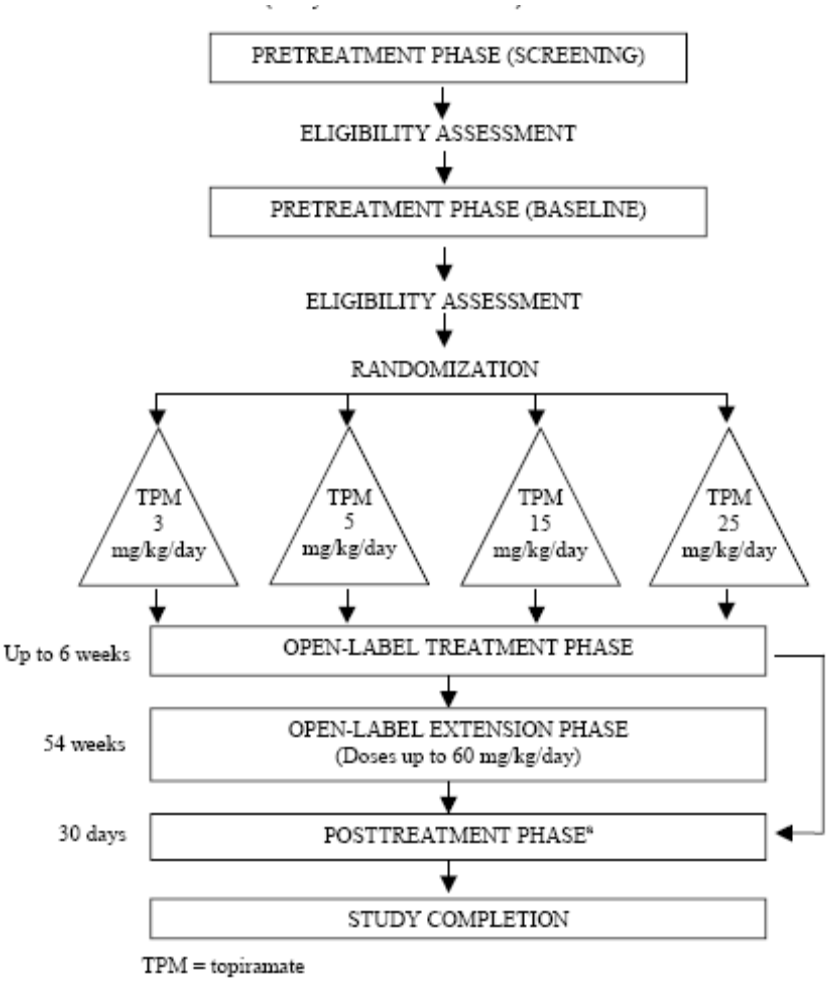
METHODS:

Study Design

The study consisted of 4 phases (Figure below): a pretreatment phase that included screening (up to 7 days) and baseline (1 day), an open-label treatment (core) phase (up to 6 weeks), an optional open-label extension phase (54 weeks), and a post-treatment phase, which included a follow-up visit (up to 4 weeks). In the open-label treatment (core) phase, subjects were randomly assigned to 1 of 4 topiramate treatments (at least 13 subjects per treatment group): 3, 5, 15, or 25 mg/kg per day. The randomization was stratified by the subject's age (1 to 6 months, 7 to 12 months, and 13 to 24 months, inclusive). Age distribution is plotted as histogram in the figure below.
Age Distribution in 1002 Study



Following schematic represents study design.



Dosage and Administration

Subjects received either topiramate sprinkle capsules or topiramate oral liquid solution. The choice of formulation depended on the weight and developmental level (ability to take solid food) of the child. The oral liquid formulation of topiramate (5 mg/mL) was to be used for infants <9 kg or those who could not take any solid or slurry foods; otherwise, subjects might receive the sprinkle formulation.

Fixed target dosages of approximately 3, 5, 15, and 25 mg/kg per day were to be achieved by titration using a schedule of adjustments every 7 days, with the final target dosage maintained until the end of the open-label treatment (core) phase. Titration schedules were as follows:

- Initiated at 3 mg/kg per day
- 5-mg/kg per day group: 3 to 5 mg/kg per day, dose escalation every7 days
- 15-mg/kg per day group: Titration doses: 3, 5, 10, 15 mg/kg per day, dose escalation every 7 days
- 25-mg/kg per day group: Titration doses: 3, 5, 10, 15, 20, 25 mg/kg per day, dose escalation every 7 days

Randomization and Blinding

The randomization was to be balanced by using randomly permuted blocks and was to be stratified by the subject's age (1 to 6 months, 7 to 12 months, and 13 to 24 months, inclusive). The randomization was not to be stratified by center.

The treatment was to be assigned after phoning into the Interactive Voice Response System. The caller had to use their own user ID and PIN, and then give the requested subject details (e.g., subject's initials and subject's date of birth). Based on this information, the Interactive Voice Response System assigned the subject to an open-label treatment arm, which dictated the treatment assignment for that subject.

Blood Sampling: Venous blood samples of 1 mL each were collected for determination of plasma topiramate concentrations at Predose, 1-3, 4-6 and 8-10 hours after study drug administration.

Analytical: Plasma samples were analyzed by a validated liquid chromatography-dual mass spectrophotometry assay for determination of topiramate concentration in plasma Assay performance during the study was acceptable.

Pharmacokinetics: The exact dates and times of blood sampling had to be recorded on the CRF or laboratory requisition form. The proposed number of subjects accounted for the sampling limitations in this population, the need for a larger sample size to perform sparse sampling than traditional pharmacokinetic studies, and the need for relatively uniform distribution of patients across age ranges. Predose concentrations that were

drawn 12 hours after the previous dose and immediately prior to dose administration on pharmacokinetic assessment days were to be used as the predose concentration as well as the 12-hour postdose concentration.

The following pharmacokinetic parameters of topiramate were to be estimated for each subject for each treatment:

- Individual plasma concentrations versus time by dose group,
- Predose drug concentration (C_{trough}),
- AUC_{12h} (area under the plasma concentration-time curve from time 0 through 12 hours as measured by linear-log trapezoidal summation); this was to be estimated for subjects with an appropriate predose plasma concentration only.
- Apparent oral clearance (CL_{ss}/F) estimated as:
  $CL_{ss}/F = Dose/AUC_{12h}$
- Creatinine clearance (CL_{CR}) was estimated using age, length and serum creatinine values recorded at Visit 5 for each individual using the Schwartz equation below.

For infants ≥1 month to <1 year of age,

$$\text{creatinine clearance} = \frac{0.45 \times \text{length (cm)}}{\text{serum creatinine (mg/dL)}}$$

For infants ≥1 year to ≤2 years of age,

$$\text{creatinine clearance} = \frac{0.55 \times \text{length (cm)}}{\text{serum creatinine (mg/dL)}}$$

The plasma topiramate concentration data from this study were to be pooled with the concentration data collected from a Phase 3 efficacy and safety study (TOPMAT-PEP-3001), to characterize the pharmacokinetics of topiramate in infants, using population pharmacokinetic analysis. The majority of the plasma concentration data were to be collected from this study and were to form the basis for the development of a pharmacokinetic model for the population pharmacokinetic analysis. These assessments were to provide preliminary information regarding the relationship between topiramate concentrations and dose. The additional concentration data collected in the current study were to further support the characterization of the steady-state pharmacokinetics of topiramate, and the evaluation of covariate effects on the pharmacokinetics of topiramate.

Safety: Safety was evaluated by examining the incidence and type of adverse events, type and number of seizures, changes in clinical laboratory results, neurologic examination, Vineland Scales of Adaptive Behavior, and renal ultrasound. Assessments for adequate food and liquid intake, hyperthermia, oligohydrosis, and rash were also to be performed.

Table 2: Time and Events Schedule
(Study TOPMAT-PEP-1002 Core Phase)

	Pretreatment Phase[a]		Open-label Treatment Phase			Posttreatment Phase[a]
Procedure	**Screening**	**Baseline**				**Follow-up**
Visit	**1**	**2**	**3[b]**	**4[c]**	**5**	**15**
Day	**-8 to –2**	**-1**	**1**	**3-21[d]**	**7-42[d]**	**Up to 30 days after prior visit**
Screening and Administrative Procedures						
Informed consent/permission	X					
Inclusion/Exclusion criteria	X	X	X	X	X	
Medical history	X					
Epilepsy history	X					
Worksheet for inadequacy of current epilepsy treatment	X					
Prestudy therapy	X					
Study-related Procedures						
Dispense take-home records	X	X	X	X	X	
Collect subject take-home records		X	X	X	X	X
Randomization		X				
Open-label topiramate			X	X	X	
Drug Accountability				X	X	X
Pharmacokinetics						
Blood samples for determination of topiramate plasma levels					X	
Record concomitant medications for PK					X	
Safety Procedures						
Neurologic examination	X	X	X	X	X	X
Vineland Scales of Adaptive Behavior	X[e]	X[e]			X	
Physical examination	X	X	X	X	X	X
Length	X	X			X	X
Head circumference	X	X			X	X
Body weight	X	X	X	X	X	X
Vital signs[f]	X	X	X	X	X	X
12-lead ECG	X[g]				X	
Renal ultrasound	X[g]				X	
Assess food and liquid intake	X	X	X	X	X	X
Assess for hyperthermia	X	X	X	X	X	X
Assess for oligohydrosis	X	X	X	X	X	X
Assess for rash	X	X	X	X	X	X
Ongoing Subject Review						
Record adverse events	X	X	X	X	X	X
Record concomitant medications	X	X	X	X	X	X
Clinical Laboratory Evaluations	X			X[h]	X	X
Venous pH					X[i]	X[i]

[a] Subjects who withdrew early or completed the open-label treatment (core) phase and did not enter the open-label extension phase underwent a withdrawal taper. There was at least 1 telephone contact or visit at the midpoint of the taper and 1 telephone contact the day after conclusion of the taper to evaluate the progress of the taper, review of seizure frequencies by subject take-home records, and review of concomitant therapies and adverse events.

[b] Visit 3 might have occurred on the same day as Visit 2. If Visit 3 occurred within 1 day of Visit 2, no procedure was repeated.

[c] For subjects received the 3-mg/kg per day dose, Visit 4 was optional at the discretion of the investigator.

[d] Study visits occurred on a specific day within the range of study days.

[e] Conducted at either Visit 1 or 2 of the pretreatment phase.

[f] Included temperature (tympanic), pulse, blood pressure, and respiratory rate. At visit 1, blood pressure and pulse were taken twice, 10 minutes apart, and both readings were recorded in the CRF.

[g] Results had to be available for review at least 24 hours before baseline.

[h] Only subjects in the 15- and 25-mg/kg per day dose groups had a clinical laboratory assessment at Visit 4.

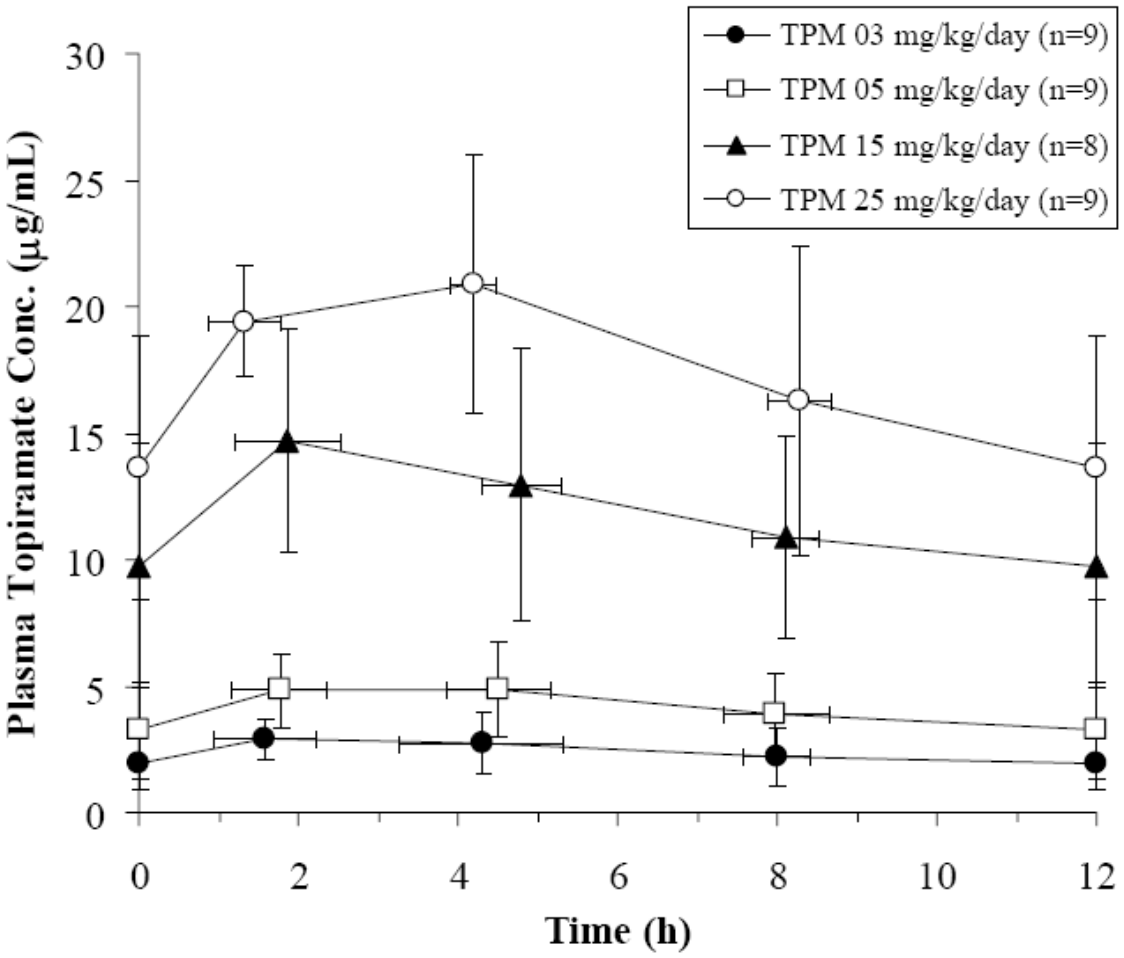
[i] Was determined if serum CO_2 levels <17 mmol/L.

RESULTS:

Pharmacokinetic Results

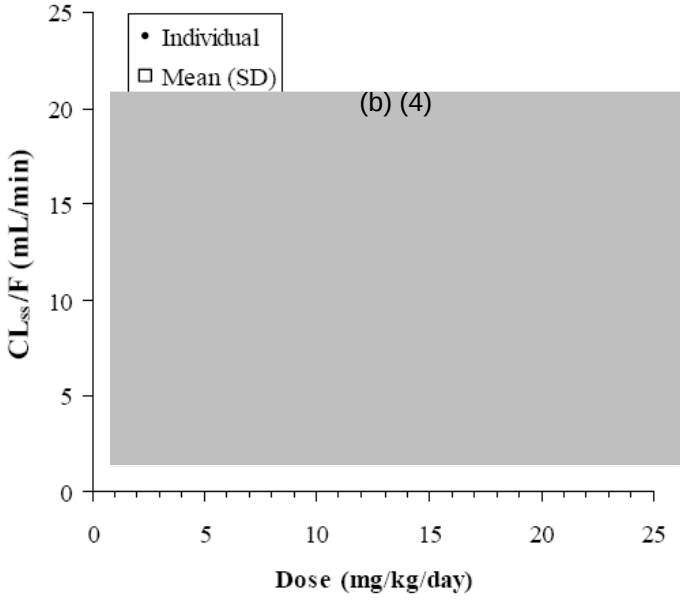
- Mean plasma topiramate concentration-time profiles following multiple oral dose of topiramate in infants 1 to 24 months old are shown in the figure below.

Figure 9: Mean (SD) Plasma Topiramate Concentration-Time Profiles Following Multiple Oral Doses of Topiramate in Infants 1 to 24 Months Old



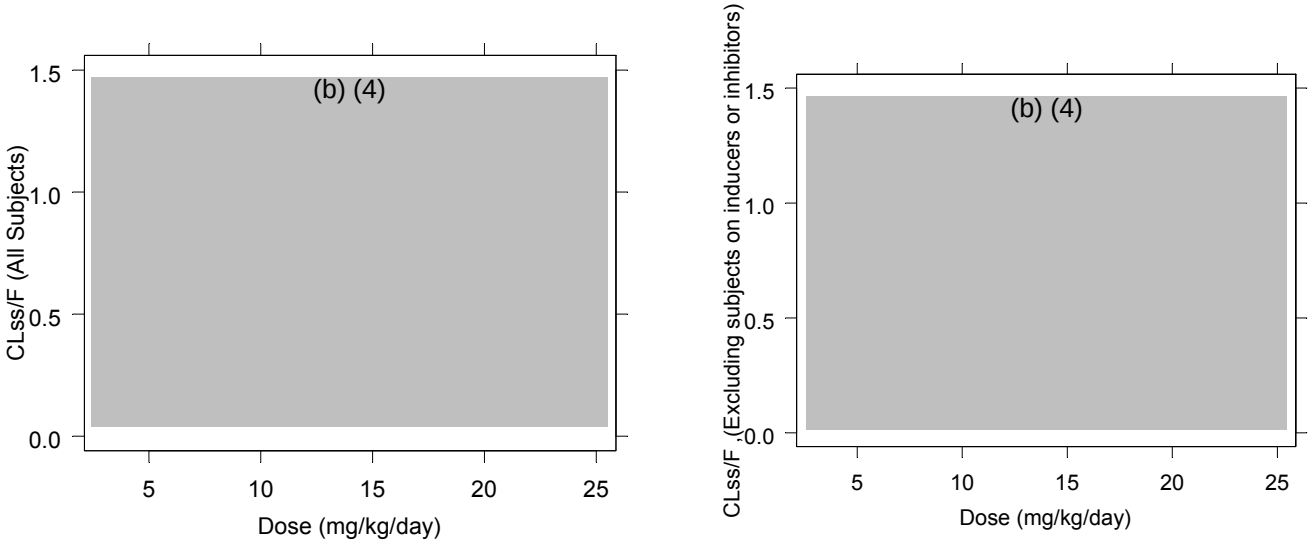
- There was a linear increase in mean plasma topiramate exposure parameters, C_{trough} and AUC_{12h} with respect to dose. Also the apparent oral clearance (CL_{ss}/F, inclusive of subjects on concomitant AEDs that are known CYP-450 enzyme inducers or inhibitors) remained similar across all dosage groups as shown in the figure below.

Figure 10: Apparent Topiramate oral clearance (CLss/F) vs. Dose



Reviewer's Comment: According to the protocol subjects on any medications (not including concomitant AEDs) that are known CYP-450 enzyme inducers or inhibitors within 1 month before the study dosing were excluded from the study. Following figures indicate apparent oral clearance in all subjects (left) compared to subjects without any inducer or inhibitor medications (right). Apparent oral clearance of topiramate appears to be linear vs. dose even in the subjects without inducers or inhibitors. However, 25 mg/kg group does not have enough subjects to extrapolate the results.

Figure 11: Apparent Topiramate oral clearance (CLss/F) vs. Dose (Left panel all subjects, right panel subjects not on inducer or inhibitor medication)



- Mean CL_{CR} values were normal for the dosage groups and ranged from 87.8 to 111 mL/min/1.73m^3 (Table below).

Table 4: Mean (SD) Plasma Topiramate Pharmacokinetic Parameters Following Multiple Oral Doses of Topiramate in Infants 1 to 24 Months Old

	Topiramate Dose Group			
PK Parameter	3 mg/kg/day (n=9)	5 mg/kg/day (n=9)	15 mg/kg/day (n=8)	25 mg/kg/day (n=9)
C_{trough}, µg/mL	1.91 (1.04)	3.25 (1.89)	9.74 (4.82)	13.6 (5.19)
AUC_{12h}, µg.h/mL	29.1 (12.4)	50.0 (19.6)	143 (53.8)	211 (58.0)
CL_{ss}/F, L/h	0.464 (0.203)	0.542 (0.274)	0.546 (0.305)	0.509 (0.147)
CL_{ss}/F, mL/min	7.73 (3.38)	9.04 (4.57)	9.10 (5.08)	8.49 (2.44)
CL_{CR}, mL/min/1.73m^3	111 (37.2)	102 (12.7)	87.8 (20.8)	90.9 (17.3)

- When individual estimates of exposure (C_{trough} and AUC_{12h}) and CL_{ss}/F were plotted as a function of age, there was no particular trend seen in any of the dosage groups.

- The overall trend appeared to be positive (increasing apparent oral clearance with increasing creatinine clearance) when CL_{ss}/F was plotted against CL_{CR}, across the dosage groups.

CONCLUSIONS:

- Increase in exposure (C_{trough} and AUC) was dose proportional (3 to 15 mg/kg/day) in infants 1 to 24 months of age with normal renal function.
- Apparent oral clearance of topiramate was independent of dose up to 15 mg/kg per day.

(Individual Study Review: Bioequivalence study)

Study Title	An Open-Label, Randomized, 2-Way Crossover Study of the Bioavailability of an Oral Liquid Formulation Relative to the Marketed Sprinkle Capsule Formulation of Topiramate RWJ-17021-000 in Healthy Subjects
Study number	TOPMAT-PEP-1001
Study Period	9 November 2004 – 21 December 2004
Study Director	Dennis Morrison
Objective	To determine relative bioavailability of oral liquid formulation and marketed sprinkle capsule formulation

Study Population: N=40
Age: 18-45 years
Gender: Healthy male and female
BMI: Between 19 -32 Kg/m^2

INTRODUCTION:

The purpose of this study is to estimate the bioavailability of an oral liquid formulation relative to the commercially available oral sprinkle capsule formulation of topiramate in healthy subjects. The sprinkle capsule formulation of topiramate is commercially available, however, its use is limited to pediatric patients who are able to ingest solid foods. An oral liquid formulation would facilitate administration of topiramate in children as young as 1 month of age, older infants who are developmentally delayed and cannot ingest solid foods, and children or adults with enteral feeding appliances such as nasogastric or gastrostomy tubes. In order to use both formulations interchangeably and provide doses of both formulations that result in equivalent systemic exposure, it is necessary to determine the relative bioavailability (F_{rel} [%]) of the oral liquid versus the sprinkle capsule formulation.

METHODS:

This was a single center, randomized, open-label, 2-way crossover, Phase 1 bioavailability study, which was conducted in 3 phases: a pretreatment phase (Days -14 to -1), a 25-day open-label treatment phase, and a 7-day follow-up phase.

Dosage and Administration

- Treatment A: Topiramate 100 mg as 20 mL of a 5-mg/mL liquid formulation;
- Treatment B: Topiramate 100 mg as 4 of the 25-mg sprinkle formulation capsules.

Doses were separated by a 3-week washout period. Subjects were not allowed to consume food until 4 hours after drug administration.

Following an overnight fast, subjects received topiramate as a single 100-mg dose of the oral liquid formulation or the oral sprinkle capsule formulation in the morning of Days 1 and 21 in the sequence specified by the randomization schedule. Serial blood samples were collected for estimation of plasma topiramate concentrations at scheduled times through 96 hours after each dose administration. Subjects were sequestered from the evenings of Days –1 and 20 through completion of the 48-hour postdose blood sample collection (Days 3 and 23, respectively) and had to return to the study site for collection of the 60-hour, 76-hour, and 96-hour postdose samples on Days 3 to 5 and 23 to 25, respectively. There was a 21-day washout period between the treatments. Safety and tolerability were monitored throughout the study.

Duration of Treatment: Each subject received 1 single topiramate dose of 100 mg as 4 X 25-mg sprinkle capsule formulation and 1 single topiramate dose of 100 mg as 20 mL of a 5 mg/mL oral liquid formulation with a 21-day washout period between the 2 doses.

PK Sampling: Blood samples of 5 mL were collected for determination of topiramate at 0 (predose), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, 76, and 96 hours postdose on Days 1 to 5 and 21 to 25.

Analytical: Plasma samples were analyzed by a validated liquid chromatography-dual mass spectrophotometry assay for determination of topiramate concentration in plasma Assay performance during the study was acceptable.

Table 5: Assay performance during the study

Parameter	**Quality Control Samples**	**Standard Curve Samples**
Quality Control or Standard Curve Concentration (µg/mL)	(b) (4)	(b) (4)
Between Batch Precision (%CV)	(b) (4)	(b) (4)
Linearity	Weighted linear equation (1/X), mean r= 0.9981	
Linear Range (µg/mL)	(b) (4)	
Sensitivity (LLOQ, µg/mL)	0.01 µg/mL	

Pharmacokinetics: The following pharmacokinetic parameters of topiramate were estimated for each subject for each treatment: C_{max}, t_{max}, $t_{1/2}$, λz, AUC_{last}, AUC_{∞}, %AUC∞,ex, CL/F, and F_{rel} (%).

Safety: Safety was evaluated by the incidence and severity of adverse events, evaluation of laboratory safety (hematology, serum chemistry and urinalysis), 12-lead ECG, vital signs, physical examination, measurements of body weight, pregnancy tests, urine toxicology tests and urine, breath or saliva alcohol test.

Statistical Methods:
Pharmacokinetics: The analyses of AUC_{last}, AUC_{∞}, and C_{max} were performed on log-transformed estimations using only the data from subjects who completed the study. Analysis of variance (ANOVA) models were fitted to the data with 1 of the estimated PK parameters of interest as the dependent variable, and the effects due to sequence group, subjects nested within the sequence groups, treatment and period as fixed effect. Testing for the treatment sequence group effect was carried out at 10% level of significance, by using the mean square due to the subjects nested within sequence groups as the error term. Testing for the period effect was carried out at 5% level using the residual error term. The estimated least square means and intrasubject variability from the ANOVA model were used to construct 90% confidence intervals for the difference in means on the log scale between the 2 treatments. The limits of the confidence intervals were retransformed using antilogarithms to obtain 90% confidence intervals for the ratio of the mean pharmacokinetic parameters before and after normalizing for treatment formulation potency using the percentage of label claim for the oral liquid formulation (99.6%) to sprinkle capsule formulation (102.2%). This normalization was made by multiplying by the ratio of the potency of the reference formulation (sprinkle) to that of the test formulation (liquid). The 2 treatments were considered bioequivalent if the 90% confidence intervals for the ratio of the means fell within 80% to 125%.

RESULTS:

Following oral administration, topiramate was absorbed with peak concentrations occurring at approximately 1 hour for the oral liquid formulation and 2 hours for the sprinkle capsule formulation. Mean topiramate C_{max} and AUC_{∞} were similar between liquid and sprinkle capsule formulations. Mean estimates for topiramate CL/F were similar for both formulations and consistent with that observed in previous studies for the tablet formulation. The relative bioavailability (F_{rel} [%]) for the oral liquid to the sprinkle capsule formulation was 100%. Mean (SD) Topiramate PK parameters are summarized below: The ratios of the geometric means for C_{max}, AUC_{last} and AUC_{∞} were between 96% and 100%. The 90% confidence intervals of the geometric mean ratios for topiramate PK parameters C_{max}, AUC_{last} and AUC_{∞} of the oral liquid formulation relative to the sprinkle capsule formulation were all contained within the 80% to 125% limits, indicating that the 2 treatments were bioequivalent.

Figure 12: Mean (SD) Topiramate Plasma Concentration-Time Profiles Following a Single Dose of Topiramate 100-mg Administered as Either the Oral Liquid or Sprinkle Capsule Formulations in Healthy Subjects

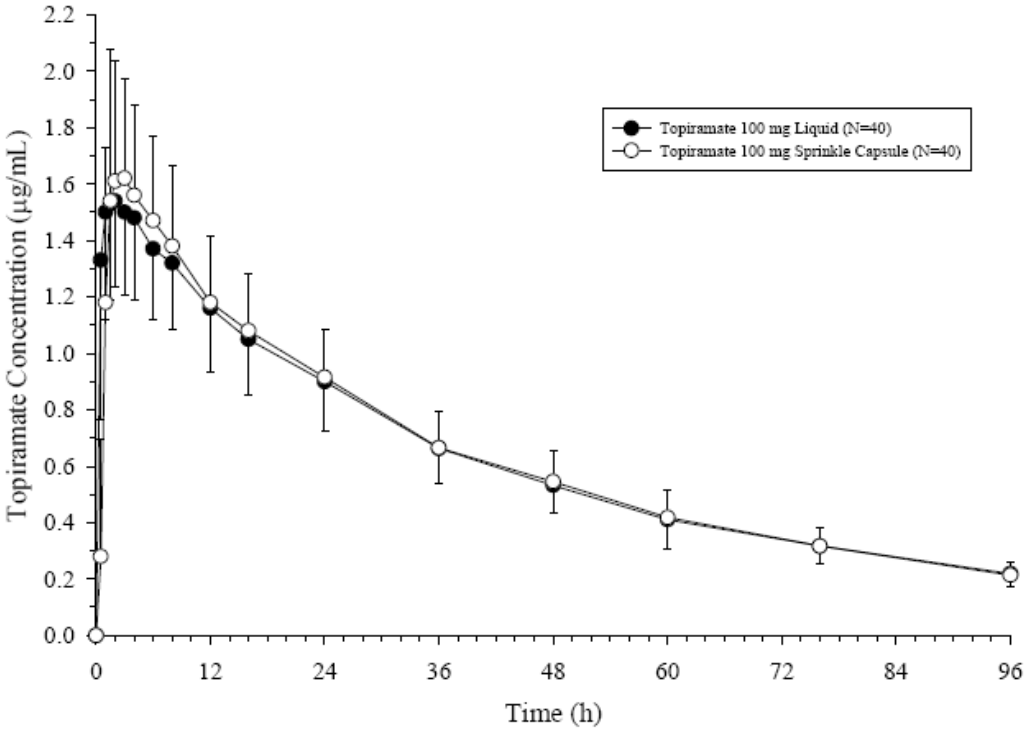


Table 6: Mean (SD) Topiramate Plasma Pharmacokinetic Parameter Estimates Following a Single Dose of Topiramate 100-mg Administered as the Oral Liquid or Sprinkle Capsule Formulations in Healthy Subjects

Parameters	Topiramate 100 mg Liquid (N=40)	Topiramate 100 mg Sprinkle Capsule (N=40)
C_{max} (µg/mL)	1.70 (0.313)	1.79 (0.363)
t_{max} [a] (h)	1.00 (0.50-4.00)	2.00 (0.50-8.00)
AUC_{last} (µg.h/mL)	61.7 (10.9)	62.2 (11.0)
AUC_{∞} (µg.h/mL)	74.0 (13.1)	73.8 (13.0)
$\%AUC_{\infty,ex}$	16.5 (4.27)	15.7 (3.41)
$t_{1/2}$ (h)	38.2 (6.08)	36.8 (4.24)
CL/F (mL/min)	23.2 (4.29)	23.2 (3.96)

[a] t_{max} represented as median (range)

Table 7: 90% Confidence Intervals for the Ratio of the Means for Topiramate Plasma Pharmacokinetic Parameters Following a Single Dose of Topiramate 100-mg Administered as Either the Oral Liquid or Sprinkle Capsule Formulations in Healthy Subjects

Parameter	Geometric Mean			90% confidence limits	
	Topiramate Liquid (test) n=40	Topiramate Sprinkle Capsule (Reference), n=40	Ratio (%)	Lower limit (%)	Upper limit (%)
C_{max} (μg/mL)	1.67	1.75	95.62	91.78	99.63
AUC_{last} (μg.h/mL)	60.78	61.27	99.20	96.47	102.01
AUC_{∞} (μg.h/mL)	72.85	72.75	100.14	97.27	103.09

Reviewer's Comment: After normalization for treatment formulation potency using percentage of label claim for oral liquid formulation (99.6%) to sprinkle capsule formulation (102.2%), 90% confidence interval limits were also with in 80-125%. (table below). Generally BE assessment does not correct for potency of each batch and should be based on label claim. In this case with or without normalization, BE can be concluded based on 90% confidence intervals being within 80-125%

Table 8: 90% Confidence Intervals for the Ratio of the Means for Topiramate Plasma Pharmacokinetic Parameters Following Normalization for Treatment Formulation Potency Following a Single Dose of Topiramate 100-mg Administered as Either the Oral Liquid or Sprinkle Capsule Formulations in Healthy Subjects

Parameter	Geometric Mean Ratio (%)	90% Confidence Limits	
		Lower Limit (%)	Upper Limit (%)
	(Liquid /Sprinkle)		
C_{max}	98.12	94.18	102.23
AUC_{last}	101.79	98.99	104.67
AUC∞	102.75	100.25	105.78

CONCLUSIONS:

The oral liquid formulation and sprinkle capsule formulations of topiramate are bioequivalent.

(Individual Study Review: Food effect study)

Study Title	An Open-Label, Randomized, Two-Way Crossover Study to Determine the Effect of a High-Fat Meal on the Pharmacokinetics of an Oral Liquid Formulation of Topiramate in Healthy Adult Subjects
Study number	TOPMAT-PEP-1004
Study Period	8 January 2007 – 13 March 2007
Study Director	Thomas Hunt, M.D., Ph.D
Objective	The objective of this study was to determine the effect of a high-fat, high-calorie meal on the pharmacokinetics of a 100-mg dose of an oral liquid formulation of topiramate in healthy adult men and women.

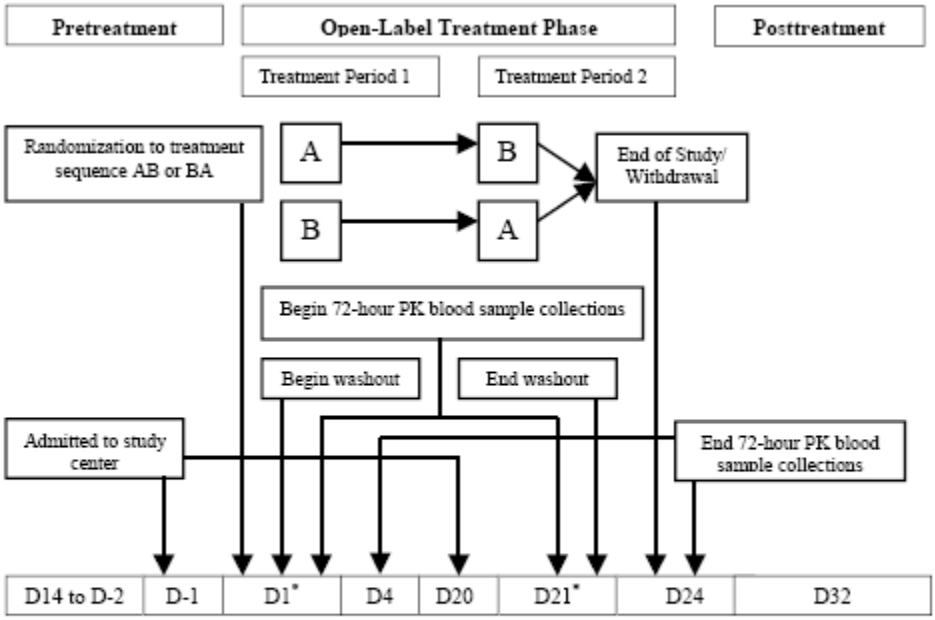
Study Population: N= 40
Age: 18-45 years
Gender: Healthy male and female
BMI: Between 18 -29 Kg/m^2

METHODS:

Study Design
This was a randomized, open-label, 2-way crossover study to evaluate the pharmacokinetics, safety, and tolerability of 2 single doses of 100-mg oral liquid formulation of topiramate in healthy men and women in the presence and absence of a high-fat, high-calorie meal. This study was conducted in 1 study center in U.S. Forty subjects participated in this study.

The study consisted of a screening phase of 14 days, an open-label treatment phase, including 2 treatment periods of 4 days each (Treatment Period 1 [Day 1 to Day 4] and Treatment Period 2 [Day 21 to Day 24]) separated by a 21-day washout period, and a post-treatment phase of 7 days.

Study Design



D=Day
A= A single dose of 100-mg topiramate liquid taken with 220 mL of water in the fasted state
B= A single dose of 100-mg topiramate liquid taken with 220 mL of water 30 minutes after the start of a high-fat, high-calorie breakfast
*Administer a single dose of 100-mg topiramate liquid

Dosage and Administration

All subjects received the following 2 treatments, one in each treatment period:

- **Treatment A:** A single 100-mg dose of an oral liquid formulation of topiramate as 20 mL of a 5-mg/mL aqueous solution taken with 220 mL of water in the fasted state
- **Treatment B:** A single 100-mg dose of an oral liquid formulation of topiramate as 20 mL of a 5-mg/mL aqueous solution taken with 220 mL of water 30 minutes after the start of a high-fat, high-calorie breakfast.

Each treatment was administered to subjects in the morning after a fast of at least 10 hours. Subjects were not allowed to consume food until 4 hours after study drug administration, with the exception of subjects receiving Treatment B who consumed a meal before study drug administration.

Randomization and Blinding

Randomization was used in the assignment of subjects to treatment sequence, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) were evenly balanced across treatment sequences, and to enhance the

validity of statistical comparisons across treatments. Subjects were assigned with equal chance to 1 of 2 treatment sequences (table below) in a 1:1 ratio based on a computer-generated randomization schedule prepared by the sponsor before the study.

Table 9: Details of the study design (Food effect study).

Treatment Sequences for Treatment Periods 1 and 2

Treatment Sequence	Treatment Period 1	Treatment Period 2
AB	100 mg topiramate fasted state (Treatment A)	100 mg topiramate fed state (Treatment B)
BA	100 mg topiramate fed state (Treatment B)	100 mg topiramate fasted state (Treatment A)

Table 10: Schedule of important study procedures.

Table 2: Schedule of Key Study Procedures
(Study TOPMAT PEP-1004)

Phase:	Pretreatment		Open-Label Treatment									Posttreatment
Period:	Screening	Baseline	Treatment Period 1, Washout of 21 days, Treatment Period 2									
Day:	-14 to –2	–1	1	2	3	4	20	21	22	23	End of Study/ Early Withdrawal 24	32
Screening and Administrative												
Informed consent	X											
Inclusion/Exclusion criteria	X	X					X					
Medical history	X											
Randomization		X										
Study drug administration			X					X				
Pharmacokinetics												
Plasma topiramate			X	X	X	X		X	X	X	X	
Safety												
Physical examination (height, weight, BMI)	X										X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X										X	
Clinical laboratory tests	X		X					X			X	
Pregnancy test	X	X					X				X	
Urine drug screen	X	X					X					
Urine alcohol test	X	X					X					
Serology testing	X											
Adverse events	Continuous											
Concomitant therapy	Continuous											

Blood Sampling: Venous blood samples of 5 mL each were collected for determination of plasma topiramate concentrations at 0 (predose), 30 minutes, 1 hour, 1 hour and 30 minutes, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours after study drug administration on Days 1 and 21 of Treatment Periods 1 and 2, respectively.

Analytical: Plasma samples were analyzed by a validated liquid chromatography-dual mass spectrophotometry assay for determination of topiramate concentration in plasma Assay performance during the study was acceptable.

Table 11: Assay performance during the study TOPMAT-PEP-1004

Parameter	Quality Control Samples	Standard Curve Samples
Quality Control or Standard Curve Concentration (µg/mL)	(b) (4)	(b) (4)
Between Batch Precision (%CV)	(b) (4)	(b) (4)
Linearity	Weighted linear equation (1/X), mean r= 0.9980	
Linear Range (µg/mL)	(b) (4)	
Sensitivity (LLOQ, µg/mL)	0.01 µg/mL	

Pharmacokinetics: The following pharmacokinetic parameters of topiramate were estimated for each subject for each treatment: C_{max}, t_{max}, $t_{1/2}$, λz, AUC_{last}, AUC_{∞}, Vd/F, CL/F, and F_{rel} (%).

Safety: Safety was evaluated by the incidence and severity of adverse events, evaluation of laboratory safety (hematology, serum chemistry and urinalysis), 12-lead ECG, vital signs, physical examination, measurements of body weight, pregnancy tests, urine toxicology tests and urine, breath or saliva alcohol test.

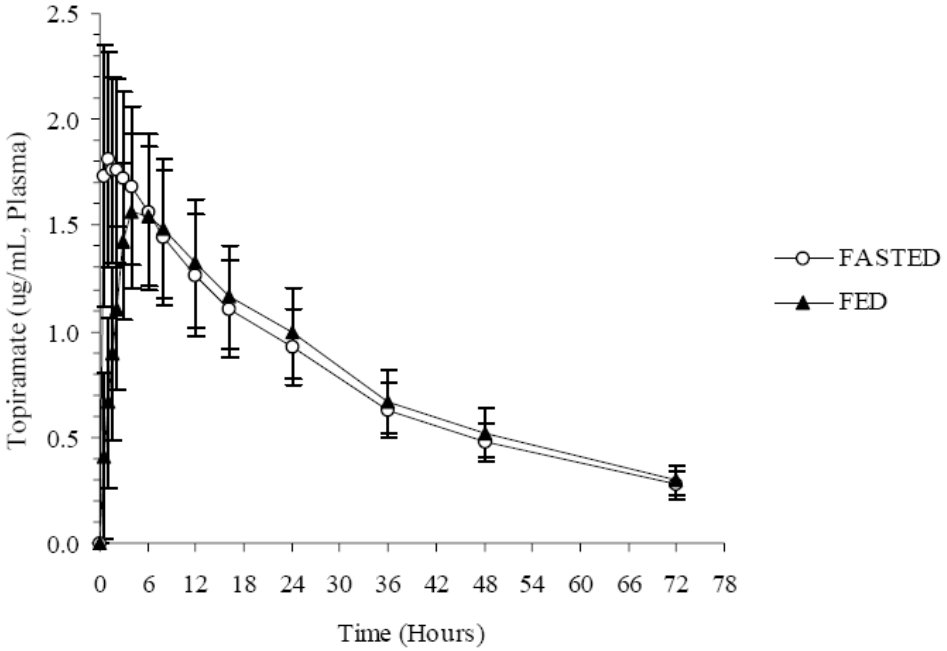
Statistical Methods:

Pharmacokinetics: The primary parameters of interest for the statistical analysis were AUCs and C_{max}. The analysis was performed on log-transformed estimated PK parameters. The data from subjects who completed the study were included in the statistical analysis. Analysis of variance model were fit to the data with one of the estimated PK parameters of interest as the dependent variable, treatment sequence, treatment period, and treatment as fixed effects, and subject as a random effect. Testing for the treatment sequence and treatment period was carried out at 10% of significance using the appropriate error terms. The estimated least squares means (LSM) and intra-subject variability from analysis of variance model were used to construct 90% confidence intervals for the difference in means on the log scale between the 2 treatments. The limits of the confidence intervals were retransformed using antilogarithms to obtain 90% confidence intervals for the ratio of the mean PK parameters obtained when administered to subjects in the fed state to those obtained when administered to subjects in the fasted state. An absence of a food effect on topiramate PK parameters was to be concluded if the 90% confidence intervals for the ratio of the mean PK parameters (AUC_{∞}, AUC_{last}, and C_{max}) with and without food fell within 80% to 125%.

RESULTS:

Pharmacokinetic Results

- Mean plasma topiramate concentration-time profiles showed no change in exposure (C_{max} and AUC). However, a delay in t_{max} was observed when topiramate liquid was administered after a high-fat, high-calorie meal (figure below).



- Topiramate pharmacokinetic parameters, including C_{max}, AUC_{last}, AUC_{∞}, and $t_{1/2}$, were similar between the fed and fasted treatment groups.

- The median t_{max} was delayed by 5 hours when topiramate was given after a high-fat, high-calorie meal.

Table 12: Mean topiramate PK parameters calculated following a single dose administration of oral liquid formulation in fed and fasting conditions.

PK Parameter	Fed n=39	Fasted n=39	F_{rel} (Fed/Fasted), % n=38
C_{max}, μg/mL	1.63 (0.381)	1.94 (0.523)	83.7 (11.2)
t_{max}[a], h	6.00 (1.50-8.00)	1.02 (0.50-4.20)	--
AUC_{last}, h. μg/mL	56.3 (11.1)	56.1 (10.7)	99.5 (7.84)
AUC_{∞}, h. μg/mL	69.3 (13.1)	68.1 (12.2)	101 (9.69)
$t_{1/2}$, h	29.9 (5.3)	29.7 (5.9)	--
λ_z, 1/h	0.0239 (0.00419)	0.0242 (0.00460)	--
Vd_z/F, L	64.3 (16.1)	64.8 (17.2)	--
CL/F, L/h	1.49 (0.276)	1.51 (0.263)	--

[a]Data presented as Median (Min-Max)

The ratios of the geometric means and their corresponding 90% confidence intervals for topiramate PK parameters are listed below.

Table 13: Ratio of the mean plasma topiramate PK parameters and 90% confidence intervals.

PK parameter	LSM		Ratio Test/Reference (Fed/Fasted), %	Confidence interval (90% classical)
	Test (Fed)	Reference (Fasted)		
Log-transformed				
C_{max}, μg/mL	1.58	1.89	83.23	80.40 - 86.16
AUC_{last}, h.μg/mL	55.36	55.53	99.71	98.09 - 101.35
AUC_{∞}, h.μg/mL	68.48	67.46	101.51	99.48 - 103.57

CONCLUSIONS:
A high-fat, high-calorie meal delays absorption of liquid topiramate without changing overall topiramate exposure when compared to fasted conditions.

Pharmacometrics review

PHARMACOMETRICS REVIEW

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1 SUMMARY OF FINDINGS

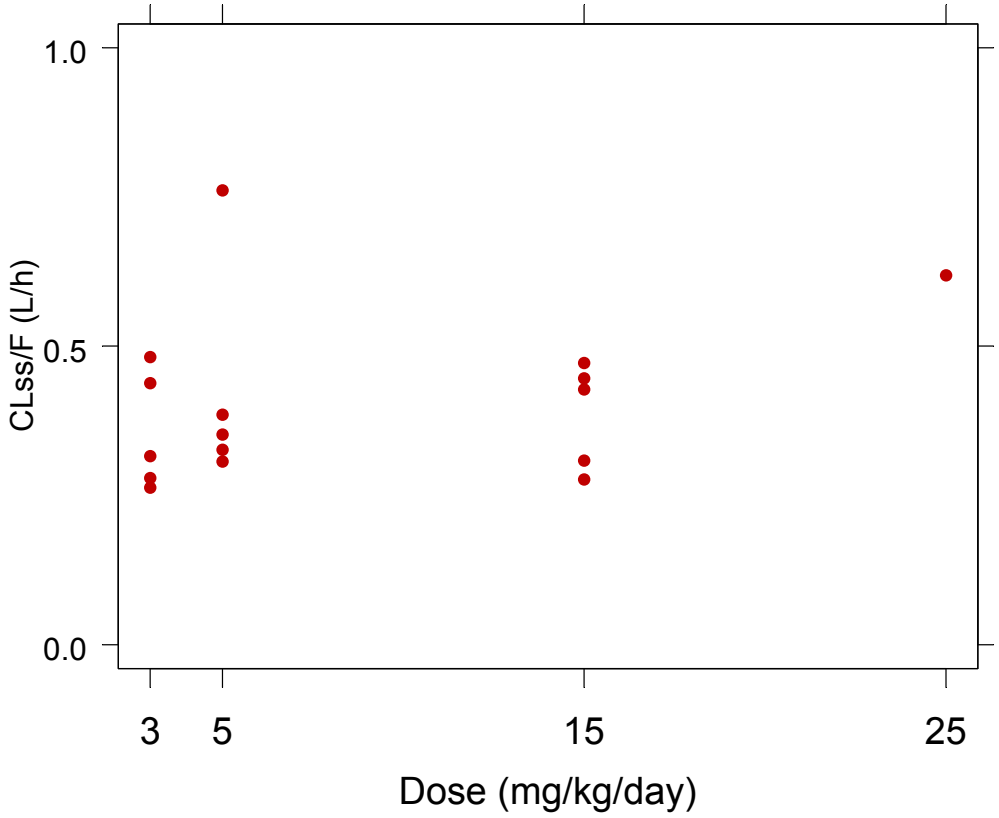
1.1 Key Review Questions

The following key questions were addressed in this pharmacometrics review.

1.1.1 (a) Does Topiramate show dose dependent increase in clearance?

No, the PK of topiramate seems to be linear over the range of 3 to 15 mg/kg/day based on stand alone pharmacokinetic study (TOPMAT-PEP-1002) in 1 month to 2 yr pediatric patients. **Figure 1** shows similar clearance over 3 to 15 mg/kg/day dose range. There were not enough subjects in the 25 mg/kg/day group to draw any conclusions.

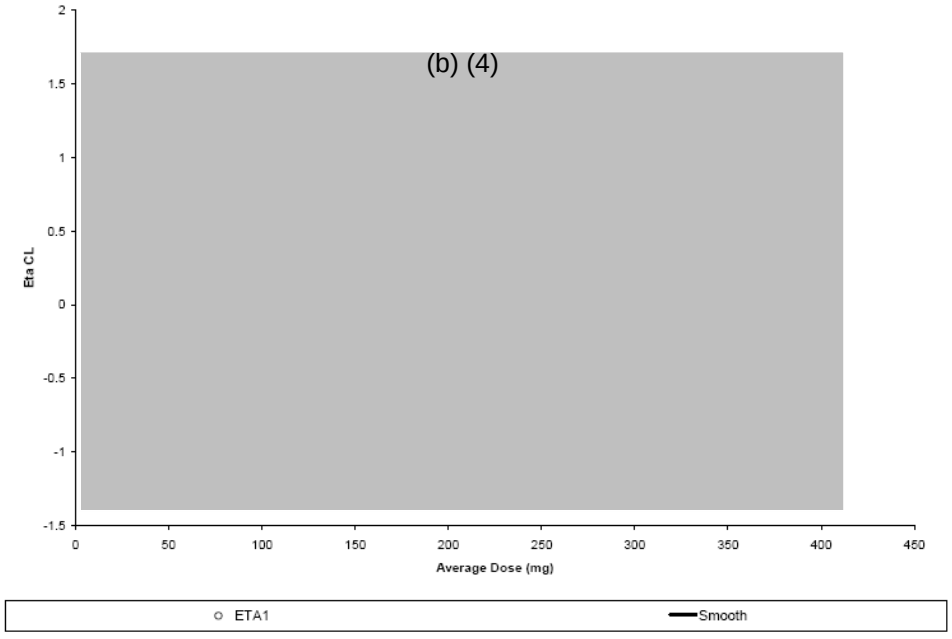
Figure 1: Steady state oral clearance in different dose groups from the study TOPMAT-PEP-1002 in patients who were not on concomitant inducers or inhibitors.



Even though the population PK analysis demonstrated a significant dose-clearance relationship in pediatric patients 1 month to 2 yrs of age, the relationship appears to be shallow. When the sponsor evaluated the relationship between interindividual variability in clearance and average dose from the original population PK model, a clear trend was seen only for 1 month to 2 yr pediatrics. Thus, they included dose as a covariate on Cl in their final model (Figure 2). However, inclusion of dose effect on clearance only

explained 6% of the interindividual variability on clearance. This contradicts the results for study TOPMAT-PEP-1002 (< 2 yr pediatric population) which concluded that there was no effect of dose on clearance. Considering that significant amount of data for less than two yr pediatrics in the model comes from open label phase of the trial which was uncontrolled in nature, it is quite possible that this Dose~Cl relationship is confounded by some unknown variable. The Dose-Cl relationship was shallow with a modest 1.7 fold increase in oral Cl over 5 fold increase in dose which should not be clinically significant given the high interindividual variability in clearance (35%). Furthemore, PK of topiramate is shown to be linear in adults (200-800 mg/day) and pediatrics (4-17 yrs, 1-9 mg/kg/day). These reasons along with the results of the standalone PK study, show that topiramate (TOPMAT-PEP-1002) did not exhibit any clinical meaningful dose dependent increase in clearance.

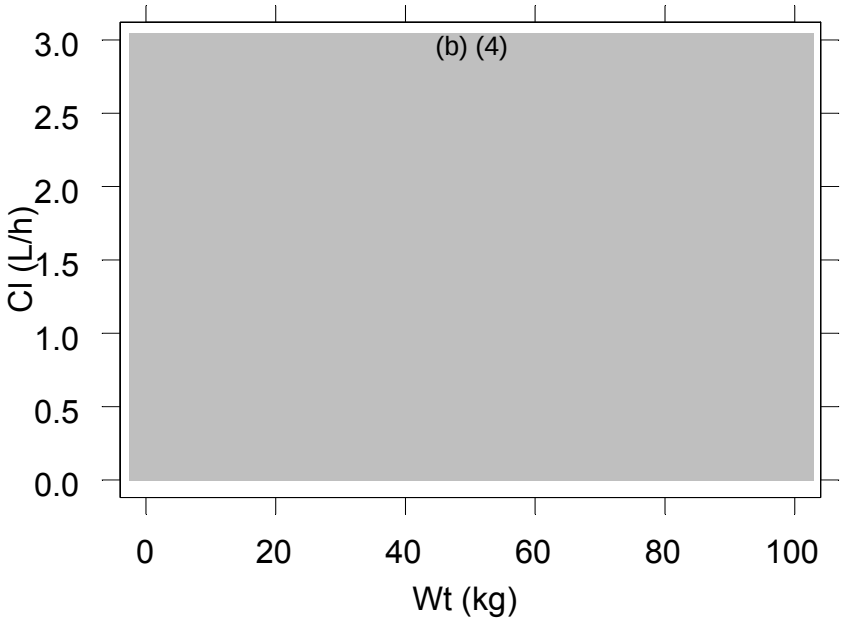
Figure 2: Interindividual variability of clearance versus dose relationship for 1 month to 2 yr pediatrics.



(b) What intrinsic and/or extrinsic factors influence pharmacokinetics of topiramate in pediatric patients?

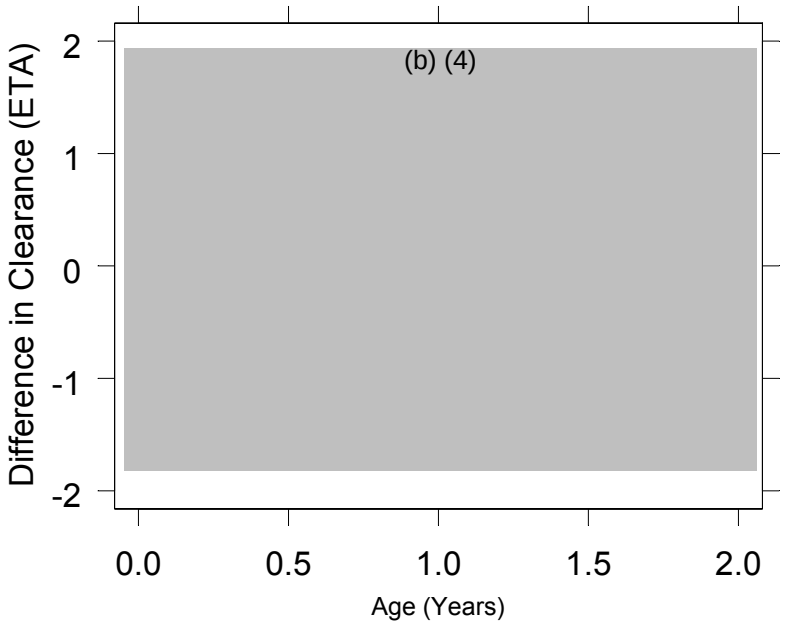
Weight is the significant covariate on clearance and volume of distribution. Age does not explain additional interindividual variability in clearance after accounting for weight and other covariates.

Figure 3: Clearance relationship with weight from the reviewer's model.



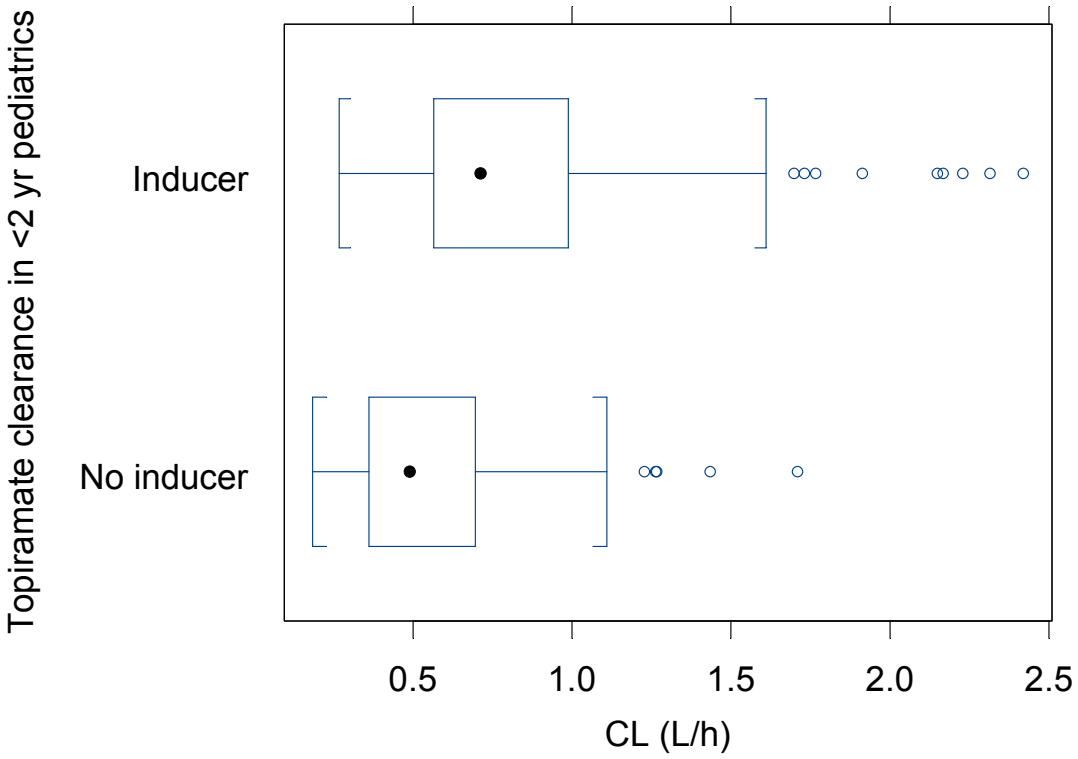
Age and body weight are highly correlated in pediatrics. After the introduction of weight as a covariate on clearance into the model, further inclusion of age neither explained the interindividual variability in clearance, nor caused a significant drop in objective function, thus was not considered as a significant covariate. The y-axis in Figure 4 depicts the interindividual variability in clearance after accounting for all factors except age. It has been seen consistently for drugs like topiramate which are primarily excreted by kidney that age has an effect on clearance after adjusting for weight. However, given the current data and model, the effect of age on clearance was not observed.

Figure 4: No effect of age in1 month-2 yr pediatrics once clearance is adjusted for body weight and other covariates.



The apparent clearance is increased by 60% in the presence of inducers, however the variability was high. This is similar to 40-48% decrease in exposure of topiramate with concurrent administration of phenytoin and carbamazepine reported in Topamax label. There are no dose recommendations for dose adjustment as the proposed indication will not be granted for pediatrics 1 month-2 yrs.

Figure 5: Difference in clearance among pediatric patients with and without co-administration of inducers.

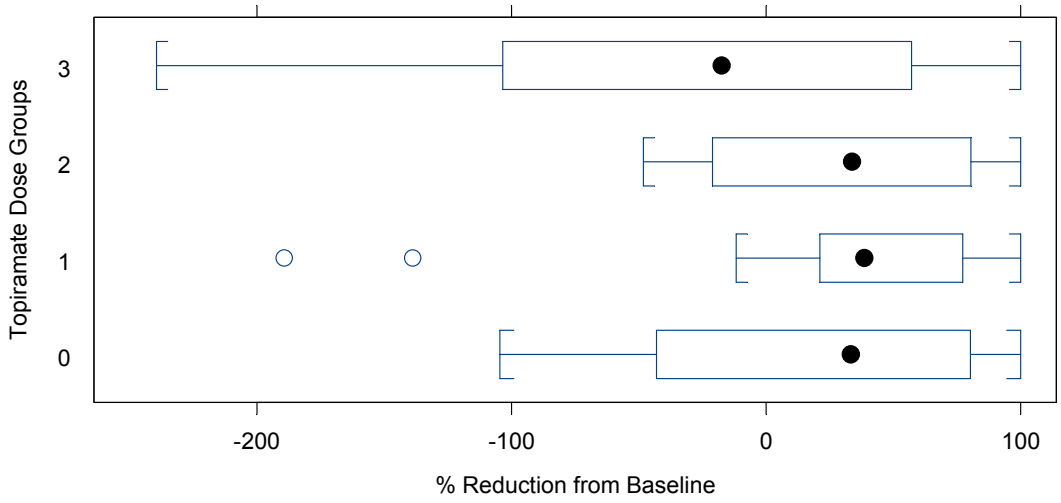


1.1.2 Is there an evidence of effectiveness of topiramate in pediatrics less than 2 yrs with at least 48h of vEEG observation and at least one episode of baseline seizure?

No, there seems to be a no treatment effect for any of the dose group when compared to placebo. This was based upon the following two analyses:
First, the primary efficacy (**Figure 8**) and other several secondary subgroup analysis conducted by the sponsor showed no treatment effect.
Second, the modified analysis performed by the reviewer after discussions with the medical officer also showed lack of any treatment effect. It is to note that in the primary efficacy analysis, the average seizure counts were imputed for 38 % of patients with less than 48 hour of vEEG observations at end point bearing the assumption the seizure rates are constant over time. In addition, the patients with

zero baseline seizure observations were also included in the analysis. In the reviewer's analysis, however, only patients with at least 48 h of vEEG data at endpoint were included as imputation of the primary efficacy endpoint may create some bias. Also, patients with zero baseline seizure rates are irrelevant as there is no scope for the drug to be superior than placebo. Therefore, patients with at least 48 h of vEEG were selected after removal of those patients with zero baseline seizure rates.

Figure 6: % Reduction in POS from baseline for patients ≥ 48 h vEEG for end point after excluding patients with zero seizure rate at baseline.

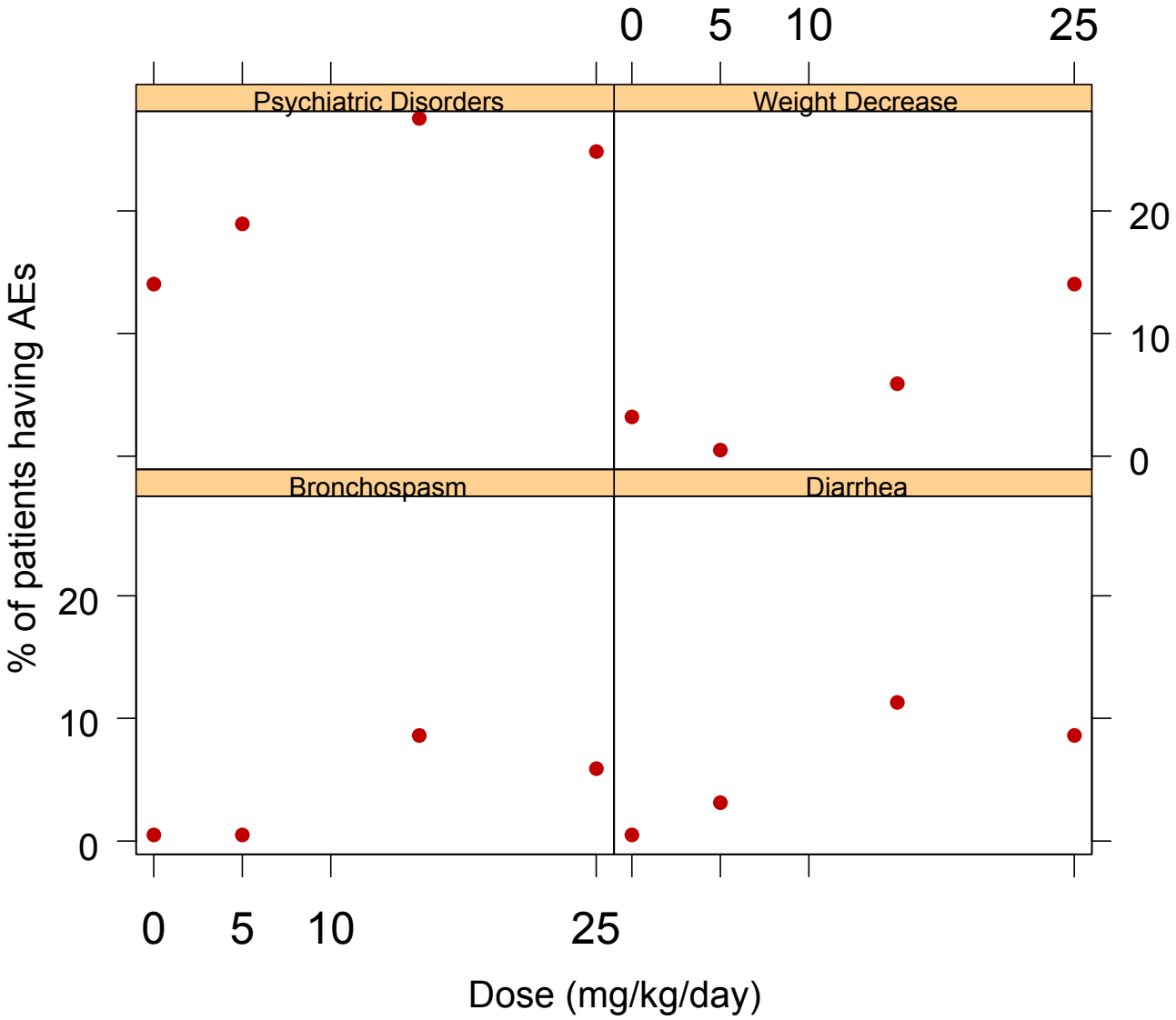


0: Placebo, 1: 5 mg/kg/day, 2: 15 mg/kg/day, 3: 25 mg/kg/day.

1.1.3 Is there an evidence of dose-exposure-safety relationship for topiramate in 1 month-2 yr pediatrics?

There seems to be dose related increase in adverse events (AEs) for psychiatric disorders (nervousness, anorexia, somnolence), weight decrease, diarrhea and bronchospasm. However, it should be noted that majority of these adverse events were mild to moderate in nature. Furthermore, the incidence of these adverse events is relatively low at the approved adult dose (2.9 -5.8 mg/kg/day for an average 70 kg adult). Higher incidences of adverse events are mainly seen at doses (15 and 25 mg/kg/day) higher than the approved adult dose.

Figure 7: % of treatment emergent adverse events for placebo and the three dose groups in the pivotal efficacy trial TOPMAT-PEP-3001. Number of patients in 0 (placebo), 5, 15 and 25 mg/kg/day dose groups are 37, 38, 37 and 37 respectively.



1.2 Recommendations

Since the pivotal trial for topiramate in 1 month-2 yr pediatrics failed and the sponsor does not seek any indication in this age group, no labeling statements describing pharmacokinetic characteristics of topiramate in 1 month-2 yr pediatric patients are proposed.

1.3 Label Statements

This was a PLR conversion of the label from the old format, there are some changes from clinical pharmacology perspective (See Appendix for the proposed label with changes highlighted in red). Below are the changes proposed by the sponsor in the current topamax label in reference to the efficacy trial TOPMAT PEP 3001 (blue text represents addition of new information (b) (4)):

(b) (4)

2 Pertinent Regulatory Background

Topiramate is approved and marketed worldwide as adjunctive treatment in adults and children (2 to 16 yrs of age) with refractory partial-onset seizures (POS) with or without secondarily generalized seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome. Topiramate is also approved for monotherapy treatment in adult and pediatric patients with newly or recently diagnosed epilepsy and in adults for the prophylaxis of migraine. Topiramate is currently marketed as coated tablets or coated beads in a gelatin capsule that can be swallowed whole or sprinkled on food for those who cannot swallow tablets. Sponsor conducted a randomized, double-blind, placebo-controlled, fixed dose-ranging study to assess the safety, tolerability, and efficacy of topiramate oral liquid and sprinkle formulations as an adjunct to concurrent anticonvulsant therapy for infants (1 to 24 months of age, inclusive) with refractory partial onset seizures, with open-label extension. The study included 4 phases: a 3-day screening phase, a 20-day double-blind treatment phase (including uptitration and stabilization of dosage), a 1-yr open-label extension phase (including a

blinded taper of double-blind treatment and uptitration of open-label treatment), and a posttreatment phase (including a withdrawal taper). Following screening procedures, which was to include a 48-hour vEEG, eligible subjects were randomized (1:1:1:1) to topiramate (5, 15, or 25 mg/kg per day) or placebo, starting at an initial dosage of 3 mg/kg per day with gradual uptitration to the target dosage for the remainder of the 20-day treatment period. No treatment effect compared to placebo or an indication of dose response was observed using primary end point (% reduction in seizures using vEEG) or other secondary endpoints. Sponsor also conducted randomized, open-label, multicenter study with open-label extension of the pharmacokinetics and safety of topiramate administered as the oral liquid and sprinkle formulations as an adjunct to concurrent anticonvulsant therapy in infants (aged 1 to 24 months, inclusive) with refractory partial-onset seizures. The details for this study can be found in Individual study reviews of the Appendix.

3 Results of Sponsor's Analysis

3.1 Population PK analysis

Sponsor conducted a population PK analysis in three stages to characterize the PK of infants with age ranging from 1-24 months. The first stage of the analysis involved evaluation of the original population pharmacokinetic model developed earlier for adult and pediatric subjects (ages 2 to 85 yrs) in the infant (1 month to 2 yrs) population. The second stage of the analysis involved pooling the original dataset with the present infant data (ages 1 month to 2 yr) and re-estimating the parameters of the population pharmacokinetic model. If the model required further adjustments those would be made at this stage. The third stage of the analysis involved using the final model developed from the pooled database (infant, pediatric and adult subjects; 1 month to 85 yrs) to simulate expected ranges of plasma concentrations for selected doses.

The original population PK model evaluated on the pediatric data from trial 1002 and 3001was a two compartmental model with first order absorption. The model included the effects of weight (allometrically scaled with power coefficient FCWT estimated) and age on oral clearance as well as the effects of concomitant medications like valproate, cytochrome inducers (INMD), and no effect medications (NEMD) on oral clearance. In addition, the model took into consideration the apparent difference in baseline clearance (ADJ) of topiramate for subjects who were treatment naïve versus those that were previously treated with other AEDs. The model also included the effect of weight (allometrically scaled with power coefficient FVWT estimated) on the central volume of distribution. The database available for the population pharmacokinetic analysis of topiramate consisted of 1518 plasma concentrations obtained from 273 infant subjects enrolled in 2 clinical trials; 1002 and 3001. The model reasonably described the data with overestimation of the interindividual variability at the peak concentrations.

When data was pooled for the second stage, the above described model was refined to include effect of dose on clearance, removal of variance term for Ka and addition of covariance between Cl and V. The pooled database used for model refinement contained 6153 observations from a total of 1490 subjects. The above modifications reduced the objective function by 393.7 points compared to the original model. The value of the

variance term on CL/F was slightly reduced and the value of variance term on V2/F was substantially reduced. Residual error was not affected by the model refinements. The final parameter estimates after refinement of the model are given in **Table 1**.

The refined model for clearance by sponsor was:

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

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

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

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

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

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

$$FCDO = \left(\frac{Dose}{100}\right)^{\theta_8}$$

$$If(AGE > 2)Then$$

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

$$Else$$

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

$$Endif$$

$$CL = TVCL \bullet Exp(\eta_1)$$

The details of the analysis can be found in population-pk-report submitted by the sponsor.

Table 1: Parameter values from pooled refined sponsor's population pharmacokinetic model.

Parameter (Units)	Typical Value (%SE)	Inter-Individual Variability (%SE)
Oral clearance (L/h)		
CLSTM (θ1)	1.24 (1.2)	33.2 (7.2)
CLSTA (effect of adjunct) (θ2)	0.752 (13.7)	
FCWT (effect of weight) (θ3)	0.54 (4.3)	
FCAGE (effect of age) (θ4)	-0.00259 (26.4)	
FCIN (effect of INMD) (θ5)	1.51 (5.6)	
FCVP (effect of valproate) (θ6)	0.73 (5.6)	
FCNE (effect of NEMD) (θ7)	0.74 (4.1)	
FCDO (Effect of Dose) (θ8)	0.326 (12.5)	
Central Volume of Distribution (L)		
VST (θ9)	7.65 (12.5)	108 (26.5)
FVWT (effect of weight) (θ10)	0.618 (12.7)	
Shape Parameter (θ11)	0.518 (33.8)	
Ka (h-1) (θ12)	0.152 (39.8)	NE
K23 (h-1) (θ13)	0.469 (17.1)	NE
K32 (h-1) (θ14)	0.0771 (30.2)	NE
CCV residual error (%CV)	30.3 (4.8)	
Additive residual error (mg/L)	0.0876 (63.4)	

The model was successfully evaluated using predictive check with steady state trough concentrations as the pharmacokinetic metric of interest.

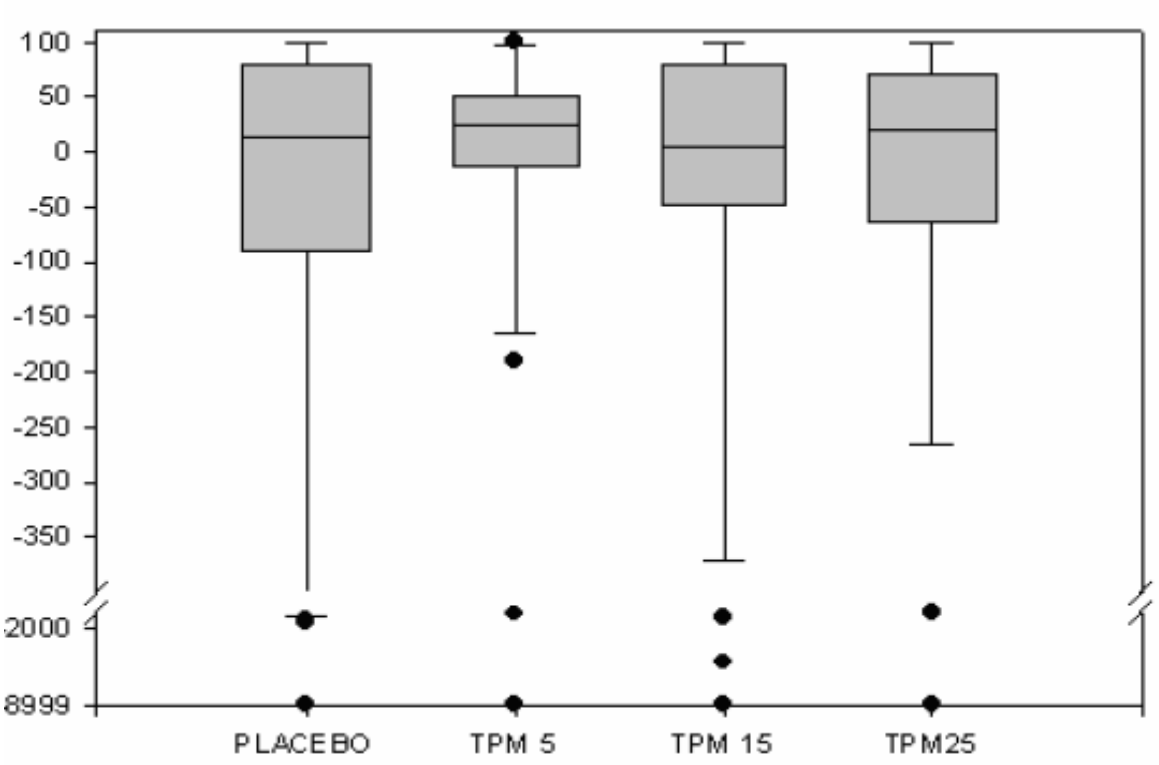
Reviewer's comments:

1. *Sponsor's analysis followed a reasonable and thorough approach in describing the pharmacokinetics of topiramate. However, the addition of dose effect on clearance in the final population PK model contradicts with the results of trial TOPMET-PEP-1002 in pediatric patients 1 -24 months. According to TOPMET-PEP-1002, which was designed to assess the pharmacokinetics and safety of topiramate administered as the oral liquid and sprinkle formulations as an adjunct to concurrent anticonvulsant therapy in infants (aged 1 to 24 months, inclusive) with refractory partial-onset seizures, apparent oral clearance was independent of dose. Moreover, inclusion of dose as a covariate only explained 6% of the interindividual variability in clearance even though it caused significant drop in objective function.*
2. *Furthermore, the exponential coefficient of the effect of age on clearance is negative which physiologically is not possible for a drug primarily eliminated by kidney.*
3. *Since log transformation was not employed for fitting the data, PRED vs DV and IPRED vs DV plots should be presented on linear scale for better visualization.*

3.2 Primary Efficacy Analysis

Data available from trial TOPMAT-PEP-3001 was subjected to primary efficacy analysis. The primary efficacy analysis compared each topiramate dosage group, from the highest (25 mg/kg per day) to the lowest dosage (5 mg/kg per day), with placebo using a step-down procedure at a 2-sided type-I error of 0.05. The null hypothesis for the higher tested dose must have been rejected before the next lower dose could be tested, and testing stopped when a dosage level was not significantly different from placebo to preserve the overall type-I error rate. The main analysis used an analysis of covariance (ANCOVA) on ranks of the percentage reduction in the modified intent-to-treat population, including age group (<6 months [180 days] vs ≥6 months [180 days] on Day 1) and treatment group as factors, and baseline POS seizure rate as a covariate. Additional analyses using the ANCOVA model were performed with additional factors of sex (male, female), baseline anti-epileptic drug category (inducer, noninducer), and number of anti-epileptic drugs (≤1, 2, >2). Three sensitivity analyses were also performed. The secondary efficacy end point on treatment responders was evaluated using a Mantel-Haenszel statistic stratified by age group. Other secondary end points were analyzed in the same manner as for the primary end point. Secondary end points were tested at a 0.05 significance level without adjustment for multiple comparisons. The 25-mg/kg per day dosage was deemed to be the highest tolerable dosage and thus was first compared with placebo in the step-down procedure. The apparently greater median percent reduction in daily POS rate with topiramate 25 mg/kg per day than with placebo (20.40% vs 13.06%) during the double-blind phase was not statistically significant (p=0.967). Response was not related to the topiramate dosage (lower dosages were not formally tested). Similar results were obtained in alternate analyses (p>0.2 using 3 additional covariates and p>0.7 in 3 sensitivity analyses). Likewise, no treatment effect compared with placebo or indication of dose-related effect was observed in any of the secondary end points, whether based on vEEG or subject takehome log data. For all efficacy end points, response appeared similar in all treatment groups (). Sponsor also conducted various other subgroup efficacy analysis requested by the FDA to explore any evidence of effectiveness. None of the analysis showed that topiramate was effective in treating partial onset seizures in 1 month to 2 yr pediatrics (**Figure 8**).

Figure 8: Box Plot of the Percentage Reduction in POS from Baseline to the End of the Double-Blind Phase Based on vEEG Data (Study TOPMAT-PEP-3001: Modified Intent-to-Treat Analysis Set).



N=28(Placebo), 34(TPM 5 mg/kg/d), 34(TPM 15 mg/kg/d), 34(TPM 25 mg/kg/d).
For subjects who had zero baseline seizure and the post treatment seizure number was more than zero, value -8999 was imputed as the percent reduction in accordance with the worst-rank analysis.

Note: The lower and higher boundaries of the boxes are the 25th and 75th percentiles. Whiskers below and above indicate the 10th and 90th percentiles. The solid lines within the boxes mark the medians. Outlying data points are extreme value.

3.3 Dose-Exposure-Safety analysis.

Sponsor provided the safety data for TOPMAT-PEP-3001 which was graphically explored (Dose-Safety) by the reviewer. Sponsor however, did not deal with exposure-safety relationship from the trial TOPMAT-PEP-1002 which was explored by the reviewer (See section 4.3)

4 Reviewer's Analysis

4.1 Population PK Analysis

The empirical evidence from the study TOPMAT-PEP-1002 showed that pharmacokinetics of topiramate in pediatrics 1-24 months is linear. Furthermore, it was seen that addition of age did not improve the model, neither did it explain the interindividual variability in Cl. Therefore the reviewer re-estimated the model parameters after excluding effect of dose and age on Cl.

4.1.1 Objectives

To re-estimate the model parameters with suitable modifications

4.1.2 Methods

FOCE estimation with interaction was used to determine the parameter estimates

4.1.3 Datasets

The combined dataset (topiramate-all-pooled-ss-22jan07-pca-dose-csv.xpt) was utilized for running the model.

4.1.4 Software

Convergence problems appeared when NONMEM V was used for parameter estimation. Therefore, NONMEM VI was utilized for the present analysis. It was noted that results of the sponsor's model were similar when NONMEM VI was used. Thus, further analysis was carried out using NONMEM VI.

4.1.5 Model

Similar model as that of sponsor was utilized with effect of dose on Cl/F removed. The effect was age was evaluated after inclusion of weight in the model. The final model of the reviewer was same as described in section 3.1 with effect of dose on Cl (FCDO) and effect of age (FCAGE) on Cl removed. Since the purpose of the analysis was only to describe the data and not to carry out predictive simulations, the model was not evaluated further.

4.1.6 Results

Table 2 compares the parameter estimates between sponsors's refined and reviewer's modified population pharmacokinetic model. The removal of the effect of dose on clearance only increased the between subject variability in Cl by 2% (35% from 33%) although there was a significant increase in objective function. Considering the fact that TOPMAT-PEP-1002 showed no effect of dose on oral clearance and the Dose-Cl

relationship shown by sponsor in the population model is shallow, resulted in the removal of this covariate. The Eta (Cl) vs Age for reviewer model shows that after adjusting for weight there is no effect of age. It has been seen consistently for drugs like topiramate which are primarily excreted by kidney that age has an effect on clearance after adjusting for weight. However, given the current data and model, the effect of age on clearance was not observed.

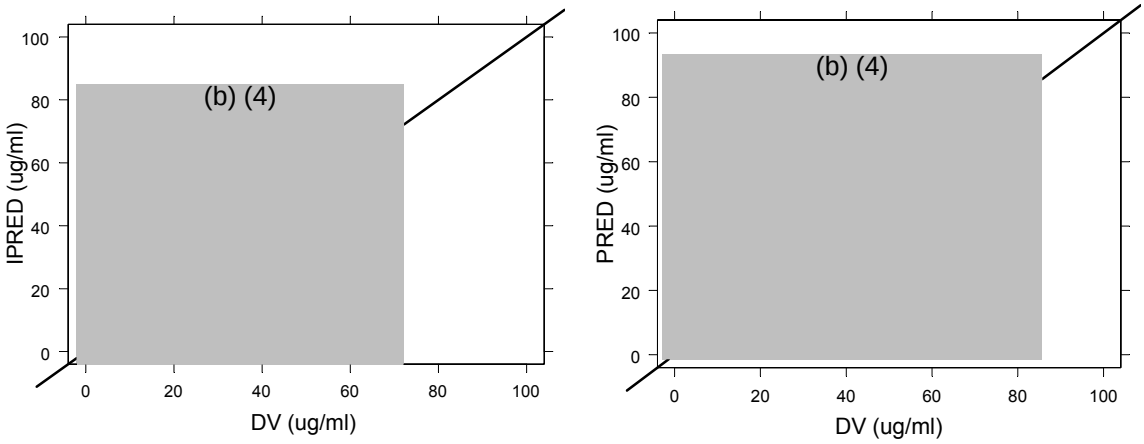
Figure 4 The IPRED vs DV and PRED vs DV plots look similar for the sponsor and the reviewer's model (**Figure 9**).

Table 2: Parameter estimates comparison between Sponsor's and Reviewer's population PK model.

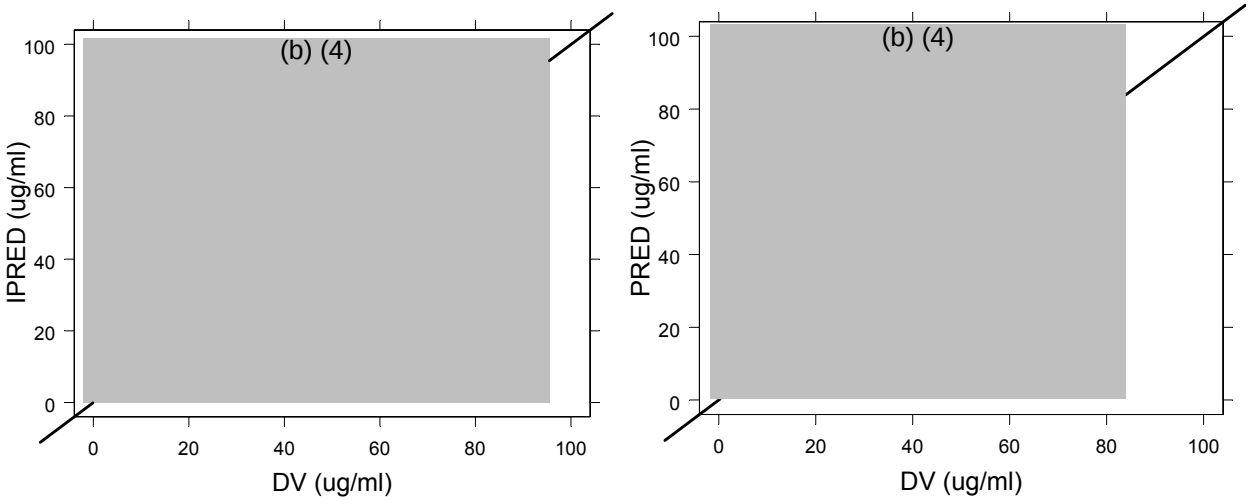
Parameter (%RSE)	Sponsor's Refined model including effect of age and dose on clearance	Reviewer's Modified model with no effect of age and dose on clearance
CLSTM (θ1)	1.24 (1.2)	1.25 (1.3)
CLSTA (effect of adjunct) (θ2)	0.752 (13.7)	0.583 (15.6)
FCWT (effect of weight) (θ3)	0.54 (4.3)	0.535 (3.6)
FCAGE (effect of age) (θ4)	-0.00259 (26.4)	-
FCIN (effect of INMD) (θ5)	1.51 (5.6)	1.62 (5.5)
FCVP (effect of valproate) (θ6)	0.73 (5.6)	0.779 (5.6)
FCNE (effect of NEMD) (θ7)	0.74 (4.1)	0.785 (4.1)
FCDO (Effect of Dose) (θ8)	0.326 (12.5)	-
VST (θ9)	7.65 (12.5)	14.4 (42.2)
FVWT (effect of weight) (θ10)	0.618 (12.7)	0.59 (8.9)
Shape Parameter (θ11)	0.518 (33.8)	0.604 (33.4)
Ka (h-1) (θ12)	0.152 (39.8)	0.274 (39.8)
K23 (h-1) (θ13)	0.469 (17.1)	0.373 (30.6)
K32 (h-1) (θ14)	0.0771 (30.2)	0.115 (20.4)
Between Subject Variability in Cl (%CV)	33.2 (7.2)	35.4 (6.9)
Between Subject Variability in VST (%CV)	108 (26.5)	98 (12.9)
Proportional Error (%CV)	30.3 (4.8)	30.9 (4.7)
Additive Error (ug/ml)	0.0876 (63.4)	0.069 (109)

Figure 9: Similarity in diagnostic plots between (a) Sponsor's and (b) Reviewer's model.

(a)



(b)



4.2 Evaluation of Effectiveness

4.2.1 Objectives

To identify the evidence of effectiveness by analyzing only those patients with at least 48h of evaluable vEEG at endpoint, and at least one episode of baseline seizure.

4.2.2 Methods

Patients with at least 48h of evaluable vEEG at the end of double blind period after removing patients with zero seizure rate at baseline were used for the analysis. % reduction from baseline was compared for different dose group with placebo. Also, data across all dose groups were pooled and compared with placebo to identify any treatment effect irrespective of doses.

4.2.3 Datasets

The seizure rate primary efficacy data from TOPMAT-PEP-3001 (keff2.xpt) was utilized for the analysis.

4.2.4 Software

SAS 9.1 was utilized for data refinement and S-Plus was used for graphical evaluations.

4.2.5 Model

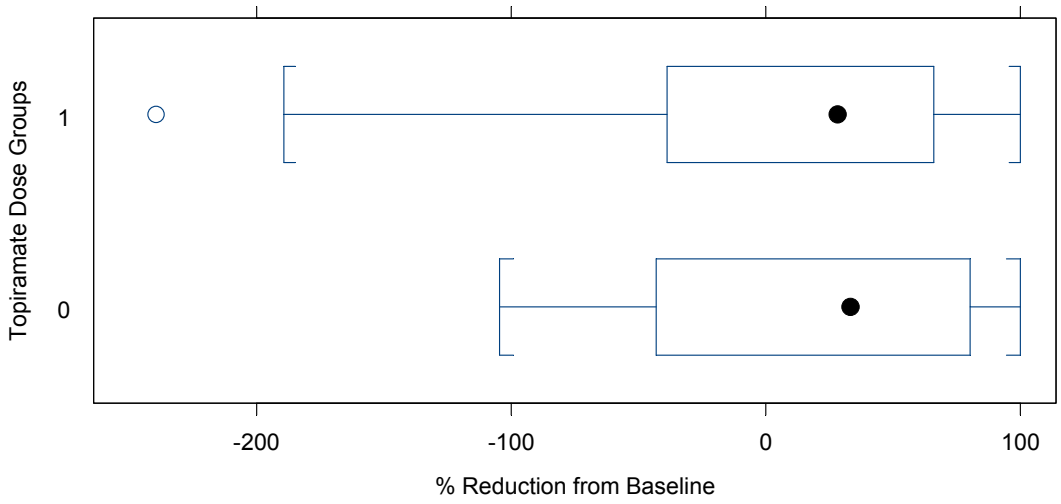
No formal statistical analysis was conducted as the aim was to graphically evaluate if there was a trend for dose response or evidence of effectiveness in various subgroups.

4.2.6 Results

There seems to be a no treatment effect for any of the dose group when compared to placebo (Figure 6) consistent with the results of sponsor's primary analysis of the trial TOPMAT-PEP-3001 (Figure 8). When data across all dose groups are pooled and compared with placebo, there seem to be similarity in response between treatment and placebo (
Figure **10**). The results appear to be similar even when stratified by age group and treatment (Figure 11). In the current exploratory analysis, after discussions with the medical officer, only data from patients with at least 48h vEEG at the end of double blind period and at least one episode of seizure at baseline was utilized for exploratory analysis. 9 of total 130 subjects had 0 baseline seizure rate and 50 with vEEG < 48 hours. In total, 56 subjects (43%) were removed from the original data set. Even though it significantly reduces the data set, it is more realistic than sponsor's approach who imputed the seizure rate in 38% patients assuming linear relationship for time and episodes of seizures. For example, a patient having only 4 h of vEEG available with one seizure is assumed to

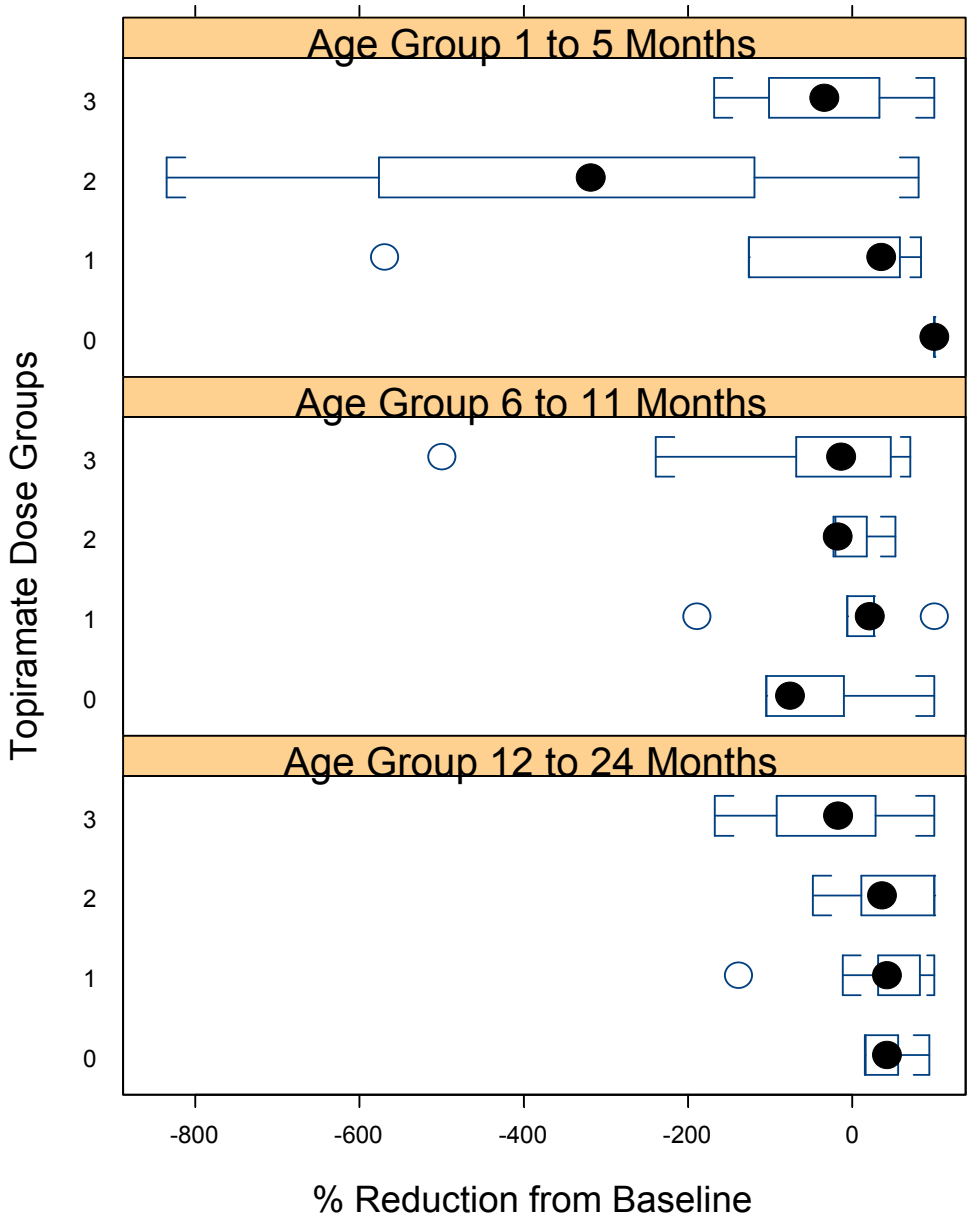
have got 12 seizures in 48 hour which might be unrealistic. Thus, taking data from patients having at least 48 h of evaluable EEG would reduce bias.

Figure 10: % Reduction in POS from baseline for patients ≥ 48 h vEEG after excluding patients with zero seizure rate at baseline.



0:Placebo
1:Treatment

Figure 11: % Reduction in POS from baseline for patient's ≥ 48 h vEEG and at least one episode of baseline seizure stratified by age groups.



0: Placebo, 1: 5 mg/kg/day, 2: 15 mg/kg/day, 3: 25 mg/kg/day

4.3 Dose-Exposure-Safety relationship

4.3.1 Objectives

To explore dose-exposure-safety relationship of topiramate in pediatrics 1 month-2 yrs.

4.3.2 Methods

Exposures for the pivotal trial (TOPMAT-PEP_3001) were not available. However, since this trial was performed at three dose levels and placebo, dose-safety relationship was explored. Percentage of subjects having adverse events of clinical significance was plotted against various dose levels to explore potential correlations. Types of adverse events were decided based on the discussion with the medical reviewer.

Exposures and safety results were available for the study TOPMAT-PEP_1002 study. Steady state trough levels were available from 42 subjects which were divided into three groups with 14 patients/group and % clinically significant AEs in each group were examined.

4.3.3 Datasets

The adverse event data from TOPMAT-PEP-1002 (kae.xpt) was utilized for the analysis.

4.3.4 Software

SAS 9.1 was utilized for data refinement and S-Plus was used for graphical evaluations.

4.3.5 Model

No formal statistical analysis was conducted as the aim was to graphically evaluate if there was a trend for dose-exposure-safety in various subgroups.

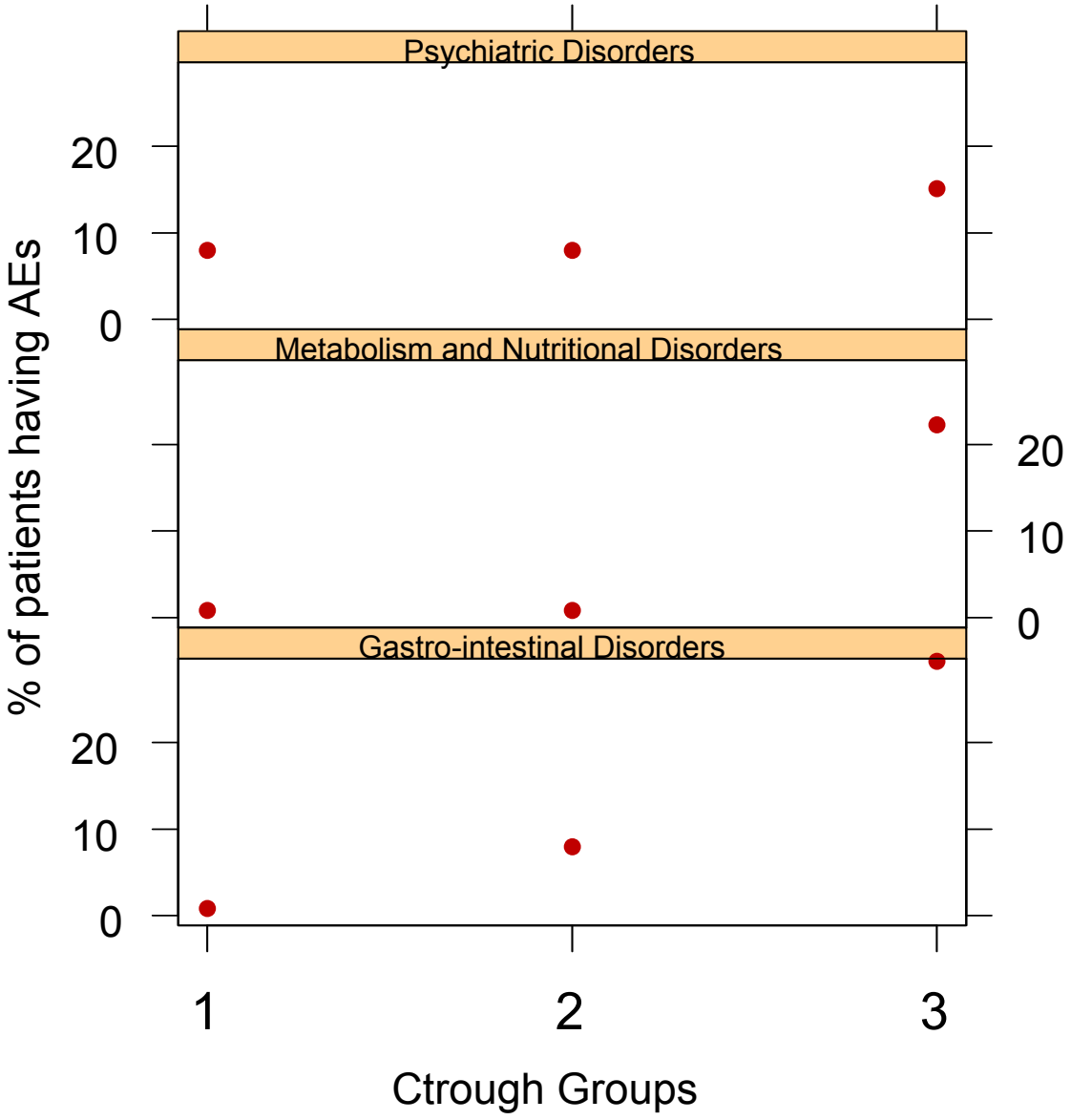
4.3.6 Results

Adverse events in several categories were explored for the study TOPMAT-PEP_3001. There appeared to be dose related increase in adverse events for psychiatric disorders (nervousness, anorexia, somnolence), weight decrease, diarrhea and bronchospasm (**Figure 7**). It should be noted however that most of these adverse events were mild to moderate in nature and occurred at the higher doses (15 and 25 mg/kg/day) than approved for adults (2.9 -5.8 mg/kg/day for an average 70 kg adult).

The steady state trough levels for TOPMAT-PEP-1002 study ranged from 0.5-2.2, 2.3-7.7 and 10.6-21.6 µg/ml for groups 1, 2 and 3, respectively (**Figure 12**). Even though

the number of subjects were few, there appears to be an exposure related increase in adverse events (**Figure 12**) of the class psychiatric disorders (anorexia, insomnia, somnolence), gastrointestinal disorders (constipation, diarrhea, vomiting) and metabolic and nutritional disorders (acidosis, dehydration, hyperammonemia, weight decrease), which is consistent with what we observed in pivotal trial TOPMAT-PEP-3001 (**Figure 7**).

Figure 12: % of treatment emergent adverse events at three levels of steady state trough groups in TOPMAT-PEP-1002. There are 14 subjects in each subgroup 1, 2 and 3.



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