CLINICAL REVIEW

Application Type	NDA
Submission Number	20844 (031), 20505 (037)
Submission Code	SE5
Letter Date	4/25/08
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PDUFA Goal Date	1/25/09
Reviewer Name	Leonard P. Kapcala, M.D.
Review Completion Date	1/23/09
Established Name	topiramate
(Proposed) Trade Name	Topamax
Therapeutic Class	anticonvulsant/anti-epileptic drug
Applicant	Johnson and Johnson Pharmaceutical Research & Development L.L.C.
Priority Designation	P
Formulation	Oral topiramate Sprinkle Capsules and oral liquid formulation
Dosing Regimen	Twice daily (once in morning and evening)
Indication	Adjunctive treatment of partial epilepsy (partial onset seizures)
Intended Population	Pediatric infants and toddlers (1-24 months)

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

- (b) (5)

- I recommend that the NDA supplement be given a Complete Response action to revise the topiramate label.

1.2 Recommendation on Postmarketing Actions

- Not applicable/None

1.2.1 Risk Management Activity

- Not applicable/None

1.2.2 Required Phase 4 Commitments

- Not applicable/None

1.2.3 Other Phase 4 Requests

- Not applicable/None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The pediatric program for infants/toddlers (1-24 months) for which Pediatric Exclusivity was sought (and recently granted by the Agency) consisted primarily of 3 studies including : 1) a randomized, double-blinded, placebo-controlled study (TOPMAT-PEP-3001; 112 patients randomized to one of 4 treatment arms including placebo, 5, 15, or 25 mg/kg/day topiramate, 149 enrolled) aiming to demonstrate efficacy and safety over 20 days of treatment; 2) an open-label pharmacokinetic (PK) study (TOPMAT-PEP-1002, 55 patients enrolled) aiming to characterize the PK of topiramate in this populations; and 3) a long-term (up to 1 year), open-label extension study aiming to characterize long-term treatment safety.

1.3.2 Efficacy

- There was no suggestion of efficacy of topiramate in the randomized, double-blinded, placebo-controlled study (TOPMAT-PEP-3001) based upon the primary analyses of the median %

reduction of daily partial onset seizure rate. The p values for all topirmate doses (vs placebo were > 0.909.

1.3.3 Safety

Overview of Safety Analyses

There are many potential safety concerns of topiramate treatment in infants/toddlers (1-24 months). Observations from these studies in infants/.toddlers and from additional data sources in some instances support the impression that topiramate either caused these adverse reactions or may have caused them (i.e., the data are at least consistent with the possibility of topiramate causality). This reviewer recommends that much of the information/data summarized here should be inserted into the topiramate label.

Results from the above controlled study, and an open-label long-term extension study in these infants/toddlers (1 to 24 months old) suggested some novel adverse reactions/toxicities (not previously observed; i.e, growth/length retardation, behavioral impairment via Vineland behavioral testing; certain clinical laboratory abnormalities), and other adverse reactions/toxicities that occurred with a greater frequency and/or greater severity than had been recognized previously from studies in older pediatric patients or adults for various indications.

The following summaries note the main findings of various analyses in different elements/domains of safety.

Treatment-Emergent Adverse Events/Reactions (TEAEs)

- Overall, the profile of specific adverse events/reactions (i.e., preferred terms-PTs) was generally similar to that previously described for topiramate treatment of adults and older pediatric patients (≥ 2 years), especially when considering the frequency of these TEAEs (vs placebo). This impression is also applicable to fatal and non-fatal serious adverse events (SAEs) and non-serious TEAEs observed in the controlled and uncontrolled studies. However, it was remarkable that the frequency of TEAEs in 2 organ system classes (i.e., respiratory and resistance mechanism-indicating infections) were notably increased with topiramate treatment (vs placebo). These very young pediatric patients appeared to experience an increased risk/frequency of resistance mechanism disorders (any topiramate dose 12 %, placebo 0 %) and of respiratory system disorders (any topiramate dose 40 %, placebo 16 %).

  The following summarizes TEAEs occurring in these 2 organs systems. A closer analysis (from the placebo-controlled trial) of TEAEs from these 2 organ systems suggested an increased risk/occurrence of a novel TEAE (i.e., bronchospasm) and that a few other TEAEs (i.e., otitis media, upper respiratory infection, cough) appeared to occur more frequently than previously recognized in controlled studies of older pediatric patients or adults for various indications. The incidence of bronchospasm was 0 % for placebo and 5 mg/kg/d, 8 % for 15 mg/kg/d, 5 % for 25 mg/kg/d, and 4 % for any topiramate dose. Other increased frequency TEAEs (i.e, infection viral, bronchitis, pharyngitis, rhinitis) occurring within these 2 organs systems appeared to occur with a relatively similar frequency as has been observed in other controlled topiramate trials.

  Certain TEAEs (i.e., ataxia, weight decrease, bronchospasm, dermatitis) that showed an increased occurrence during topiramate treatment (vs placebo) were also found to occur more frequently in association with laboratory diagnosed metabolic acidosis in the placebo-

controlled study based upon analyses showing the relative risk of the specific TEAE in patients with metabolic acidosis vs those without metabolic acidosis. These increased frequencies suggested the possibility that metabolic acidosis may have contributed to the risk of occurrence of these adverse reactions.

Reviewer Comment

- (b) (5)

Clinical Laboratory Findings

- There were changes in several clinical laboratory analytes in these very young pediatric patients that were remarkable, especially because most of them appeared to be novel and had not previously been described or noted in placebo-controlled studies of older pediatric or adults. Most of the notable observations relative to clinical laboratory analytes were derived from the placebo-controlled study. Topiramate produced notable changes in mean change from baseline or outliers in several clinical laboratory analytes (serum potassium, creatinine, BUN, total protein, alkaline phosphatase, bicarbonate, chloride, total eosinophil count) during the placebo-controlled study.

  Mean change from baseline was dose-related for all these analytes. The mean treatment difference/effect (25 mg/kg/d topiramate – placebo) was - 5.9 mEq/L for bicarbonate, + 4.6 mEq/L for chloride, - 0.4 mmol/L for potassium, + 1 mmol/L for BUN, + 7.7 mmol/L for creatinine, + 3.6 g/L for protein, and + 191 nkat/L for alkaline phosphatase. Although the decrease in serum bicarbonate and increase in serum chloride are commonly recognized effects of topiramate in producing non-anion gap, hyperchloremic metabolic acidosis, the magnitude and severity of these changes of metabolic acidosis (serum bicarbonate $\leq$ 20 mEq/L) are notably greater than that (mean serum bicarbonate decrease ~ 4 mEq/L) observed previously in controlled trials in older children and adults. The incidence of metabolic acidosis (when baseline serum bicarbonate was $\geq$ 20 mEq/L) was 0 % for placebo, 30 % for 5 mg/kg/d, 50 % for 15 mg/kg/d, and 45 % for 25 mg/kg/d. The incidence of "markedly abnormal changes" (< 17 mEq/L and > 5 mEq/L decrease from baseline of $\geq$ 20) was 0 % for placebo, 4% for 5 mg/kg/d, 5 % for 15 mg/kg/d, and 5 % for 25 mg/kg/d.

  The following quoted statements by the sponsor are considered to be some noteworthy summary conclusions that were provided in the ISS regarding metabolic acidosis :

- **<u>"Overall, the acidosis in this infant population is more severe than that in older populations" (including older pediatric patients and adults).</u>** One possible explanation for this observation might be the observation that topiramate doses used in many of the infant/toddler patients were **<u>generally</u>** higher than doses used in older pediatric patients

- "**In general, acidosis was successfully managed with alkali treatment and dose reductions."**

  The other topiramate-induced changes in serum creatinine, BUN, alkaline phosphatase and total protein have not previously been described. However, the current label (based upon a CBE submitted 4/07) does note that the frequency of hypokalemia (< 3.5 mmol/L) is increased with topiramate (0.4 %) vs placebo (0.1 %). Furthermore, results from topiramate treatment of adjunctive partial epilepsy in placebo-controlled trials in adults in the original NDA submission for initial topiramate approval showed an increased incidence (topiramate 3 %, placebo 1 %) of markedly abnormally increased values for serum alkaline phosphatase. In the placebo-controlled trial, there were abnormal outliers relative to the normal reference range. Topiramate treatment resulted in an increased incidence of patients with increased creatinine (any topiramate dose 5 %, placebo 0 %), BUN (any topiramate dose 3 %, placebo 0 %), and protein (any topiramate dose 34 %, placebo 6 %), and an increased incidence of decreased potassium (any topiramate dose 7 %, placebo 0 %). This increased frequency of abnormal values was not dose-related. Creatinine was the only analyte showing a noteworthy increased incidence (topiramate 25 mg/kg/d 5 %, placebo 0 %) of a markedly abnormal change (an increase). Topiramate treatment also produced a noteworthy dose-related increase in the percentage of patients who had a shift from normal at baseline to high/increased (above the normal reference range) in total eosinophil count at the end of treatment. The incidence of these abnormal shifts was 6 % for placebo, 10 % for 5 mg/kg/d, 9 % for 15 mg/kg/d, 14 % for 25 mg/kg/d, and 11% for any topiramate dose.

  Based upon the results of the long-term, open-label safety study, it is not clear that these clinical laboratory abnormalities showed a notably increased incidence of markedly abnormal changes of significant clinical concern after long-term open-label treatment.

  <u>Reviewer Comment</u>

- (b) (5) **.** Of potential interest, topiramate treatment of older pediatric patients (e.g., adolescents, 12-16 years) for migraine prophylaxis treatment produced a dose-related increased shift in serum creatinine from normal at baseline to an increased value at the end of 4 months treatment in adolescent patients. The incidence of these abnormal shifts was 4 % for placebo, 4 % for 50 mg, 18 % for 100 mg, and 11% for any topiramate dose.

- (b) (5) **. Of potential interest, the investigators found the metabolic acidosis to be of sufficient concern to administer alkali treatment in ~ 23 % of all the patients (N=284) in the open-label extension study (usually in the open-label, extension study.**

- (b) (5) Although there were no clear changes in serum phosphorus in the placebo-controlled phase of the infant/toddler studies, there appears to be an increased incidence of hypophosphatemia with topiramate treatment. Results (shown in the DNDP Clinical Review by Dr. Cynthia McCormick) from topiramate treatment of adjunctive partial epilepsy in placebo-controlled trials in adults in the original NDA submission for initial topiramate approval showed an increased incidence (topiramate 6 %, placebo 2 %) of markedly abnormally decreased values for serum phosphorus and an increased incidence (topiramate 3 %, placebo 1 %) of markedly abnormally increased values for serum Alkaline phosphatase (b) (4)

  Of potential relevance, a dose-related increase in serum alkaline phosphatase occurred in the placebo-controlled study of infants/toddlers.

  The significance of these changes in serum phosphorus remain to be shown. However, considering that metabolic acidosis increases phosphate excretion, conceivably the development of metabolic acidosis could be at least partially contributing to the lowering of serum phosphorus. In addition, there is a theoretical risk of osteomalacia from metabolic acidosis and chronic hypophosphatemia can also result in osteomalacia, that can be associated with an increased serum alkaline phosphatase.

Vital Signs (VS)

- I did not find any remarkable, clinically significant changes in the various analyses of VS consisting of pulse and blood pressure. There were changes in growth (i.e., weight, length, head circumference that occurred during the long-term, open-label treatment that I considered noteworthy. Of relevance here, length was carefully and systemically measured in these studies. As would like be expected, there were no clear noteworthy changes in weight, length, or head circumference that occurred during the very short placebo-controlled treatment period (20 days).

- Reductions in length, weight, and head circumference were observed during long-term (up to 1 year) treatment in the open-label extension study of these infants/toddlers (1-24 months) with topiramate (from low doses < 5 mg/kg/day up to 60 mg/kg/day) based upon decreases from baseline in Z-scores. Z scores, which reflect the standard deviation from standardized data of expected height/length or weight during the whole spectrum of pediatric development, are derived from data from normal pediatric subjects and not from patients such as these with seizures, all of whom were also taking other anticonvulsants. Over 52 weeks of treatment (all topiramate doses), the mean Z score reduction from pre-treatment/baseline for weight (-0.8) and length (-0.8) was progressive and did not plateau or stabilize. Mean Z score reduction for weight and length were greater for patients with metabolic acidosis than for those without metabolic acidosis. The mean Z score reduction from baseline progressively decreased for head circumference up to week 20 (-0.3) and then appeared to stabilize up to week 52. There was no apparent correlation of metabolic acidosis on mean Z score for head circumference. Although there appeared to be a shallow dose-response curve for topiramate dose across a range of doses analyzed (up to 60 mg/kg/d) for the mean Z score reductions for weight and length, there did not appear to be dose-related effect of topiramate dose on Z score reduction for head circumference.

- The sponsor presented the following summary about growth :
  "The differences in the effects on growth in this open-label extension study compared to those in older children and also to those in infants on lower doses are likely attributable to the higher doses of topiramate administered to this infant population, possibly mediated, at least in part, through the metabolic acidosis. The findings in this open-label integrated dataset are, however, limited by the absence of a control group and the background of poor growth in children with refractory epilepsy."

Reviewer Comment

- Although it is not possible to conclude that these reductions in Z scores for weight, length, and head circumference were definitely related to topiramate treatment because these data were not derived from a randomized, double-blinded, placebo-controlled study, I believe that it is difficult to dismiss that they are not possibly related to topiramate treatment, at least to a partial degree. A considerable number of these very young patients had various neurological abnormalities and were likely to have various development impairments. Thus, at least some reductions in Z scores for these parameters relative to the standard (healthy pediatric subjects) would be expected.

- The Endocrine consult (obtained to assess the possibility that topiramate was impairing growth) thought that changes in weight and length were sufficiently impressive to reflect a "suppressive effect" during treatment, possibly related to topiramate and perhaps throught topirmate's effect on weight loss or rate of increase and on the development of metabolic acidosis. Although the data did not permit a mechanistic explanation for these changes, the consult noted that the changes in weight scores appeared to precede the changes in length scores, further suggesting that changes in weight may have contributed to the decrease in length Z scores. The consult further commented that there was no clear, unequivocal dose-response effect of topiramate based primarily upon various modal dose ranges (e.g., < 20, 20-40, > 40 mg/kg/d) analyzed.

- Various subgroup analyses (regarding metabolic acidosis or threshold weight reduction in Z score) were conducted. In general, patients with metabolic acidosis in the long-term, open-label extension study, had greater mean Z score reductions from baseline (for weight and length, but not head circumference than patients without metabolic acidosis suggesting the possibility that metabolic acidosis was at least partially contributing to this change.

  I also believe that there is some evidence for a dose-related effect of long-term topiramate treatment based upon analyses that show that the relative risk (based upon the ratio of the incidence of various threshold Z score reductions from baseline such as $\geq$ 0.5, $\geq$ 1.0, and $\geq$ 2.0 for patients with metabolic acidosis compared to those without metabolic acidosis. This relative risk for the various threshold Z score reductions increased with increasing dose range.

- I recognize that it is difficult to conclude definitively if topiramate's effect on metabolic acidosis and/or weight caused these adverse changes in Z scores observed for weight, length, and head circumference However, topiramate's influence on the development of metabolic acidosis and weight loss and possible secondary effects on bone metabolism suggest that this adverse effect on weight, length, and head circumference is biologically plausible.

- (b) (5)

Electrocardiograms (ECGs)

Reviewer Comment

- I did not find any remarkable, clinically significant changes in the analyses of ECGs.

Events of Special Interest

Behavioral Effects

Topiramate is known to produced significant cognitive dysfunction. Considering this observarion, behavioral testing was conducted in all studies to assess the effect of topiramate treatment. Of potential interest, mean baseline scores for all testing domains (i.e., communication, daily living skills, motor skills, socialization and the composite score of these domains was decreased with mean scores ranging from ~ 75 -85. Of further interest, patients taking concomitant valproic acid (VPA) typically had lower mean scores than patients on other AEDs (excluding VPA).

Whereas significant behavioral effects (as reflected by Vineland adaptive composite behavioral scale testing including the 4 domains noted) were not observed in a 20 day placebo-controlled study, they were observed in the long-term, open-label study of infant/toddlers with topiramate. There were noteworthy decreases (from pre-treatment/baseline) in all behavioral domains (i.e., communication, daily living skills, motor skills, socialization) and the composite adaptive behavior score ranging from 18 % to 24 % observed during treatment over 52 weeks/1 year. These decreases were progressive over 1 year.

Reviewer Comment

- Because these results were not collected in a placebo-controlled study, and the study population consisted of many neurologically affected individuals, it is not possible to determine the unequivocal causality of topiramate. One published study of newly diagnosed young pediatric patients with epilepsy showed that there was progressive deterioration over time (along with various anticonvulsant therapy) but the magnitude was not as great as that in the patients in these infant/toddler studies. However, it is likely that that the patients in the studies under review were more developmentally impaired and had a higher percentage of neurological abnormalities than the patients in the published study who likely represented a an overall less impaired population of patients.

- Nevertheless, despite the above caveat and limitations of the data, I believe that least some, significant portion of these changes (e.g., deterioriation of scores) were likely due to topiramate. I have this belief because of the magnitude (~ 18-23 % decrease from baseline) marked reductions in all scores associated with chronic topiramate treatment over a relatively limited period of time (many weeks up to 52 weeks/1 year) and the well known fact that topiramate treatment produces cognitive dysfunction. Longer term (than 20 days), topiramate treatment (ideally with several fixed doses of topiramate) under placebo-controlled conditions are needed to establish clearly whether topiramate is causal in these adverse changes.

Hyperammonemia / Encephalopathy

The present label notes a risk of hyperammonemia with or without encephalopathy during topiramate treatment in conjunction with concomitant valproic acid (VPA) treatment, based upon post-marketing reports. (b) (4)

(b) (4)

Ammonia levels were measured in the the studies in infants/toddlers.

Topiramate produced a dose-related increased incidence of treatment-emergent hyperammonemia to values above the reference range and to markedly abnormal values in the short-term (20 day) placebo-controlled trial. The incidence of these increased values (above the reference range) for patients on any concomitant antiepileptic drug was 4 % for placebo, 11 % for 5 mg/kg/d, 4 % for 15 mg/kg/d, 13 % for 25 mg/kg/d, and 8% for any topiramate dose. Subgroup analyses showed that hyperammonia (above the normal reference range) occurred more frequently than placebo in patients taking topiramate with VPA but not in those taking topiramate without VPA. The incidence of hyperammonemia to markedly increased values for patients on any concomitant antiepileptic drug was 0 % for placebo and 5 mg/kg/d, 4 % for 15 mg/kg/d, 9 % for 25 mg/kg/d, and 3 % for any topiramate dose. In the subgroup analyses, the incidence of hyperammonemia to markedly increased values for patients on a concomitant AED **excluding VPA** was 0 % for placebo, 5 mg/kg/d, and 15 mg/kg/d, 9 % for 25 mg/kg/d, and 1 % for any topiramate dose. The incidence of hyperammonemia to markedly increased values for patients on a concomitant AED **including VPA** was 0 % for placebo, and 5 mg/kg/d, 7 % for 15 mg/kg/d, 8 % for 25 mg/kg/d, and 4 % for any dose.

The increased incidence of hyperammonemia was observed particularly in patients on concomitant valproic acid (VPA). An increased incidence of hyperammonemia to markedly abnormal values was observed in both patients with and without concomitant VPA. Long-term, open-label high dose (> 40 mg/kg/d) topiramate treatment was associated with increased (vs patients on lower doses) plasma ammonia increments from baseline in patients with and without concomitant VPA. Some patients who developed hyperammonemia in the open-label treatment study also developed symptoms of encephalopathy.

Reviewer Comment

- I interpret these data to suggest that topirmate without concomitant VPA has the potential to increase ammonia levels and produce hyperammonemia with or without encephalopathic symptoms. However, I believe that the risk for developing hyperammonemia is greater when topiramate is used along with VPA.

- I believe that there are other sources of data information that support the possibility that topiramate treatment without VPA can increase the risk for hypermmonemias. First, topiramate monotherapy (up to 4 months in patients who were prohibited from using any concomitant antiepileptic drug) of adolescent pediatric patients (12-16 years) as migraine prophylaxis increased plasma ammonia levels (i.e., hyperammonemia) to levels above the normal reference range and to markedly abnormally increased levels (with and without encephalopathic symptoms). The incidence of these increased values (above the reference range) at any visit was 22 % for placebo, 26 % for 50 mg/day, 41 % for 100 mg/day, and 33 % for any topiramate dose. The incidence of hypermmonemia at the final visit was 0 % for placebo, 15 % for 50 mg/day, 6 % for 100 mg/day, and 11 % for any topiramate dose. The incidence of hyperammonemia to markedly abnormally increased values at any visit was 6 % for placebo, 6 % for 50 mg/day, 12 % for 100 mg/day, and 9 % for any topiramate dose. 6 % for 100 mg/day, and 11 % for any topiramate dose. The incidence of hyperammonemia to markedly abnormally increased values at the final visit was 0 % for placebo, 3 % for 50 mg/day, 3 % for 100 mg/day, and 3 % for any topiramate dose.

Second, there are several AERS post-marketing reports of hyperammonemia in patients who were taking topiramate without VPA.

Third, an acute pharmacological effect of topiramate (with TOPAMAX and similarly also with an (b) (4)) increased plasma ammonia ~ 50 % above baseline and several pts developed hyperammonemia (increased above reference range).

- (b) (5)

Maternal Fetal Health Consult

A Maternal Fetal Health consult was about regarding a potential concern that chronic metabolic acidosis could have deleterious effects on the fetus during pregnancy and possibly at the time of labor. (b) (5) .

1.3.4 Dosing Regimen and Administration

- Not applicable

1.3.5 Drug-Drug Interactions

- Not applicable

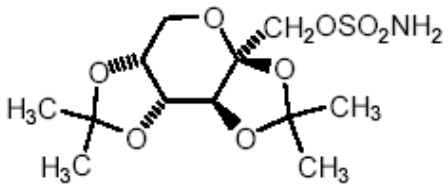
1.3.6 Special Populations

- Not applicable

2 INTRODUCTION AND BACKGROUND

Product Description

Topiramate (RWJ-17021 000), the active ingredient in TOPAMAX®, is a sulfamate-substituted monosaccharide (chemical name: 2,3:4,5-Di-*O*-iso propylidene-β-D-fructopyranose sulfamate; molecular formula: $C_{12}H_{21}NO_8S$; molecular weight: 339.37). The structural formula of topiramate is:



TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures; as adjunctive therapy for adults and pediatric patients ages 2 - 16 years with partial onset seizures, or primary generalized tonic-clonic seizures; in patients 2 years of age and older with seizures associated with Lennox- Gastaut syndrome and for the prophylaxis of migraine headache in adults.

sNDA Submission

The current supplemental NDA (sNDA) is provided in response to the 14 December 2005 Written Request for Pediatric Studies (WR) to investigate the tolerability, efficacy and safety of topiramate as adjunctive therapy for the treatment of refractory POS in infants aged 1 to 24 months, sent by the FDA under the Best Pharmaceuticals for Children Act of 2002 (BPCA) and contains a request for 6-months of pediatric exclusivity under BPCA. The development program in support of the sponsor's commitment was discussed in several major meetings; at the Type A meetings held on 02 March 2006 (FDA-Approved Minutes) and 05 September 2007 (Sponsor's Minutes) and further discussed at the 01 November 2007 Type B: Pre-sNDA meeting (Sponsor's Minutes). An Annotated WR, outlining the sponsor's actions towards satisfying the specific WR requirements, is provided in Module 1.9.6. As agreed at the Pre-sNDA meeting, the sponsor is cross-referencing the complete Chemistry, Manufacturing and Controls information contained in NDAs 20-505 (TOPAMAX® Tablets) and 20-844 (TOPAMAX® Sprinkle Capsules) and Drug Master File (b) (4) The sponsor is also cross-referencing the nonclinical pharmacology, toxicology and ADME study reports contained in NDA 20-505. Therefore, this submission does not contain Modules 3 or 4. Results of the pivotal Phase III study (Double-Blind Phase of Study TOPMAT-PEP-3001), were not supportive of efficacy or dose response for topiramate in reducing seizures in this very young age group with refractory POS. As such, (b) (4)

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

- Not applicable

3.2 Animal Pharmacology/Toxicology

- No animal data were submitted with this application.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

All documents reviewed for this NDA submission are in electronic form. The path to CDER Electronic Document Room for documents of this NDA submission is listed below :

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Some subsequent submissions were sent to the EDR to NDA 20844.

4.2 Tables of Clinical Studies

LISTING OF CLINICAL STUDIES

Study Number[a] (Coordinating) Principal Investigator (Country) Start/End Date (day Month year)	Study Description/Design, Objectives, Type of Control	Subjects Evaluated Sex M/F Age: Mean (Range) Race (W/B/Ot)	Treatment Regimen/ Duration	Study Status Type of Study Report CTD Location of Report
Comparative Bioavailability and Bioequivalence Studies				
TOPMAT-PEP-1001 Synopsis Dennis Morrison, D.O. (United States) 9 November 2004/ 21 December 2004	A Phase 1, open-label, randomized, 2-way crossover study to determine the relative bioavailability of oral liquid formulation vs. sprinkle capsule formulation in healthy adult subjects. Each subject received 1 dose of 100 mg sprinkle capsule and 1 dose of 100 mg oral liquid with a 21-day washout period between the 2 doses. The pharmacokinetic parameters estimated included: C_{max}, t_{max}, $t_{1/2}$, λ_z, AUC_{last}, AUC_∞, $\%AUC_{\infty,ex}$, CL/F, and F_{rel} (%).	Topiramate: 40 Sex: M 63%/F 38% Age: 25.7 years (18-43) Race: W 95%/B 5%/Ot 0	1 dose of 100 mg sprinkle capsule: 4×25-mg 1 dose of 100 mg oral liquid: 20 mL of 5 mg/mL solution	Completed Full report Module 5.3.1.2

Patient Pharmacokinetic and Initial Tolerability Studies				
TOPMAT-PEP-1002 open-label treatment (core) phase Synopsis Vinay Puri, M.D. (United States) 15 June 2006/ 29 January 2007	A Phase 1 randomized, open-label, multicenter study to determine the concentration-time profile for topiramate, using a sparse sampling scheme, following topiramate administration at fixed doses between 3 and 25 mg/kg per day of either oral liquid or sprinkle capsule formulations in infants aged 1 to 24 months, inclusive, with refractory partial-onset seizures (POS), taking at least 1 concomitant antiepileptic drug.	TPM 3 mg/kg per day: 14 TPM 5 mg/kg per day: 13 TPM 15 mg/kg per day: 13 TPM 25 mg/kg per day: 15 Sex: M 58%/F 42% Age: 11.4 months (2-22) Race: W 78%/B 7%/Ot 15%	Target dose (3, 5, 15 or 25 mg/kg per day) was reached through gradual titration (dose escalation every 7 days starting from 3 mg/kg per day) and maintained for 7 days.	Completed Full report Module 5.3.3.2 CRFs
Extrinsic Factor Pharmacokinetic Studies				
TOPMAT-PEP-1004 Synopsis Thomas Hunt, M.D., Ph.D. (United States) 8 January 2007/ 13 March 2007	A Phase 1, open-label, randomized, 2-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. Each subject received 2 single doses of 100-mg topiramate liquid (one dose with food and the other without food) with a 21-day washout period in between the 2 doses. The pharmacokinetic parameters estimated included: C_{max}, t_{max}, AUC_{∞}, AUC_{last}, $t_{1/2}$, and F_{rel}.	Topiramate: 40 Sex: M 53%/F 48% Age: 25.4 years (18-45) Race: W 78%/B 20%/Ot 3%	Two doses of 100 mg oral liquid: 20 mL of 5 mg/mL solution	Completed Full report Module 5.3.1.1

Listing of Clinical Studies (Continued)

Efficacy and Safety Controlled Clinical Studies				
TOPMAT-PEP-3001 double-blind (core) phase Synopsis James B. Renfroe, M.D. (United States) 30 September 2005/ 1 June 2007	Phase 3, multicenter, randomized, double-blind (DB), placebo-controlled, video-recorded electroencephalogram (vEEG) rater-blinded, parallel group, fixed dose-ranging study to compare the effectiveness of topiramate 5, 15, or 25 mg/kg per day (administered as either sprinkle capsules or oral liquid formulation) with that of placebo as an adjunct to concurrent anticonvulsant therapy in reducing daily POS rates in infants (1 to 24 months of age, inclusive) with refractory POS after 20 days of double-blind treatment.	TPM 5 mg/kg per day: 38 TPM 15 mg/kg per day: 37 TPM 25 mg/kg per day: 37 Placebo: 37 Sex: M 52%/F 48% Age: 12 months (1-24) Race: W 61%/B 3%/Ot 36%	Target dose (5, 15 or 25 mg/kg per day) was reached through gradual titration (dose escalation every 3 days starting from 3 mg/kg per day) and maintained for 7 days.	Completed Full report Module 5.3.5.1 CRFs
Efficacy and Safety Uncontrolled Clinical Studies				
TOPMAT-PEP-1002 and TOPMAT-PEP-3001 combined open-label extension Synopsis Michael Duchowny, M.D. (United States) May 26, 2005/ 1 November 2007	Multicenter, open-label, 52- to 54-week extension phase of TOPMAT-PEP-3001 and TOPMAT-PEP-1002 to evaluate the safety and tolerability of topiramate oral liquid and sprinkle formulations in infants with refractory POS at dosages up to 60 mg/kg per day.	Topiramate: 284 Sex: M 54%/F 46% Age: 12.2 months (1-24) Race: W 62%/B 5%/Ot 33%	Subjects were titrated to maximal tolerated dosage, seizure freedom, or to 60 mg/kg per day topiramate, whichever occurred first, and stayed on topiramate for approximately 1 year.	Completed Full report Module 5.3.5.2 CRFs

[a] The sponsor is Johnson & Johnson Pharmaceutical Research & Development (J&JPRD).
KEY: TPM=topiramate; CRF=case report form; M=male; F=female; mg=milligram; W=White; B=Black; Ot=other (e.g., Asian).

4.3 Review Strategy

I focused the efficacy review primarily on Study TOPMAT-PEP-3001, the randomized, double-blind, placebo-controlled, multiple fixed dose arm study. For the safety review, I focused particularly on the placebo-controlled study and the corresponding open-label extension study in which patients rolleded from study 3001, or 3002, or were enrolled as de novo patients who had not been in a previous study.

4.4 Data Quality and Integrity

Data quality was considered to be reasonably good. There were no questions related to the integrity of the data. .

4.5 Compliance with Good Clinical Practices

The studies appeared to have been conducted according to Good Clinical Practices.

4.6 Financial Disclosures

There were no problems/concerns with financial disclosures.

5 CLINICAL PHARMACOLOGY

See Clinical Pharmcology and Pharmacometrics Review (by Drs. Nitin Mehrotra, Hao Zhu, Jagan Parepally, and Ramana Uppoor)for information on pharmacokinetics, pharmacodynamics, and exposure-response relationships.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication is for the adjunctive treatment of partial epilepsy in very young, pediatric patients (i.e., infants and toddlers 1-24 months old).

6.1.1 Methods

The sole trial conducted to show efficacy of topiramate as adjunctive treatment of partial epilepsy in very young, pediatric patients (i.e., 1-24 months old) was a randomized, double-blind, placebo-controlled, multiple fixed dose arm study (TOPMAT-PEP-3001).

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint was the median percentage reduction (at the end of the double-blind period) from baseline in the daily rate of partial seizures based upon video EEG (vEEG) data. The median percentage reduction from baseline in the rate (based upon various time perspectives (e.g., daily, weekly, or monthly) of partial seizures is a common primary efficacy endpoint for adjunctive treatment of partial epilepsy. However, this endpoint is most typically based upon seizure rate determined from a daily seizure diary. It was believed that vEEG data based upon

"reading"/ingterpretation by a blinded reader might be a more "objective" method for quantifying the seizure frequency in these very young pediatric patients because of potential difficulties in quantifying seizure frequency. (b) (5)

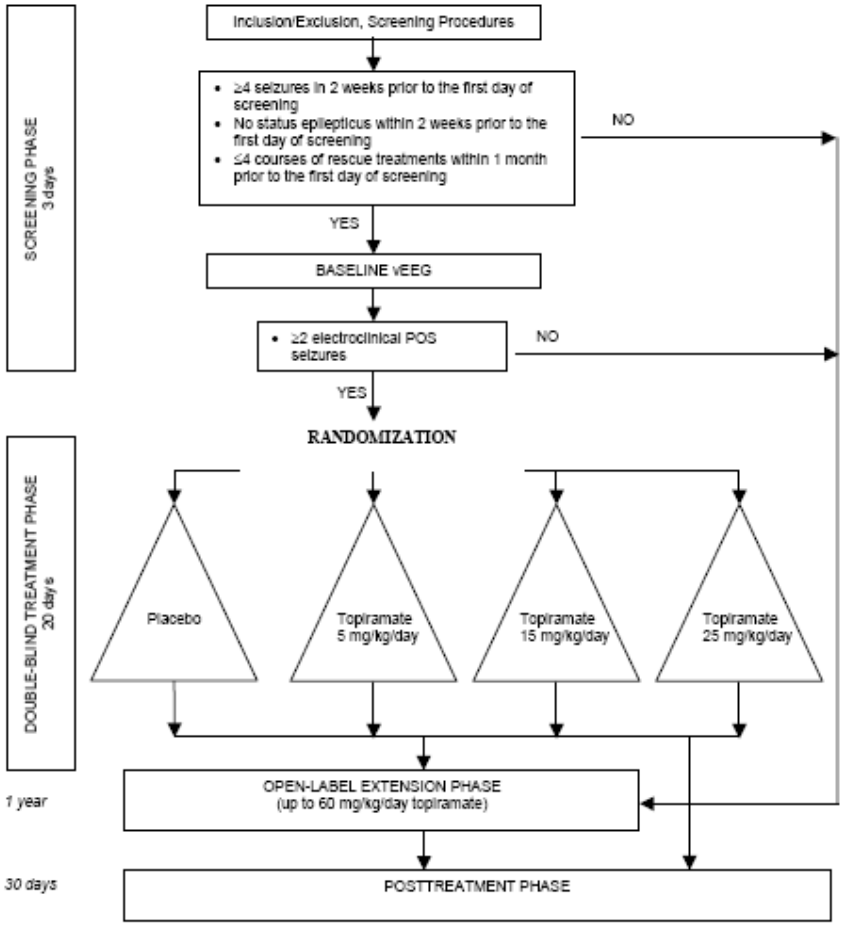
6.1.3 Study Design

Study TOPMAT-PEP-3001 was an international, multicenter, randomized, double-blind, placebo-controlled, video electroencephalogram (vEEG) rater-blinded, parallel-group, 4-arm, fixed dose-ranging study to evaluate the tolerability, safety, and efficacy of topiramate 5, 15, and 25 mg/kg per day as an adjunct to concurrent anticonvulsant therapy in infants, aged 1 to 24 months, with refractory POS with or without secondary generalization.

Fifty-two centers participated in this study: Argentina (4 centers), Belgium (1 center), Canada (1 center), Chile (3 centers), Finland (1 center), France (1 center), Hungary (4 centers), India (6 centers), Mexico (1 center), the Netherlands (1 center), Norway (1 center), Poland (2 centers), Republic of Korea (1 center), Russia (6 centers), South Africa (1 center), Spain (1 center), Thailand (1 center), Ukraine (3 centers), and the United States (13 centers). One to 16 subjects were treated at each center. Approximately 53% of subjects were randomized at the 9 highest enrolling centers (≥6 subjects).

The study consisted of 4 phases: a 3-day screening phase, a 20-day double-blind treatment phase (including uptitration and stabilization of the target dosage), a 1-year open-label extension phase (including a blinded withdrawal taper of double-blind treatment and uptitration of open-label study medication), and a posttreatment phase (including a withdrawal taper at the discretion of the investigator and a follow-up visit 30 days after the last treatment visit). The following schematic diagram outlines the study design.

Figure 1: Study Design
(Study TOPMAT-PEP-3001)



Subjects with a history of at least 4 seizures in the 2 weeks before the first day of screening and who met other inclusion criteria underwent a baseline 48-hour vEEG during the screening phase. Those with at least 2 countable, electroclinical POS (as read by the investigator) with either electroencephalogram (EEG) or clinical evidence of focal origin during the baseline vEEG were allowed to enter the double-blind treatment phase of the study. Subjects with fewer than 2 POS during the baseline vEEG were allowed to enter the open-label extension phase directly.

For the double-blind treatment phase of the study, approximately 120 subjects (30 per arm) were to be randomized (1:1:1:1) by Interactive Voice Response System (IVRS) to 1 of 4 treatment arms to receive study medication orally, twice daily (topiramate starting at 3 mg/kg per day, with uptitration every 3 days until the final target dosage of 5, 15, or 25 mg/kg per day or the maximum dosage tolerated had been achieved or placebo) in addition to their existing regimen of anti-epileptic drugs (AEDs). Topiramate and matching placebo were administered as either the oral liquid formulation or the sprinkle capsule formulation. The topiramate dosage strengths were 5 mg/mL (oral liquid) and 25 mg (sprinkle capsule). Subjects weighing less than 9 kg, those who could not take solid foods either because of a documented impairment in the ability to take solid food or because of a feeding tube of any type, and heavier subjects (≥9 kg) with agreement of parents or legally-acceptable representatives, the investigator, and the sponsor's medical monitor were given topiramate or placebo as the oral liquid formulation. All others were given topiramate or placebo as the sprinkle capsule formulation. If the sprinkle capsule formulation was not available, all infants were given the oral liquid formulation. During the double-blind treatment phase, a single dosage reduction of study drug

was allowed for safety and tolerability concerns, with subjects remaining at the reduced dosage for the remainder of the double-blind phase. Alternatively, the investigator could have paused uptitration and maintained a stable dosage, with the option of later resuming uptitration. Regardless of any pauses or reductions, the duration of the double-blind phase was not to be extended beyond the originally scheduled 20-day period (± 3 days). The number and dosages of concomitant nonstudy AEDs were to remain constant immediately prior to the baseline vEEG and during the double-blind phase to minimize any confounding effects of changes in baseline AED regimen. Dosage reductions because of elevated AED levels or side effects were permitted.

During the double-blind treatment phase, subjects were to be discontinued if any of the following occurred :

• Their average daily seizure rate, based on take-home records, for any 3-day interval was more than twice the average daily rate over the 3 consecutive days of the screening phase.
• They developed status epilepticus not controlled by a single course of rescue treatment.
• They developed new seizure types (with discontinuation at the discretion of the investigator).
• They required addition of another anticonvulsant (or a change in other AED therapy except for dosage reduction for elevated AED levels) other than allowed rescue treatments.
• They were unable to tolerate study medication following the single allowed reduction or pause in dosage.
• The investigator believed that for safety reasons (e.g., adverse event, elevated hepatic enzymes) it was in the best interest of the subject to stop treatment.

Subjects who completed or discontinued early from the double-blind phase could continue in the open-label extension phase of the study. Subjects who withdrew early from the study, or who chose not to enter the open-label extension phase, were offered a blinded withdrawal taper of study medication over a period of up to 2 weeks with addition, and uptitration if necessary, of a marketed medication over an appropriate length of time as determined by the investigator. Subjects who withdrew early from the double-blind phase were to complete the assessments scheduled for the end of the double-blind phase (Visit 4), including an end-point vEEG examination. A posttreatment follow-up visit was performed 30 days after Visit 4 (end of double-blind treatment phase or early withdrawal) which included safety assessments and review of information on the take-home record.

Efficacy evaluation was primarily based on vEEG data regarding seizure type and frequency. These results were to be evaluated by a central reader blinded to the subject identity, treatment group, dosing schedule, and center.

In addition, seizure type and frequency were to be documented on subject take-home records.

6.1.4 Efficacy Findings

Study Completion/Withdrawal Information

• Of the 149 subjects who were enrolled and randomized in the double-blind phase of the study (ITT analysis set), 130 (87%) completed it (see table below). The completion rate was higher among subjects randomized to topiramate than to placebo (90% vs.78%).

Table 5: Study Completion/Withdrawal Information - Double Blind Phase
(Study TOPMAT-PEP-3001: Intent-to-Treat Analysis Set)

	Placebo	TPM 5 mg/kg/d	TPM 15 mg/kg/d	TPM 25 mg/kg/d	All TPM	Total
	(N=37)	(N=38)	(N=37)	(N=37)	(N=112)	(N=149)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Completed	29 (78)	34 (89)	33 (89)	34 (92)	101 (90)	130 (87)
Withdrawn	8 (22)	4 (11)	4 (11)	3 (8)	11 (10)	19 (13)
Adverse event	2 (5)	1 (3)	2 (5)	1 (3)	4 (4)	6 (4)
Subject choice (parent withdrew consent)	1 (3)	0	0	0	0	1 (1)
Other	5 (14)	3 (8)	2 (5)	2 (5)	7 (6)	12 (8)

Note: Percentages calculated with the number of subjects in each group as denominator.
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• In total, 19 subjects (13%) discontinued double-blind treatment, with most discontinuations due to "other" reasons and the percentage withdrawing for "other"reason was highest in the placebo group vs each of the topiramate groups. The "other" reasons as given by the investigator included meeting the escape criterion (7 subjects) and doubling of seizure rate (i.e., met escape criterion, 1 subject), as well as multiple seizures, more than 1 dose reduction, incorrect dosing, and unknown (1 subject each). One subject was discontinued when consent was withdrawn because of the time involved.

• Six subjects discontinued double-blind treatment because of a treatment-emergent adverse event, which was a serious adverse event in 3 cases. The rates of early withdrawal due to an adverse event were similar in all treatment groups and showed no apparent relationship to the topiramate dose.

• Completion rates for the MITT analysis set were higher than for the ITT set. Of the 130 subjects who were included in the MITT analysis set, 122 (94%) completed the study (95% and 89% of subjects in the topiramate and placebo groups, respectively.

Demographic and Baseline Characteristics

The following table shows the demographic characteristics of patients in each treatment group.

Table 6: Demographic and Baseline Characteristics - Double Blind Phase
(Study TOPMAT-PEP-3001: Intent-to-Treat Analysis Set)

	Placebo (N=37)	TPM 5 mg/kg/d (N=38)	TPM 15 mg/kg/d (N=37)	TPM 25 mg/kg/d (N=37)	All TPM (N=112)	Total (N=149)
Age (months)						
N	37	38	37	37	112	149
Category, n (%)						
1 to 5 months	6 (16)	9 (24)	7 (19)	7 (19)	23 (21)	29 (19)
6 to 11 months	14 (38)	9 (24)	10 (27)	16 (43)	35 (31)	49 (33)
12 to 24 months	17 (46)	20 (53)	20 (54)	14 (38)	54 (48)	71 (48)
Mean (SD)	11.8 (5.91)	13.3 (7.56)	12.4 (6.15)	10.2 (5.16)	12.0 (6.46)	12.0 (6.31)
Median	11.0	13.5	12.0	9.0	11.0	11.0
Range	(1;23)	(2;24)	(1;24)	(3;22)	(1;24)	(1;24)
Sex, n (%)						
N	37	38	37	37	112	149
Male	14 (38)	22 (58)	19 (51)	23 (62)	64 (57)	78 (52)
Female	23 (62)	16 (42)	18 (49)	14 (38)	48 (43)	71 (48)
Race*, n (%)						
N	37	38	37	37	112	149
White	26 (70)	25 (66)	19 (51)	21 (57)	65 (58)	91 (61)
Black or African American	1 (3)	1 (3)	1 (3)	2 (5)	4 (4)	5 (3)
Asian	9 (24)	7 (18)	11 (30)	7 (19)	25 (22)	34 (23)
Other	1 (3)	5 (13)	6 (16)	7 (19)	18 (16)	19 (13)
Ethnicity, n (%)						
N	37	38	37	37	112	149
Hispanic or Latino	7 (19)	6 (16)	3 (8)	4 (11)	13 (12)	20 (13)
Not Hispanic or Latino	30 (81)	32 (84)	34 (92)	33 (89)	99 (88)	129 (87)
Weight (kg)						
N	37	38	37	37	112	149
Mean (SD)	8.59 (2.391)	8.95 (2.540)	8.56 (2.469)	8.29 (2.182)	8.60 (2.397)	8.60 (2.388)
Median	8.50	8.80	8.50	8.10	8.40	8.50
Range	(3.6;14.4)	(4.8;14.5)	(4.2;15.4)	(4.0;13.6)	(4.0;15.4)	(3.6;15.4)
Length (cm)						
N	36	38	37	37	112	148
Mean (SD)	73.2 (8.88)	73.8 (11.15)	73.9 (8.54)	70.7 (8.33)	72.8 (9.47)	72.9 (9.30)
Median	74.9	76.3	76.0	70.6	72.9	73.1
Range	(51;85)	(54;95)	(53;90)	(51;87)	(51;95)	(51;95)
Head Circumference (cm)						
N	37	38	37	36	111	148
Mean (SD)	42.3 (3.75)	42.9 (4.00)	42.1 (3.55)	41.7 (3.60)	42.2 (3.73)	42.2 (3.72)
Median	43.0	42.8	42.0	41.5	42.0	42.3
Range	(35;49)	(35;51)	(36;49)	(34;49)	(34;51)	(34;51)
Time (days) since first seizure						
N	36	38	37	37	112	148
Mean (SD)	272.9 (180.11)	310.3 (197.90)	269.1 (176.77)	262.9 (160.35)	281.0 (178.83)	279.1 (178.56)
Median	246.5	260.0	247.0	261.0	254.0	253.5
Range	(35;704)	(34;712)	(42;666)	(32;679)	(32;712)	(32;712)
Time (days) since epilepsy diagnosis						
N	37	38	37	37	112	149
Mean (SD)	234.8 (169.95)	241.4 (187.28)	221.1 (177.76)	206.6 (153.49)	223.2 (172.59)	226.1 (171.44)
Median	197.0	196.0	157.0	187.0	187.5	188.0
Range	(22;602)	(8;683)	(9;635)	(9;618)	(8;683)	(8;683)

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*Categories AMERICAN INDIAN OR ALASKAN NATIVE and NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER not presented in this table due to zero counts in data collected from the CRF.

• The study population was 52% male and 61% white, with 13% Hispanic/Latino ethnicity. Consistent with entry criteria, subject age ranged from 1 to 24 months, with a mean age of 12 months. In total, 23% of subjects were reported as Asian. In addition all subjects reportedly of "other" races were Indian (from India) except 1 Thai (5 mg/kg per day group).

• Demographics and baseline characteristics of subjects in the 4 treatment groups were generally similar, with the exception of smaller proportions of females and white race among subjects randomized to topiramate than placebo (43% vs. 62% females and 58% vs. 70% white, respectively).

• At baseline, a mean 279.1 days had elapsed since the first seizure and a mean 226.1 days since epilepsy was diagnosed, with a wide range for both time periods.

• **As central reading of the vEEG was not possible in a timely fashion for inclusion of subjects in the study, all subjects entered the double-blind phase based on the investigator reading of the baseline vEEG. Differences in interpretation of the baseline vEEG between the investigator and the blinded central reader occurred (discussed further below).**

• The daily POS rate for the ITT population as determined by the blinded central reader is shown in the following table. The distribution of subjects by this daily POS rate at baseline appeared similar in all treatment groups. The number of subjects who had fewer than 2 actual POS during vEEG was 3, 3, 3, and 2 for the placebo, topiramate 5 mg/kg, 15 mg/kg, and 25 mg/kg groups respectively. The central reader reported only 1 subject with a generalized seizure during the baseline vEEG and no subject with infantile spasms or other seizure types.

Table 8: Demographic and Baseline Characteristics: Distribution of Baseline Daily Seizure Rates From vEEG
(Study TOPMAT-PEP-3001: Intent-to-Treat Analysis Set)

Seizure Type* Seizure Rate	Placebo (N=37) n (%)	TPM 5 mg/kg/d (N=38) n (%)	TPM 15 mg/kg/d (N=37) n (%)	TPM 25 mg/kg/d (N=37) n (%)	All TPM (N=112) n (%)	Total (N=149) n (%)
Partial	35 (95)	37 (97)	37 (100)	37 (100)	111 (99)	146 (98)
0	3 (8)	2 (5)	2 (5)	2 (5)	6 (5)	9 (6)
>0 - <1	1 (3)	1 (3)	2 (5)	1 (3)	4 (4)	5 (3)
1-<2	3 (8)	3 (8)	5 (14)	1 (3)	9 (8)	12 (8)
2-<3	3 (8)	3 (8)	2 (5)	5 (14)	10 (9)	13 (9)
3-<6	8 (22)	3 (8)	5 (14)	4 (11)	12 (11)	20 (13)
6-<10	3 (8)	9 (24)	4 (11)	5 (14)	18 (16)	21 (14)
10-<20	4 (11)	5 (13)	6 (16)	8 (22)	19 (17)	23 (15)
20-<40	6 (16)	5 (13)	6 (16)	2 (5)	13 (12)	19 (13)
≥40	4 (11)	6 (16)	5 (14)	9 (24)	20 (18)	24 (16)
Generalized	35 (95)	37 (97)	37 (100)	37 (100)	111 (99)	146 (98)
0	34 (92)	37 (97)	37 (100)	37 (100)	111 (99)	145 (97)
>0 - <1	1 (3)	0	0	0	0	1 (1)
Infantile spasms	35 (95)	37 (97)	37 (100)	37 (100)	111 (99)	146 (98)
0	35 (95)	37 (97)	37 (100)	37 (100)	111 (99)	146 (98)
Other	35 (95)	37 (97)	37 (100)	37 (100)	111 (99)	146 (98)
0	35 (95)	37 (97)	37 (100)	37 (100)	111 (99)	146 (98)
All seizures	35 (95)	37 (97)	37 (100)	37 (100)	111 (99)	146 (98)
0	3 (8)	2 (5)	2 (5)	2 (5)	6 (5)	9 (6)
>0 - <1	1 (3)	1 (3)	2 (5)	1 (3)	4 (4)	5 (3)
1-<2	3 (8)	3 (8)	5 (14)	1 (3)	9 (8)	12 (8)
2-<3	3 (8)	3 (8)	2 (5)	5 (14)	10 (9)	13 (9)
3-<6	8 (22)	3 (8)	5 (14)	4 (11)	12 (11)	20 (13)
6-<10	3 (8)	9 (24)	4 (11)	5 (14)	18 (16)	21 (14)
10-<20	4 (11)	5 (13)	6 (16)	8 (22)	19 (17)	23 (15)
20-<40	6 (16)	5 (13)	6 (16)	2 (5)	13 (12)	19 (13)
≥40	4 (11)	6 (16)	5 (14)	9 (24)	20 (18)	24 (16)

Note: Percentages calculated with the number of subjects in each group as denominator.
*Partial includes partial on-set seizures with or without secondarily generalized. Generalized includes tonic-clonic and tonic seizures. All seizures includes all types listed above.
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• On the epilepsy history, multiple POS were reported for most subjects, with 34% having a medical history of infantile spasm. Ten subjects had no reported history of POS but rather had a history of infantile spasms and/or other seizure types. Upon being queried, the investigators confirmed that these subjects met inclusion/exclusion criteria for study entry. In the database, 1 additional subject (300462) is listed as having 0 POS on the epilepsy history because the reported "too numerous to count" POS was inadvertently not quantified upon data entry. Generalized (tonic-clonic and tonic) seizures, infantile spasms, and other seizure types were reported for 15%, 34%, and 7% of subjects, respectively, per the epilepsy history.

• The reason for the small numbers of seizure types other than POS on vEEG, for the inclusion of the subjects with no POS in their epilepsy history, and for the apparent discrepancy between the vEEG and the seizure history, is that the definition of partial seizures in the protocol for inclusion, and used by the central reader, is sometimes broader than that used in clinical practice. Thus, any seizure with an element of focality was classified as a partial seizure by the central reader, while it may have been classified as, for example, an infantile spasm (with focal onset), by the investigator in the seizure history.

• Demographics and baseline characteristics of the MITT analysis set were similar to those in the ITT set. The number of subjects who had fewer than 2 actual POS during vEEG was 3, 3, 3, and 2 for the placebo, topiramate 5 mg/kg, 15 mg/kg, and 25 mg/kg groups respectively.
• The distribution of subjects in the MITT set by daily POS rate at baseline appeared similar in each treatment group. However, the median daily POS rate at baseline was lower in the placebo and topiramate 5 mg/kg per day groups (6.39 and 6.75, respectively) than in the topiramate 15 and 25 mg/kg per day groups (8.33 and 10.00, respectively; see Table 13). Seizure counts from the epilepsy history are summarized in Attachment 1.3.2. Demographics and baseline characteristics are summarized for the MITT analysis set in Attachment 1.3.3, and for the safety analysis set (identical to the ITT set) in Attachment 1.3.4. The distribution of the baseline daily seizure rates in the MITT analysis set is provided in Attachment 1.3.5.

Prior and Concomitant Therapies

• All subjects were on one or more AEDs at baseline, with 55% on 1 AED and 44% on 2 AEDs. One subject in the placebo group was on more than 2 AEDs. The most frequently used AEDs at baseline were valproic acid, phenobarbital, and carbamazepine (56%, 29%, and 17% of subjects, Respectively. These were also the most frequently used AEDs prestudy.

• Except in rare cases, baseline AED regimens were continued unchanged throughout the double-blind phase as specified in the protocol, with all subjects continuing to receive at least 1 concomitant AED
.
• Rescue medication (for seizure exacerbation or status epilepticus) was needed by 13 subjects during the double-blind phase as shown in the following table. The rescue medication administered included phenobarbital, diazepam, lorazepam, and in one case, chloral hydrate (specified as rescue medication by the investigator).

Table 9: Rescue Medication Received During the Double Blind Phase
(Study TOPMAT-PEP-3001: Intent-to-Treat Analysis Set)

ATC Class Medication Generic Term	Placebo (N=37) n (%)	TPM 5 mg/kg/d (N=38) n (%)	TPM 15 mg/kg/d (N=37) n (%)	TPM 25 mg/kg/d (N=37) n (%)	All TPM (N=112) n (%)
Total no. subjects who received rescue medication	4 (11)	5 (13)	2 (5)	2 (5)	9 (8)
Antiepileptics	0	1 (3)	1 (3)	1 (3)	3 (3)
Phenobarbital	0	1 (3)	1 (3)	1 (3)	3 (3)
Anxiolytics	3 (8)	4 (11)	1 (3)	2 (5)	7 (6)
Diazepam	2 (5)	4 (11)	1 (3)	2 (5)	7 (6)
Lorazepam	1 (3)	1 (3)	0	0	1 (1)
Hypnotics and sedatives	1 (3)	0	0	0	0
Chloral hydrate	1 (3)	0	0	0	0

Note: Percentages calculated with the number of subjects in each group as denominator. Chloral hydrate specified as rescue medication by the investigator.
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• During the double-blind phase, 71% of subjects received at least 1 non-AED as concomitant medication, with the most frequent categories being other analgesics and antipyretics (19% of subjects, mainly paracetamol) and beta-lactam antibacterials, penicillin (15% of subjects.

• No clinically relevant differences in prior or concomitant medications among the different treatment groups were apparent.

Protocol Deviations

• Thirty-eight (26%) subjects in the ITT analysis set had a deviation from the protocol (see the following table), with unmet selection criteria being the most frequent major deviation. For the most part, the unmet selection criteria were not inclusion/exclusion criteria related to the primary efficacy parameter.

Table 10: Protocol Deviations - Double Blind Phase
(Study TOPMAT-PEP-3001: Intent-to-Treat Analysis Set)

Protocol Deviation Coded Term	Placebo (N=37) n (%)	TPM 5 mg/kg/d (N=38) n (%)	TPM 15 mg/kg/d (N=37) n (%)	TPM 25 mg/kg/d (N=37) n (%)	All TPM (N=112) n (%)	Total (N=149) n (%)
Total no. subjects with deviation	13 (35)	8 (21)	8 (22)	9 (24)	25 (22)	38 (26)
Excluded concomitant medication	0	2 (5)	0	0	2 (2)	2 (1)
Procedure not followed	5 (14)	1 (3)	1 (3)	1 (3)	3 (3)	8 (5)
Selection criteria not met	9 (24)	6 (16)	4 (11)	8 (22)	18 (16)	27 (18)
Treatment deviation	0	1 (3)	5 (14)	0	6 (5)	6 (4)
Other	1 (3)	0	1 (3)	0	1 (1)	2 (1)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: A subject may have more than one protocol deviation.
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• The proportion of subjects with a deviation appeared higher in the placebo group (35%) than in any of the topiramate groups (21% to 24%).

• The sponsor noted that protocol deviations were not considered to have affected study results.

Treatment Compliance

Study drug was administered by subject's parents or caregivers, and details of each administration, including dose, date, time, and any vomited dose were recorded on the subject take-home records. The investigator or designated study personnel maintained a log of all study treatment dispensed and returned. Study treatments for each subject were inventoried and reconciled throughout the study. One patient in the placebo group discontinued due to non-compliance with the study medication. This patient was incorrectly dosed and thus never titrated, and is included among the patients who discontinued due to "other" reasons. No subjects discontinued double-blind treatment with topiramate due to non-compliance with study medication.

Data Sets Analyzed

Efficacy analyses were performed using two analysis sets. The MITT analysis set was used for the analysis of vEEG data, and the ITT analysis set was used for sensitivity analyses of the primary end point and analyses based on subject take-home records.

• Nineteen of the 149 randomized subjects did not have evaluable vEEG data, and hence were excluded from the MITT analysis set.
Evaluable vEEG data were defined as:
– Baseline vEEG must have been before the first dose of study medication
– Final vEEG must have been within 2 days of the last dose of study medication
– Both a baseline and final vEEG must have been available and evaluable
– vEEG must have been interpretable
– vEEG must not have been within 48 hours after a rescue treatment
– vEEG must not have been immediately after a significant change in maintenance AED
– There must not have been a change in maintenance AEDs between the baseline and final vEEGs

• The proportion of subjects included in the MITT population was similar in each topiramate group (89% to 92%) but was lower in the placebo group (76%) due to the greater number of subjects without an evaluable vEEG at baseline and/or end point in the placebo group (9 subjects vs.4, 3, and 3 subjects in the topiramate 5-, 15-, and 25-mg/kg per day groups, respectively).

• The ITT and safety analysis sets were identical and included all 149 randomized subjects, since all 149 randomized subjects took at least 1 dose of study drug and had at least 1 postbaseline efficacy assessment. The following table shows the number of patients in each treatment group for each analysis set.

Table 12: Number of Subjects in Each Analysis Set for Double Blind Phase (Study TOPMAT-PEP-3001)

	Placebo	TPM 5 mg/kg/d	TPM 15 mg/kg/d	TPM 25 mg/kg/d	Total
Analysis Set	n	n	n	n	n
Randomized	37	38	37	37	149
Safety	37	38	37	37	149
ITT	37	38	37	37	149
MITT*	28	34	34	34	130

*Used for primary efficacy analysis.
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Efficacy Results

Primary Efficacy Analysis

The primary efficacy end point for the double-blind phase of the study was the percent reduction from baseline to the end of the double-blind treatment phase in daily POS rate based on vEEG data. The analysis of the primary efficacy endpoint will be tested using the step-down procedure, starting from the 25-mg/kg per day dose compared with placebo.

• Results for daily POS rate based on vEEG for each treatment group are shown in the following table. The median daily POS rates at baseline were higher in the topiramate 15- and 25-mg/kg per day groups than in the other 2 treatment groups.

Table 13: Summary of Percent Reduction in Daily Partial Onset Seizure Rate From Baseline to End of the Double Blind Phase, Based on vEEG
(Study TOPMAT-PEP-3001: Modified Intent-to-Treat Analysis Set)

Seizure Type: Partial	Placebo (N=28)	TPM 5 mg/kg/d (N=34)	TPM 15 mg/kg/d (N=34)	TPM 25 mg/kg/d (N=34)
Baseline				
N	28	34	34	34
Median (Range)	6.39 (0.0;148.7)	6.75 (0.0;158.6)	8.33 (0.0;176.4)	10.00 (0.0;148.1)
End Point				
N	28	34	34	34
Median (Range)	6.43 (0.0;105.0)	6.99 (0.0;192.3)	6.17 (0.0;186.1)	7.53 (0.0;110.5)
Percent Reduction from Baseline[b]				
N	28	34	34	34
Median (Range)	13.06 (-8999.0;100.0)	23.83 (-8999.0;100.0)	5.53 (-8999.0;100.0)	20.40 (-8999.0;100.0)
P-value(versus Placebo)[a]		0.909	0.969	0.967

[a] Test for no difference between treatments based on an analysis of covariance model using ranked data with factors for treatment group, age stratification at randomization (<6 months vs. 6 to 24 months) and baseline POS rate as covariate.

Note: A step down testing procedure was used, first testing the TPM 25 group vs.placebo. Since this was not significant, testing of the lower doses was not conducted. P-values for TPM 15 and TPM 5 are nominal p-values.

[b] For subjects who had zero baseline seizure and the postseizure number is more than zero, value -8999 was imputed as the percent reduction in accordance with the worst-rank analysis.

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• The percent reduction from baseline in daily POS rate based on vEEG in the topiramate 25-mg/kg per day group was not statistically significantly different from that in the placebo group (p=0.967).

• In accordance with the planned step-down procedure, treatment differences between the lower topiramate dosages and placebo were not formally tested. Nominal p values calculated for these comparisons were not statistically significant (p=0.969 for the 15 mg/kg/d group and p=0.909 for the 5 mg/kg/d group), and the percent reductions observed in the topiramate groups showed no apparent dose relationship.

• Similar results for the comparison between topiramate 25 mg/kg per day and placebo were obtained when the analysis was additionally adjusted for sex (p=0.277, AED category (inducer, noninducer AED use at baseline; p=0.589, or number of AEDs at baseline (p=0.930).

• Results for the comparison between topiramate 25 mg/kg per day and placebo were also similar in each of the 3 prespecified sensitivity analyses performed on the ITT population (p=0.753, 0.992, and 0.908, respectively). Additionally, no treatment effect was observed with either of the lower topiramate dosages (15 and 5 mg/kg per day) in the 3 sensitivity analyses (all nominal p values >0.5).

• Variability in both assessed values and the percentage reduction was high in all treatment groups. At least 1 subject in each treatment group had 0 POS at baseline (and were unable to show a reduction), and at least 1 subject in each treatment group had 100% reduction in daily POS rate. In addition, those subjects who had 0 POS at baseline and more than 0 POS at end point were assigned the worst percentage reduction (−8999%).

Results of additional analyses (including 3 sensitivity analyses) in which an additional factor of sex, AED category (inducer, noninducer), or number of AEDs at baseline were included were also conducted, and were also negative, not suggesting efficacy of topiramate.

Secondary Efficacy Analyses

Treatment Responders

A treatment responder was defined as a subject who had at least a 50% reduction from baseline in seizure rate for a specific seizure type based on vEEG data.

• For each of the topiramate dosages, the proportion of subjects who were treatment responders with regard to POS was not different from that on placebo ($p > 0.4$ for all comparisons; see following table).

Table 14: Summary of Treatment Responders (>=50% Reduction in Seizure Rate) for POS, From Baseline to End of the Double Blind Phase, Based on vEEG
(Study TOPMAT-PEP-3001: Modified Intent-to-Treat Analysis Set)

	Placebo		TPM 5 mg/kg/d		TPM 15 mg/kg/d		TPM 25 mg/kg/d	
	n	%	n	%	n	%	n	%
Responder: End Point								
Yes	10	35.7	9	26.5	13	38.2	15	44.1
No	18	64.3	25	73.5	21	61.8	19	55.9
Total	28		34		34		34	
P-value(versus Placebo)*				0.435		0.839		0.533

* Pairwise comparison: Generalized Cochran-Mantel-Haenszel test controlling for age groups (<6 months vs. 6 to 24 months).

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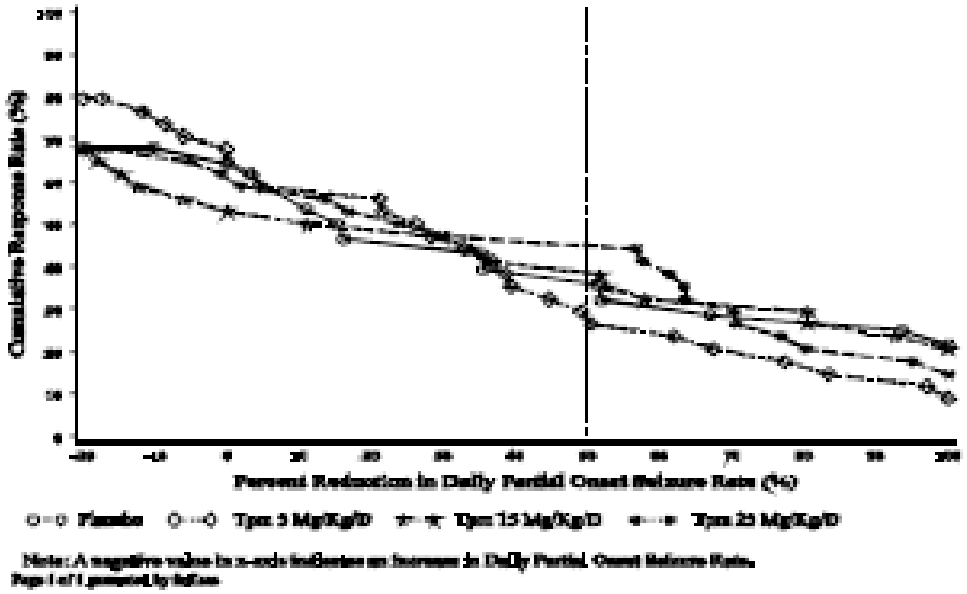
• To allow treatment comparisons based on subjects who had any response rather than only those with at least 50% reduction, the cumulative response rate was plotted against the percent to the range of –20% (representing an increase in 20%) to 100% (seizure free) (see the following figure). This presentation also showed a similar response rate in each of the 4 treatment groups.

Figure 4: Cumulative Response Rate for the Daily Percentage Reduction in POS Seizure Rate During the Double-Blind Phase
(Study TOPMAT-PEP-3001: Modified Intent-to-Treat Analysis Set)



• The proportions of subjects who were treatment responders with regard to all seizure types were similar to those for POS, showing no difference between treatment group.

Seizure Rate for All Seizures Based on vEEG

• The median percentage reduction in seizure rate for all seizure types based on vEEG data for each of the topiramate dosages (20.40%, 5.53%, and 23.83% for 25, 15, and 5 mg/kg per day, respectively) was not different from that on placebo (15.68%, $p > 0.9$ for all comparisons).

Seizure Rate for POS and All Seizures Based on Subject Take-Home Records

• The median percentage reduction in daily POS rate based on subject take-home records for each of the topiramate dosages (15.79%, 0.08%, and 29.63% for 25, 15, and 5 mg/kg per day, respectively) was not different from that on placebo (9.87%, $p>0.4$ for all comparisons.

• The median percentage reduction in seizure rate for all seizure types based on subject take-home records for each of the topiramate dosages (25.00%, 5.69%, and 22.22% for 25, 15, and 5 mg/kg per day, respectively) was not different from that on placebo (9.87%, $p > 0.2$ for all comparisons.

Additional DNP Requested Efficacy Analyses of Primary Efficacy Endpoint and Other Clinical Relevant Endpoints

Many additional post-hoc, exploratory analyses were conducted regarding the primary efficacy endpoint and other relevant efficacy endpoints. These analyses also looked at the absolute change in seizure rates and studied completer and patient with varying quanitities of vEEG data (e.g,, at least 48 hrs, 24-48 hrs, 24 hrs, etc) and also countable baseline vEEG seizure rates, and also these same

analyses based upon diary data and calculated daily seizure rates (DSR). Unfortunately none of these additional, DNP requested analyses provided much insight into why this study may have failed except one that showed that the DSR was quite variable when different methodological approaches (vEEG, DSR by seizure diary over a prolonged period vs only last 2 days of baseline and historical recollection of DSR, etc) were used to assess DSR.

When one looks at the following table of the DSR by different methods and time period for characterizing the partial DSR for individuals who had baseline/screening data collected and then were treated with placebo, it is apparent that in many instances there appears to be a poor correlation of the actual DSR by different approaches including throughout and at the end of treatment. In some instances there are very marked discrepancies in DSR and also instance of when the DSR at the final end of study vEEG DSR is considerably higher than at baseline.

Output LEFF18: Listing of Daily Partial Onset Seizure Rates Based on Seizure Log and Video EEG
(Study TOPMAT-PEP-3001: Modified Intent-to-Treat Analysis Set)

Subject Number	Dsr in the 3-month Retrospective Baseline (computed Number of Days)*	Baseline Dsr Slog - Whole Baseline Period (Number of Days)	Baseline Dsr Slog - Last 2 Days of Baseline Period (Number of Days)	Baseline Dsr Veeg (duration of Veeg in Days)	Db Dsr Veeg(duration of Veeg in Days)	Db Dsr Slog - Last 2 Days of the Db Phase (Number of Days)	Db Dsr Slog - Whole Db Phase (Number of Days)
Treatment Group: Placebo							
300043							
300063							
300171							
300188							
300218							
300241							
300247							
300248							
300278							
300331							
300398							
300412							
300415							
300421							
300462							
300474							
300477							
300478							
300495							
300500							
300505							
300510							
300606							
300636							
300637							
300673							
300685							
300691							

6.1.5 Clinical Microbiology

- Not applicable

6.1.6 Efficacy Conclusions

A formal statistical review was not conducted because everyone agreed that the pivotal study was clearly negative and there was no suggestion of efficacy of topiramate.

Sponsor Efficacy Conclusions

• The percent reduction from baseline in daily POS in the topiramate 25-mg/kg per day group was not statistically significantly different from that in the placebo group (p=0.967). Median percent reductions from baseline in daily POS rate with topiramate 5, 15, and 25 mg/kg per day were 23.83, 5.53, and 20.40, respectively, versus 13.06 for placebo.

• Following the step-down procedure, the lower dosages used in the study were not formally tested, but nominal p values and median percent reductions indicated neither a treatment effect nor a dose relationship.

• All analyses of the primary end point, including additional adjustments and sensitivity analyses, were consistent in that the small reduction in daily POS rate with topiramate 25 mg/kg per day versus placebo was not significantly different, and there was no indication of a treatment effect with the lower dosages.

• Findings for all secondary end points were similar to those for the primary end point, with no apparent differences between topiramate and placebo treatments.

Reviewer Efficacy Conclusions

- I agree with the sponsor's conclusions that the randomized, double-blinded, placebo-controlled study 3001 did not indicate that topiramate was effective in controlling partial onset seizures in this very young population.

- Neither did many additional,DNP-requested, post-hoc, exploratory efficacy analyses of the primary efficacy endpoint and other efficacy endpoints of interest even come at all close (e.g., approaching a p value of ≤ 0.10) toward suggesting efficacy of topiramate in this population for this indication.

- Considering that many neurologists "believe" that topiramate is effective for this indication in this population, one has to think that the failure to demonstrate efficacy in this study was either because : 1) topiramate is not really effective for this indication in this young population for unknown./unclear reasons; or 2) there was a type 2 error in which the study did not show efficacy despite the fact that topiramate is really effective. This latter possibility may perhaps be related to several study design issues/concerns.

- The sponsor was asked to address possible reasons that this study may have failed considering that topiramate really is effective. However, the sponsor did not provide any significant insight into this issue.

- I speculate that there are several reasons why results of this study could have been a type 2 error in which study design issues could have accounted for this failure. It is possible that pharmacodynamic steady state was not achieved. In theory, the patients randomized to the highest topiramate dose (25 mg/kg/day) in this relatively short study (20 days) would just have been approaching and may not have even achieved pharmacokinetic (PK) steady state considering the titration rate. It is not know. how long it takes to achieve pharmacodynamic steady state with topiramate treatment once PK steady state has been achieved. Results from our experience with another anticonvulsant (b) (4) suggested that pharmcodynamic steady state was not achieved soon after PK steady state was achieved because efficacy was progressively increasing throughout the study many weeks after titration ceased and after PK steady state was achieved.

  The pre-treatment/baseline daily seizure rate (DSR) was not similar in all the randomized groups. The median DSR in the placebo and 5 mg/kg/d groups was 6.4 and 6.8 respectively, but the median DSR was 8.3 in the 15 mg/kg/d group and 10.0 in the 25 mg/kg/d group. Thus, surprisingly despite randomization, for unclear reasons it appeared that the patients randomized to the 2 highest doses of topiramate had greater seizure rates. This observation would seem to bias efficacy results against the highest doses in which patients had greater DSRs and perhaps more severe epilepsy.

  Another potential problem may have been the outcome measure (e.g. vEEG) used for the primary efficacy endpoint. The use of vEEG by a blinded reader theoretically appears to be a good outcome measure for assessing It is not clear that vEEG has been validated as an appropriate and reliable efficacy, especially in very young patients nor that there is a clear method for reliably quantifying DSRs in such a young population.

- The listing of DSR in different individual randomized to placebo shows that the DSR can be quite variable and that it is not clear how well diary data correlates with vEEG data. Furthermore, seizure frequency is not necessarily linear and collecting data over a short period (e.g. if less than 24 hours) and proportionately estimating the DSR from short period can be problematic and introduce noise to the efficacy measurement.

- Different inclusion criteria for DSR were applied that could allow a patient to enroll and not have the requisite desired DSR. In addition, the baseline vEEG was read locally by different people than those reading the post-treatment vEEG and this can introduce more variance to the measurments and even allow patients to be treated who did not have the minimal DSR by vEEG.

- Finally, the sponsor powered the study based primarily on a treatment effect of 37 % mostly from adult data when a small study of pediatric patients from 2-16 years showed a treatment effect of 23 %.

- Altogether, many these issue could have contributed to a failed study result for topiramate by study design problems/issues.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Reviewer Overview and Perspective of Safety Analyses

The safety of topiramate in infants (1-24 months old) was derived from 3 studies (TOPMAT-PEP-3001, the randomized, double-blind, placebo-controlled study, and TOPMAT-PEP- 3002, the relatively short PK study, and the open-label extension of these studies) At the Pre-NDA meeting and after this meeting, significant feedback was given to the sponsor (by the DNP and particularly this reviewer) about the nature and format of various, desired safety analyses. In addition, various safety analyses were requested during the review of this NDA. Overall, the sponsor did a good job in providing desired safety analyses and in the format requested. The result of these safety analyses was the some novel/unique toxicities were observed (that had not previously been observed). Some other, noteworthy toxicities (previously recognized as occurring in adults and older pediatric patients) were also shown to occur in this population with either a greater frequency and/or greater severity.

Some analyses presented by the sponsor for the open-label extension dataset shows groups according to the treatment group in either core study (PEP-3001 for placebo or TPM or PEP-3002 TPM) or for patients who were not enrolled in either core study before entry into the open0-label extension study but who entered the open-label study directly (i.e., PEP-3001 shunt).

The sponsor noted that an adverse event was defined as any untoward medical occurrence, such as intercurrent illness or injury, which occurred during the study. Adverse events (verbatim terms) were coded using the TWA92 dictionary, a modified version of the World Health Organization Adverse Reaction Terminology (WHOART) dictionary.

All adverse events that occurred between the first and the last study-related procedure were reported. These were assessed at each study visit as well as through the subject take-home records in which adverse events seen and action taken were described by the subject's parent (or legally acceptable representative). Information recorded for each adverse event included description, dates of onset and resolution (if applicable), investigator's assessment of severity (mild, moderate, or severe), investigator's assessment of relationship to the study medication (not related, doubtful, possible, probable, or very likely), and whether or not the adverse event was serious or treatment limiting. A treatment-emergent adverse event was any adverse event that was new (i.e., after first dose date) in onset or was aggravated in severity or
frequency following treatment.

Serious adverse events were defined as any event that was fatal or immediately life-threatening, persistently or significantly disabling, resulted in or prolonged an existing hospitalization, congenital anomaly/birth defect, or required medical or surgical intervention to prevent permanent sequelae or any of the previously mentioned outcomes. Serious adverse events that occurred between the first study-related procedure and 30 days after the last study-related procedure were reported.

7.1.1 Deaths

PK Study TOPMAT-PEP-1002 Open-Label Treatment (Core) Phase

There were no deaths during the core phase of this study

Study TOPMAT-PEP-3001 Double-Blind (Core) Phase

There were no deaths during the double-blind treatment phase of the study. One subject (300299), a 6-month-old male who was randomized to the topiramate 5 mg/kg/d treatment group, died due to staphylococcaemia, which began after the last dose of study drug. A brief description of this subject follows here.

Subject 300299 (5 mg/kg/d topiramate; Poland; Death: sepsis; Serious adverse event leading to discontinuation: hematemesis):
This 6-month-old, 7.5-kg, white male had a medical history of POS, psychomotor delay, gastroesophageal reflux, cryptochordism, and atrial-septal defect. On Day 6, the subject had hypoproteinemia, peripheral edema, and infection viral, bacterial, and fungal. On Day 10, while receiving liquid topiramate 10.7 mg/kg/d (16 mL/d), he had hematemesis for 3 days, which led to hospitalization. The investigator considered the event serious, severe, and possibly related to the study medication. Study medication was stopped the same day, and the subject was withdrawn from the study. On Day 12, the patient had recovered from the hematemesis. On an unknown date, possibly within 30 days after the subject's discontinuation from the trial, he had staphylococcemia (WHOART: sepsis) for an unknown duration, which resulted in hospitalization and led to the death of the patient on an unspecified date. The investigator considered the death to have a doubtful relationship to study medication. [Manufacturer's Control No: PL-JNJ-FOC-20060101629(1) and PL-JNJ-FOC-20060110114(1)]

Studies TOPMAT-PEP-1002 and -3001 Integrated Open-Label Extension

There were 8 deaths during the open-label extension of Study TOPMAT-PEP-3001 and none in Study TOPMAT-PEP-1002. Six subjects in the "PEP-3001 TPM" analysis category died: Subject 300263 (gastroenteritis and dehydration), Subject 300621 (pneumonia), Subject 300648 (cardio-respiratory arrest, pneumonia aspiration), Subject 300701 (pneumonia, viral infection, brain edema, and pulmonary sclerosis), Subject 300703 (aspiration, respiratory failure), and Subject 300704 (gastrointestinal infection, septic shock). Two subjects in the "PEP-3001 shunt" analysis category died: Subject 300194 (pneumonia) and Subject 300017 (cardio-respiratory arrest).

All adverse events with an outcome of death were considered by the investigator to be "not related" or to have a "doubtful" relation to study medication. Brief descriptions of each subject who died appear below here. Full narratives were also provided.

Subject 300263 ("PEP-3001 TPM" analysis category; India; Death: gastroenteritis (acute gastroenteritis) and dehydration (dehydration); Special safety concerns: poor growth, acidosis, and oligohidrosis):
This 8-month-old, 6.5-kg, "other race" male had a medical history that included delayed mental and motor age, microcephaly, and epilepsy. The subject had metabolic acidosis on Day 19 (CO_2 11 mmol/L) that persisted. After completing the core double-blind phase (topiramate 25 mg/kg/d group), the subject entered the open-label extension phase on Day 21. The subject had poor growth by measured weight on Day 98, a the weight z-score decrease on Day 109 (6.7 kg, z-score: −3.9971), while the subject was receiving liquid topiramate 24.2 mg/kg/day, triggered a special safety concern of poor growth. On Day 182, the subject had severe gastroenteritis and dehydration that led to a 1-day hospitalization on Day 183. The diarrhea and vomiting persisted, and the subject died on Day 184. The investigator considered the gastroenteritis and dehydration to be unrelated to the study medication. [Manufacturer's Control No.: IN-JNJFOC-20060800608(5)]

Subject 300621 ("PEP-3001 TPM" analysis category; India; Death: pneumonia; Special safety concerns: poor growth, acidosis, and rash):
This 3-month-old, 6-kg, "other race" male had a medical history that included hypertonia, delayed development, and epilepsy. After completing the double-blind (core) treatment phase (topiramate 25 mg/kg/d group), the subject entered the open-label extension phase on Day 20. On Day 19, while receiving liquid topiramate 24.6 mg/kg/day (30 mL/day), the subject had acidosis (CO_2 12 mmol/L), for
which he received alkali treatment; the event persisted until the subject's death. The subject's weight z-score decreased on Day 19 (6.1 kg, z-score: -0.7521) from screening (Day -1) and continued to be decreased until Day 67 (6.2 kg, z-score: -1.7742). On Day 73, while receiving liquid topiramate 29 mg/kg/d (36 mL/d), he was hospitalized due to pneumonia. The subject developed severe respiratory failure and required mechanical

ventilation and intravenous fluids, antibiotics, and anticonvulsants. The subject was discharged from the hospital on Day 91. On Day 96, the subject experienced persistent maculopapular rash all over his body. On Day 97, while still receiving liquid topiramate 29 mg/kg/d (36 mL/d), he again developed pneumonia. The investigator advised hospitalization, but it was refused. On Day 98, the subject died due to pneumonia. The investigator considered the pneumonia to be unrelated to study medication. [Manufacturer's Control No.: IN-JNJFOC-20060900806(3)]

Subject 300648 ("PEP-3001 TPM" analysis category; India; Death: cardiac arrest (cardio pulmonary arrest) and pneumonitis (aspiration pneumonitis); Serious adverse events: bronchospasm (bronchiolitis) and pneumonia :

This 8-month-old, 4.8 kg, "other race" female had a medical history that included delayed development and epilepsy. After completing the double-blind (core) phase (topiramate 15 mg/kg/d group), the subject entered the open-label extension phase on Day 21. On Day 12, while receiving liquid topiramate 14.6 mg/kg/d (7 mL/d), the subject had bronchospasms that led to hospitalization on Day 13. The event resolved on Day 14, when the subject was discharged from the hospital. On Day 20, the subject developed pneumonia and was hospitalized on Day 21. The event resolved on Day 28 when the subject was discharged from the hospital. No dosing information is available after Day 164. On Day 200, the subject died of cardiac arrest and pneumonitis. The investigator considered the events to be unrelated to study medication. [Manufacturer's Control Nos.: IN-JNJ-FOC-20060806634(4), IN-JNJ-FOC-20060903282(4), and IN-JNJ-FOC-20070301639(1)]

Subject 300701 ("PEP-3001 TPM" analysis category; Russia; Death and serious adverse events: pneumonia (acute pneumonia), oedema cerebral (cerebral edema), pneumosclerosis (pulmonary sclerosis), and infection viral (acute viral infection); Special safety concern: acidosis):

This 16-month-old, 8.9-kg, white male had a medical history that included hypotonia, spastic tetraparesis, microcephaly, psychomotor and psychic development delay, and epilepsy. After completing the core double-blind phase (topiramate 15 mg/kg/d group), the subject entered the open-label extension phase on Day 21. Between the 4th month and the time of his death, while receiving sprinkle topiramate 28.4 mg/kg/d (250 mg/d), he experienced pneumosclerosis that led to hospitalization of unknown duration. On Day 106, while receiving sprinkle topiramate 27.2 mg/kg/day, the subject had low serum CO_2 at 14 mmol/L, which triggered a special safety concern of acidosis. During the 5th month of the study, he was hospitalized (again for unknown duration) for infection viral and pneumonia. On Day 178, while receiving sprinkle topiramate 28.8 mg/kg/d (300 mg/d), he experienced edema cerebral and was admitted to an intensive care unit on Day 179. He died on Day 180. An autopsy showed pneumosclerosis and upper lobar pneumonia (right side). The investigator considered these events to be doubtfully related to study medication. [Manufacturer's Control No.: RU-JNJFOC-20070401022(6)]

Subject 300703 ("PEP-3001 TPM" analysis category; Russia; Death: aspiration (aspiration syndrome) and respiratory insufficiency (acute respiratory insufficiency); Serious adverse events: bronchitis (acute broncho obstructive syndrome), aspiration (aspiration syndrome) and respiratory insufficiency (acute respiratory insufficiency); Special safety concerns: poor growth and hyperammonemia):

This 6-month-old, 6.7-kg, white male had a medical history that included bradypnea aspirational syndrome, bradycardia, microcephalus, developmental delay, and epilepsy. After completing the core double-blind phase (topiramate 25 mg/kg/d group), the subject entered the open-label extension phase on Day 20. The subject's weight z-score decreased on Day 10 (6.8 kg, z-score: -1.6500) from Day -6 and remained below -1. He experienced the following serious adverse events that required hospitalization during the course of the study: bronchitis on Day 6 while receiving liquid topiramate 6 mg/kg/d, and convulsions aggravated on Day 33, apnea on Day 35, and bronchitis on Day 36 while receiving sprinkle topiramate 21.1 mg/kg/d. On Day 38, while receiving both liquid and sprinkle topiramate 27.8 mg/kg/day, the subject had high a serum ammonia level at 150 µmol/L, which triggered a special safety concern of hyperammonemia; serum ammonia levels were within normal limits at all other measurements. On Day 241, he was hospitalized for aspiration and respiratory insufficiency, at which time topiramate was discontinued. The subject died from these events on Day 242. The investigator considered the events leading to death to be doubtfully related to the study medication. [Manufacturer's Control No.: RU-JNJFOC-20061002525(4) and RU-JNJFOC-20070600892(3)]

Subject 300704 ("PEP-3001 TPM" analysis category; Ukraine; Death: gastroenteritis (acute gastrointestinal infection), circulatory failure (septic shock); Special safety concerns: hyperammonemia and acidosis):
This 9-month-old, 7-kg, white male had a medical history that included influenza, acute bronchitis, microcephaly, strabismus convergence, spastic tetraparesis, mental retardation, and epilepsy. After completing the core double-blind phase (topiramate 25 mg/kg/d group), the subject entered the open-label extension phase on Day 21. On Day 66, adverse events of hyperammonemia of moderate severity and acidosis of mild severity were reported. On Day 66, the subject's ammonia level was 154 µmol/L (normal: 10-64 µmol/L), CO_2 was 16 mmol/L (normal: 18-27 mmol/L), and protein was 77 g/dL (normal: 56-74 g/dL), and his respiration rate was 45 breaths/minute; chloride level was normal. On Day 68, while receiving sprinkle topiramate 27.8 mg/kg/d (250 mg/d), the subject was hospitalized for gastroenteritis. On Day 69, he developed circulatory failure (verbatim: "septic shock") and died. The investigator considered the hyperammonemia and acidosis to be probably related to the study medication and the acute gastrointestinal infection and septic shock to be doubtfully related to the study medication. [Manufacturer's Control No.: UA-JNJFOC-20061205774(1)]

Subject 300194 ("PEP-3001 Shunt" analysis category; United States; Death: pneumonia); Special safety concern: poor growth):
This 3-month-old, 4.8-kg, white female had a medical history that included inability to suck or swallow and hyperimmunoglobulin E syndrome. The epilepsy history revealed partial evolving to secondary generalized seizures and partial seizures. The subject entered the open-label extension phase directly (Day 1). The subject's weight z-score continued to be decreased from Day -1 (4.8 kg, z-score: -1.3852), to −1.5807 (5.5 kg) on Day 50, to a low on Day 85 (5.3 kg, z-score: -2.5810). On Day 141, while receiving an unknown dosage of study medication [last known dose was 60 mg/kg/d (66 mL/d) recorded on Day 84], the subject was hospitalized for pneumonia and was treated with antibiotics. While hospitalized, the subject's care was changed to palliative only. She was released from the hospital on Day 147 and died at home on Day 153. The investigator considered the pneumonia to be doubtfully related to the study medication. [Manufacturer's Control No.: US-JNJFOC-20061003092(3)]

Subject 300017 ("PEP-3001 Shunt" analysis category; United States; Death: cardiac arrest (cardiopulmonary arrest); Serious adverse events: pneumonia (aspiration pneumonia), respiratory disorder (tachypnea), anemia (anemia), and granulocytopenia (neutropenia)):
This 10-month-old, 10.8-kg, white female had a medical history that included viral upper respiratory infection, encephalopathy, and panhypopituitarism. The epilepsy history revealed partial evolving to secondary generalized, generalized tonic-clonic, tonic, partial, and gelastic seizures. The subject entered the open-label extension phase directly (Day 1). On Day 5, the subject was hospitalized with pneumonia and treated with antibiotics. She was discharged from the hospital on Day 8 and rehospitalized on Day 13 for respiratory disorder (tachypnea) and pneumonia and was treated again with antibiotics. On Day 36, while still hospitalized and receiving study medication, the subject experienced SAEs of anemia and granulocytopenia (neutropenia). She was discharged on Day 57. On Day 70, the subject had cardiac arrest and died before she could be hospitalized. The dose of topiramate from Day 50 through Day 70 is not known because the subject diary was destroyed; the last reported dose on Day 49 was 4.9 mg/kg/d (12 mL/d). The investigator considered all events to be doubtfully related to the study medication. [Manufacturer's Control Nos.: US-JNJFOC-20050602072(7) and US-JNJFOC-20050801140(1)]

Reviewer Comment

- It is difficult to conclude that topiramate was a direct or immediate cause of death in any of these cases. However, it is interesting to note that all of the patients who died had experienced infection and also some of them (Subjects #300621, 300701, 300704,) also experienced metabolic acidosis. Considering that the controlled study showed that patients treated with topiramate experienced an increased incidence of infections and metabolic acidosis compared to those treated with placebo, it is intriguing to speculate whether the increased risk for infections may be related to the metabolic acidosis and some alteration of immune function and "resistance," and whether the development of these adverse reactions contributed in any way to the fatal outcome.

7.1.2 Other Serious Adverse Events

Study TOPMAT-PEP-1002 Open-Label Treatment (Core) Phase
• One or more SAEs were reported for 6 subjects during the open-label treatment (core) phase. The most frequently reported were infection-related SAEs, including infection in Subject 101022 (3 mg/kg/d group), infection viral and upper respiratory tract infection in Subject 101048 and infection viral in Subject 101144 (15 mg/kg/d group), upper respiratory tract infection in Subject 101102 and urinary tract infection in Subject 101070 (25 mg/kg/d group).

• Subject 101092 in the 3 mg/kg/d group and Subject 101144 in the 15 mg/kg/d group had convulsions aggravated reported as SAEs, and Subject 101092 also had SAEs of splenomegaly and hepatomegaly.

• **None of the SAEs were considered by the investigator to be related to study medication.** One subject (101144) discontinued from the study due to SAEs of upper respiratory tract infection and convulsions aggravated.

Study TOPMAT-PEP-3001 Double-Blind (Core) Phase
• Treatment-emergent SAEs occurred in 8% of topiramate-treated subjects and 8% of placebo-treated subjects.

• Among the topiramate-treated subjects, most serious adverse events were respiratory and/or infection related. For the placebo group, most were related to increased seizures. All SAEs were resolved by study end.

• Treatment-emergent SAEs in 3 of the 9 topiramate-treated subjects were considered by the investigator to be possibly or probably related to study medication: hematemesis in Subject 300299 (5 mg/kg/d group); acidosis, respiratory disorder, and hyperammonemia in Subject 300276 (15 mg/kg/d group); and bronchospasm in Subject 300703 (25 mg/kg/d group).

• SAEs resulted in study discontinuation for 2 subjects treated with topiramate: Subject 300299 in the 5 mg/kg/d group (hematemesis) and Subject 300276 in the 15 mg/kg/d group (hyperammonemia). One subject in the placebo group (Subject 300691) discontinued due to an SAE of convulsions aggravated.

Studies TOPMAT-PEP-1002 and -3001 Integrated Open-Label Extension

Table 9 summarizes SAEs for the Integrated Open-Label Extension Safety Analysis Set and shows groups according to the previous treatment assignment in either core study or open-label extension study.

• In the integrated analysis set (including events already described above that occurred during the core phases), treatment-emergent SAEs occurred in 40% of subjects. The most common SAEs involved respiratory system disorders (19% overall), followed by central and peripheral nervous system disorders (12% overall), metabolic and nutritional disorders (9% overall), and resistance mechanism disorders (9% overall).

• Most of the treatment-emergent SAEs were not treatment limiting, were considered by the investigator to be unrelated or of doubtful relation to study medication, and were known to have resolved.

Table 9: Treatment-Emergent Serious Adverse Events by Body System and Preferred Term - Core Phase and Open-Label Extension Phases Combined (TOPMAT-PEP-1002 and TOPMAT-PEP-3001 Integrated OL Extension: Safety Analysis Set)

WHO Body System WHO Preferred Term	PEP-1002 (N=50) n (%)	PEP-3001 PBO (N=36) n (%)	PEP-3001 TPM (N=108) n (%)	PEP-3001 Shunt (N=90) n (%)	Total (N=284) n (%)
Total no. subjects with serious adverse events	20 (40)	15 (42)	46 (43)	34 (38)	115 (40)
Respiratory system disorders	11 (22)	7 (19)	17 (16)	20 (22)	55 (19)
Pneumonia	4 (8)	4 (11)	8 (7)	10 (11)	26 (9)
Bronchitis	2 (4)	0	9 (8)	3 (3)	14 (5)
Upper resp tract infection	2 (4)	1 (3)	3 (3)	6 (7)	12 (4)
Pharyngitis	1 (2)	1 (3)	2 (2)	3 (3)	7 (2)
Bronchospasm	1 (2)	1 (3)	2 (2)	1 (1)	5 (2)
Pneumonitis	0	1 (3)	1 (1)	1 (1)	3 (1)
Stridor	1 (2)	0	0	2 (2)	3 (1)
Aspiration	0	0	1 (1)	0	1 (<1)
Laryngitis	0	0	1 (1)	0	1 (<1)
Pulmonary sclerosis	0	0	1 (1)	0	1 (<1)
Respiratory disorder	0	0	0	1 (1)	1 (<1)
Respiratory insufficiency	0	0	1 (1)	0	1 (<1)
Centr & periph nerv syst disorders	5 (10)	4 (11)	15 (14)	11 (12)	35 (12)
Convulsions aggravated	3 (6)	3 (8)	12 (11)	9 (10)	27 (10)
Convulsions grand mal	3 (6)	2 (6)	0	3 (3)	8 (3)
Encephalopathy	0	1 (3)	1 (1)	0	2 (1)
Ataxia	0	0	1 (1)	0	1 (<1)
Convulsions	0	1 (3)	0	0	1 (<1)
Dizziness	0	0	0	1 (1)	1 (<1)
Fever convulsions	0	0	0	1 (1)	1 (<1)
Gait abnormal	0	0	1 (1)	0	1 (<1)
Meningitis	0	0	1 (1)	0	1 (<1)
Oedema cerebral	0	0	1 (1)	0	1 (<1)
Metabolic and nutritional disorders	6 (12)	2 (6)	11 (10)	7 (8)	26 (9)
Dehydration	4 (8)	1 (3)	3 (3)	3 (3)	11 (4)
Acidosis	0	1 (3)	4 (4)	2 (2)	7 (2)
Hyperammonaemia	2 (4)	0	2 (2)	0	4 (1)
Growth retarded	0	0	2 (2)	1 (1)	3 (1)
Cachexia	0	0	1 (1)	0	1 (<1)
Hypokalaemia	0	0	1 (1)	0	1 (<1)
Weight decrease	0	0	0	1 (1)	1 (<1)
Resistance mechanism disorders	7 (14)	2 (6)	11 (10)	5 (6)	25 (9)
Infection viral	5 (10)	0	6 (6)	1 (1)	12 (4)
Infection	2 (4)	0	4 (4)	2 (2)	8 (3)
Otitis media	1 (2)	0	1 (1)	1 (1)	3 (1)
Sepsis	0	2 (6)	0	1 (1)	3 (1)
Gastro-intestinal system disorders	2 (4)	5 (14)	10 (9)	7 (8)	24 (8)
Gastroenteritis	2 (4)	3 (8)	7 (6)	3 (3)	15 (5)
Diarrhoea	0	1 (3)	0	3 (3)	4 (1)
Enterocolitis	0	1 (3)	1 (1)	1 (1)	3 (1)
Vomiting	0	0	2 (2)	1 (1)	3 (1)
Gastroesophageal reflux	0	1 (3)	0	1 (1)	2 (1)
Gastritis	0	0	1 (1)	0	1 (<1)
Body as a whole - general disorders	3 (6)	1 (3)	8 (7)	5 (6)	17 (6)
Fever	1 (2)	1 (3)	5 (5)	4 (4)	11 (4)
Injury	0	0	2 (2)	0	2 (1)
Adverse event NOS	1 (2)	0	0	0	1 (<1)
Drug level increased	1 (2)	0	0	0	1 (<1)
Fatigue	0	0	1 (1)	0	1 (<1)
Unexpected therapeutic effect	0	0	0	1 (1)	1 (<1)

(Continued)

Table 9 (Continued)

Urinary system disorders	1 (2)	0	4 (4)	4 (4)	9 (3)
Urinary tract infection	1 (2)	0	2 (2)	2 (2)	5 (2)
Pyelonephritis	0	0	2 (2)	1 (1)	3 (1)
Renal calculus	0	0	0	1 (1)	1 (<1)
Psychiatric disorders	1 (2)	0	5 (5)	2 (2)	8 (3)
Somnolence	1 (2)	0	3 (3)	2 (2)	6 (2)
Anorexia	0	0	2 (2)	1 (1)	3 (1)
Red blood cell disorders	1 (2)	0	1 (1)	2 (2)	4 (1)
Anaemia	0	0	1 (1)	2 (2)	3 (1)
Splenomegaly	1 (2)	0	0	0	1 (<1)
Liver and biliary system disorders	1 (2)	0	1 (1)	1 (1)	3 (1)
Hepatic enzymes increased	0	0	0	1 (1)	1 (<1)
Hepatocellular damage	0	0	1 (1)	0	1 (<1)
Hepatomegaly	1 (2)	0	0	0	1 (<1)
Cardiovascular disorders, general	0	0	2 (2)	0	2 (1)
Cardiomegaly	0	0	1 (1)	0	1 (<1)
Circulatory failure	0	0	1 (1)	0	1 (<1)
Heart rate and rhythm disorders	0	0	1 (1)	1 (1)	2 (1)
Cardiac arrest	0	0	1 (1)	1 (1)	2 (1)
Musculo-skeletal system disorders	0	1 (3)	1 (1)	0	2 (1)
Bone development abnormal	0	0	1 (1)	0	1 (<1)
Osteomyelitis	0	1 (3)	0	0	1 (<1)
Neoplasms	1 (2)	0	1 (1)	0	2 (1)
Brain neoplasm benign	1 (2)	0	0	0	1 (<1)
Neoplasm nos	0	0	1 (1)	0	1 (<1)
White cell and RES disorders	0	0	0	2 (2)	2 (1)
Granulocytopenia	0	0	0	1 (1)	1 (<1)
Leucopenia	0	0	0	1 (1)	1 (<1)
Lymphadenopathy	0	0	0	1 (1)	1 (<1)
Neonatal and infancy disorders	1 (2)	0	0	0	1 (<1)
Psychomotor development impaired	1 (2)	0	0	0	1 (<1)
Platelet,bleeding & clotting disorders	0	0	0	1 (1)	1 (<1)
Thrombocytopenia	0	0	0	1 (1)	1 (<1)
Skin and appendages disorders	0	0	1 (1)	0	1 (<1)
Rash	0	0	1 (1)	0	1 (<1)
Vascular (extracardiac) disorders	0	0	1 (1)	0	1 (<1)
Arteritis	0	0	1 (1)	0	1 (<1)

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Cross-reference: Mod5.3.5.2\TOPMAT-PEP-1002_3001OLE\Table 14

Reviewer Comment

- There were no specific treatment emergent (TE) -SAEs that stood out as being frequent and more common in any topiramate dose group or the overall topiramate treatment group compared to placebo in the short-term, placebo-controlled study.

- The most common($\geq$ 3 %) TE-SAEs based upon incidence occurring in any of the studies were pneumonia, bronchitis, URI, consulsions aggravated, convulsions grand mal, dehydration, infection viral, infection, gastroenteritis, and fever.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Study TOPMAT-PEP-3001 Double-Blind (Core) Phase
The following table shows the overall profile of dropouts (i.e., patients who discontinued from the study prematurely) in the placebo-controlled study.

Table 5: Study Completion/Withdrawal Information - Double Blind Phase
(Study TOPMAT-PEP-3001: Intent-to-Treat Analysis Set)

	Placebo	TPM 5 mg/kg/d	TPM 15 mg/kg/d	TPM 25 mg/kg/d	All TPM	Total
	(N=37) n (%)	(N=38) n (%)	(N=37) n (%)	(N=37) n (%)	(N=112) n (%)	(N=149) n (%)
Completed	29 (78)	34 (89)	33 (89)	34 (92)	101 (90)	130 (87)
Withdrawn	8 (22)	4 (11)	4 (11)	3 (8)	11 (10)	19 (13)
Adverse event	2 (5)	1 (3)	2 (5)	1 (3)	4 (4)	6 (4)
Subject choice (parent withdrew consent)	1 (3)	0	0	0	0	1 (1)
Other	5 (14)	3 (8)	2 (5)	2 (5)	7 (6)	12 (8)

Note: Percentages calculated with the number of subjects in each group as denominator.
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• Of the 149 subjects who were enrolled and randomized in the double-blind phase of the study (ITT analysis set), 130 (87%) completed it (see table below). The completion rate was higher among subjects randomized to topiramate than to placebo (90% vs.78%).

• In total, 19 subjects (13%) discontinued double-blind treatment, with most discontinuations due to "other" reasons and the percentage withdrawing for "other"reason was highest in the placebo group vs each of the topiramate groups. The "other" reasons as given by the investigator included meeting the escape criterion (7 subjects) and doubling of seizure rate (i.e., met escape criterion, 1 subject), as well as multiple seizures, more than 1 dose reduction, incorrect dosing, and unknown (1 subject each). One subject was discontinued when consent was withdrawn because of the time involved.

• Six subjects discontinued double-blind treatment because of a treatment-emergent adverse event, which was a serious adverse event in 3 cases. The rates of early withdrawal due to an adverse event were similar in all treatment groups and showed no apparent relationship to the topiramate dose.

Study TOPMAT-PEP-1002 Open-Label Treatment (Core) Phase

The following table shows the overall profile of dropouts (i.e., patients who discontinued from the study prematurely) in the "brief" PK study.

Table 3: Study Completion/Withdrawal Information
(Study TOPMAT-PEP-1002 Core Phase: All Randomized Subjects Analysis Set)

Age Group: 1 to 24 months	TPM 3 mg/kg/day (N=14) n (%)	TPM 5 mg/kg/day (N=13) n (%)	TPM 15 mg/kg/day (N=13) n (%)	TPM 25 mg/kg/day (N=15) n (%)	Total (N=55) n (%)
Completed open-label treatment (core) phase	14 (100)	12 (92)	11 (85)	13 (87)	50 (91)
Withdrawn	0	1 (8)	2 (15)	2 (13)	5 (9)
Lost to follow-up	0	0	0	1 (7)	1 (2)
Adverse event	0	1 (8)	2 (15)	0	3 (5)
Subject choice (parent withdrew consent)	0	0	0	1 (7)	1 (2)

TPM = topiramate
Note: Percentages calculated with the number of subjects in each group as denominator.
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• Of the 55 subjects enrolled, 50 completed the open-label treatment (core) phase.

• Three subjects (5%) discontinued during the open-label treatment (core) phase of the study because of TEAEs.

Studies TOPMAT-PEP-1002 and -3001 Integrated Open-Label Extension

The following table shows the overall profile of dropouts (i.e., patients who discontinued from the study prematurely) in the large, integrated, open-label extension study.

Table 4: Study Completion/Withdrawal Information
(TOPMAT-PEP-1002 and TOPMAT-PEP-3001 Integrated OL Extension: Safety Analysis Set)

	PEP-1002 (N=50) n (%)	PEP-3001 PBO (N=36) n (%)	PEP-3001 TPM (N=108) n (%)	PEP-3001 Short (N=80) n (%)	Total (N=284) n (%)
COMPLETED*	16 (32)	17 (47)	45 (42)	57 (63)	135 (48)
WITHDRAWN DUE TO EARLY STUDY TERMINATION BY SPONSOR	20 (40)	10 (28)	24 (22)	4 (4)	58 (20)
WITHDRAWN PER PROTOCOL	14 (28)	9 (25)	39 (36)	29 (32)	91 (32)
LOST TO FOLLOW-UP	0	0	3 (3)	3 (3)	6 (2)
ADVERSE EVENT	6 (12)	1 (3)	8 (7)	2 (2)	17 (6)
DEATH	0	0	6 (6)	2 (2)	8 (3)
SUBJECT CHOICE(PARENT WITHDREW CONSENT)	5 (10)	5 (14)	8 (7)	12 (13)	30 (11)
OTHER*	3 (6)	3 (8)	14 (13)	10 (11)	30 (11)

Note: Percentages calculated with the number of subjects in each group as denominator.
* One subject (300644) listed as withdrawn with the reason "other" actually completed the study (see Attachment 1.3).
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• An IDMC (safety monitoring committee) initiation meeting was held on 30 September 2005, followed by IDMC safety data review meetings conducted approximately every 3 months until sponsor termination of study in September 2007. The recommendation from each IDMC meeting was "To continue the study unmodified until the next scheduled meeting".

• After the double-blind phase of TOPMAT-PEP-3001 did not demonstrate efficacy, the Sponsor made an assessment of the overall risk/benefit, and decided to end the open-label extension phase early. This decision was discussed with the Food and Drug Administration and IDMC.

• Of the 284 subjects who were enrolled in the open-label extension phase (Safety analysis set), 136 (48%) completed the study.

• Fifty-eight subjects (20%) were withdrawn when the Sponsor prematurely terminated the study in September 2007.

• Ninety subjects (32%) were withdrawn per protocol, with most discontinuations due to withdrawn consent (30 subjects, 11%) or "other" reasons (29 subjects, 10%). For subjects withdrawing due to "other", the reason was most commonly related to lack of efficacy.

• Eight subjects (3%) withdrew from the studies due to death. Seventeen additional subjects (6%) withdrew from the open-label extension phase because of a TEAE. The rates of early withdrawal due to a TEAE were generally similar between analysis categories.

7.1.3.2 Adverse events associated with dropouts

Study TOPMAT-PEP-1002 Open-Label Treatment (Core) Phase

• Three subjects discontinued study medication due to TEAEs (i.e., somnolence, maculopapular rash, viral infection and aggravated convulsions).

• TEAEs that required dosage adjustment were as follows: vomiting and somnolence (3 subjects each), anorexia (2 subjects), convulsions aggravated, diarrhea, and insomnia (1 subject each).

Study TOPMAT-PEP-3001 Double-Blind (Core) Phase

• Six subjects, 4 who received topiramate and 2 who received placebo, discontinued from the double-blind (core) phase because of 1 or more TEAEs.

• For 2 of the 4 topiramate-treated subjects who discontinued, the TEAE (hematemesis, **hyperammoenemia**) aggravated convulsions, rash) leading to discontinuation was serious (i.e., TE-SAEs.

• The TEAEs (rash, aggravated convusions) in the other 2 topiramate-treated subjects who discontinued were non-serious. :

• All treatment-limiting events are known to have resolved following discontinuation of study drug in all subjects but one, who had a skin rash of moderate severity; no follow-up information was available..

• Dose adjustments because of a TEAE were infrequently needed but did occur among subjects receiving topiramate due to anorexia (4 subjects), somnolence (2 subjects), aggressive reaction, ataxia, fatigue, and hyperkinesia (1 subject each).

Studies TOPMAT-PEP-1002 and -3001 Integrated Open-Label Extension

Table 10 summarizes TEAEs leading to discontinuation during the open-label extension for subjects in the Integrated Open-Label Extension Safety Analysis Set.

• Twenty subjects (7%) had TEAEs leading to discontinuation from either the core or open-label extension phases. The most common event leading to discontinuation was convulsions aggravated (6 subjects, 2%); all other events were reported in 1 or 2 subjects only.

• Eight TEAEs leading to discontinuation were considered by the investigator to be unrelated or doubtfully related to study medication. Sixteen TEAEs were considered by the investigator to be at least possibly related to

study medication. The latter group comprised metabolic and nutritional disorders, central and peripheral nervous system disorders, urinary system disorders, psychiatric disorders, and skin and appendages disorders.

• The TEAEs leading to discontinuation were serious (i.e., TE-SAEs) for 8 subjects, as follows : convulsions grand mal, convulsions aggravated, hepatomegaly, splenomegaly, brain neoplasm benign, injury, renal calculus, and convulsions aggravated.

Table 10: Treatment-Emergent Adverse Events Leading to Study Discontinuation - Core Phase and Open-Label Extension Phases Combined (TOPMAT-PEP-1002 and TOPMAT-PEP-3001 Integrated OL Extension: Safety Analysis Set)

WHO Body System WHO Preferred Term	PEP-1002 (N=50) n (%)	PEP-3001 PBO (N=36) n (%)	PEP-3001 TPM (N=108) n (%)	PEP-3001 Shunt (N=90) n (%)	Total (N=284) n (%)
Total no. subjects with adverse events leading to study discontinuation	6 (12)	3 (8)	9 (8)	2 (2)	20 (7) [a]
Centr & periph nerv syst disorders	2 (4)	1 (3)	4 (4)	1 (1)	8 (3)
Convulsions aggravated	1 (2)	1 (3)	3 (3)	1 (1)	6 (2)
Ataxia	0	0	1 (1)	0	1 (<1)
Convulsions grand mal	1 (2)	0	0	0	1 (<1)
Metabolic and nutritional disorders	2 (4)	0	1 (1)	0	3 (1)
Weight decrease	1 (2)	0	1 (1)	0	2 (1)
Calcinosis	1 (2)	0	0	0	1 (<1)
Psychiatric disorders	0	0	3 (3)	0	3 (1)
Anorexia	0	0	2 (2)	0	2 (1)
Somnolence	0	0	1 (1)	0	1 (<1)
Urinary system disorders	1 (2)	0	0	1 (1)	2 (1)
Renal calculus	1 (2)	0	0	1 (1)	2 (1)
Body as a whole - general disorders	0	0	1 (1)	0	1 (<1)
Injury	0	0	1 (1)	0	1 (<1)
Gastro-intestinal system disorders	0	1 (3)	0	0	1 (<1)
Vomiting	0	1 (3)	0	0	1 (<1)
Liver and biliary system disorders	1 (2)	0	0	0	1 (<1)
Hepatomegaly	1 (2)	0	0	0	1 (<1)
Neoplasms	1 (2)	0	0	0	1 (<1)
Brain neoplasm benign	1 (2)	0	0	0	1 (<1)
Red blood cell disorders	1 (2)	0	0	0	1 (<1)
Splenomegaly	1 (2)	0	0	0	1 (<1)
Skin and appendages disorders	0	1 (3)	0	0	1 (<1)
Rash maculo-papular	0	1 (3)	0	0	1 (<1)

[a] The number of subjects with adverse events leading to discontinuation includes 3 subjects (300001, 300504, and 300691) who discontinued from the core phase but entered the open-label extension (see Table 2).
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Cross-reference: Mod5.3.5.2\TOPMAT-PEP-1002_3001OLE\Table 15

7.1.3.3 Other significant adverse events

Safety Findings of Special Interest

The following events, based upon discussion with the DNP, were designated to be safety events of special interest. Analyses of these topics includes laboratory and other assessments in addition to TEAEs. A relatively broad list of predefined PTs of TEAEs that might potentially reflect the event of special interest was typically used to screen for various PTs for these events of special interest. Abnormal tests (e.g., usually a laboratory test for a clinical laboratory analyte and also renal sonograms) were also used to suggest the possibility of the occurrence of an event of special interest.

Oligohidrosis/Hyperthermia

Among the 54 subjects (19%) with a TEAE related to a broad list of PTs possibly reflecting oligohidrosis/hyperthermia, the most common TEAEs were sweating decreased and dehydration (16 subjects each).

Among the 16 subjects (6% overall) with sweating decreased, the event was mild in 13 subjects and moderate in 3 subjects. Three subjects with sweating decreased had their topiramate dose adjusted; none had topiramate stopped temporarily or permanently.

Among the 16 subjects (6% overall) with dehydration, the event was mild, moderate, or severe in 2, 8, and 6 patients, respectively. One subject with dehydration had his or her topiramate dose adjusted; none had topiramate stopped temporarily or permanently.

None of the cases appeared to represent a clear, serious case of oligohydrosis/hyperthermia.

Metabolic Acidosis

During the double-blind (core) phase of Study TOPMAT-PEP-3001, mean change in serum bicarbonate was 0.72, -3.31, -4.07, and -5.15 mmol/L observed for the placebo, 5, 15, and 25 mg/kg/d groups, respectively Ten topiramate-treated subjects had a TEAE, laboratory value, or concomitant treatment indicative of metabolic acidosis (9% vs. none on placebo). Six were detected by lab findings only, 1 was on alkali treatment only, 2 were only reported as a TEAE, and 1 was both a lab finding and a TEAE. For 6 of the 10 topiramate-treated subjects, low serum bicarbonate values without a related TEAE was the event of interest. For 3 of these 6 subjects, the asymptomatic serum bicarbonate presented during topiramate treatment and returned toward normal values following the end of double-blind treatment with topiramate. All but 1 of these subjects entered the open-label extension: Subject 300276 (topiramate 15 mg/kg/d) was hospitalized on Day 18 with metabolic acidosis and on Day 19 was discontinued from the study due to hyperammonemia.

• For the Integrated Open-Label Extension Safety Analysis Set, 33 patients with metabolic acidosis had their topiramate dose adjusted; none had topiramate stopped temporarily or permanently.
– The overall mean change serum in CO_2 concentration was -3.40 mmol/L.
– Overall, 46 subjects (18%) had a shift in bicarbonate concentration from normal or high at pretreatment baseline to low at open-label extension end point.
– Markedly low serum bicarbonate was observed in 115 subjects overall (40%).Sixty-six subjects overall (23%) had persistent (defined as <17 mmol/L at 2 consecutive visits) treatment-emergent decreases in serum bicarbonate.
– Review of the selected narratives showed that although there was a tendency for acidosis to develop early, overall no strict temporal relationship to the start of treatment is apparent. The duration of acidosis varied. Acidosis was detected by routine laboratory assessments and was otherwise free of acute symptoms (e.g., lethargy, vomiting, hyperventilation). Even subjects with bicarbonate of $\leq$ 12 mmol/L were reported as asymptomatic. The lowest bicarbonate levels occurred together with a coinciding acute infectious illness or in subjects who were acidotic at baseline. **In 65 subjects, metabolic acidosis was treated with some form of alkali therapy**. In general, metabolic acidosis improved or resolved with this treatment. Reduction of study

drug dose also had some effect. bicarbonate levels generally stabilized after an initial decrease and usually improved to normal range during the study. Only 30 subjects still had a bicarbonate below 17 mmol/L at their last measurement. When a blood pH was assessed it was usually normal.
– Nine subjects had an isolated aTEAE of renal calculus. In these subjects serum bicarbonate was either normal throughout the entire study or normal during the period prior to and at the time of stone detection.
– Sixty-six subjects had persistent metabolic acidosis. Five subjects had an adverse event of renal calculus concurrently with acidosis. Three of these subjects had persistent acidosis. Three of these 5 subjects also had delayed growth. There were 37 subjects with both persistent acidosis and delayed growth.
– There was 1 report each of hypophosphatemia and hypothyroidism, together with acidosis.
– Overall, metabolic acidosis tended to occur early in treatment but could be detected at any time. The duration varied. Acidosis was asymptomatic from the perspective of changes in vital signs or other acute symptoms and either resolved on its own or could be managed with alkali treatment or dose reductions.

With regard to knowledge about metabolic acidosis in its databases, the sponsor noted that "similar decreases from baseline to endpoint (−4.2 mmol/L) have been reported for adjunctive topiramate therapy in 2,067 patients (1,757 adults and 310 pediatric patients 2 to 16 years old) **during double-blind and open-label studies**." In In In Study YP (the study used to obtain approval of adjunctive treatment of topiramate in partial epilepsy in older pediatric patients (ages 2 to 16 years), mean change in serum bicarbonate was 0.0 mmol/L for placebo and – 3.6 mmol/L (treatment difference/effect = - 3.6 mmol/L or mE /l) for topiramate (target dose of 6 mg/kg/day).[7] The incidence of markedly abnormally low serum bicarbonate (absolute value <17 mmol/L and >5 mmol/L decrease from pretreatment) in the pooled population of 2,067 adults and pediatric subjects who received topiramate in adjunctive epilepsy trials was 15%; these events of low bicarbonate were rarely below 15 mmol/L. They were usually single transient occurrences and did not remain markedly low at the final visit.

Bone-related TEAEs were reported for 33 of the 2,067 subjects (1.6%). Also, observed decreases in serum Bicarbonate in topiramate-treated subjects were rarely symptomatic. In the integrated analysis set for the infant population presented in this ISS, 38% of subjects developed a treatment-emergent serum bicarbonate value at any visit of <17 mmol/L and >5 mmol/L decrease from baseline, and 63 of the 261 subjects (24%) who had a baseline bicarbonate value ≥15 mmol/L had a value <15 mmol/L at any visit.

As in the older population, metabolic acidosis was rarely symptomatic. Among the integrated analysis set, 5 subjects had a TEAE of renal calculus concurrently with metabolic acidosis. Three of these subjects had persistent acidosis. Three of these 5 subjects also had delayed growth. There were 37 subjects with both persistent acidosis and delayed growth. Two subjects with metabolic acidosis had coexisting bone-related adverse events including hypothyroidism and hypophosphatemia.

The frequency, severity, and clinical consequences of metabolic acidosis described in this ISS are generally consistent with the findings of the literature review and postmarketing summary in infants. Bone abnormalities were infrequently reported in the literature and were rarely observed in this infant population.

"Overall, the acidosis in this infant population is more severe than that in older populations" (quoted statement by sponsor). The differences, particularly the increase of treatment-emergent markedly abnormal values and values <15 mmol/L, may be attributable to the higher dosages used in Studies TOPMAT-PEP-1002 and TOPMAT-PEP-3001 (mean daily dose of topiramate in the integrated analysis set was 21.7 mg/kg/d). By comparison, the target topiramate dosage for pediatric subjects 2 to 16 years old in Study YP was 6 mg/kg/d; for the 2,067 subjects in the
pooled adult and pediatric population, topiramate dosage ranged from 200 mg/day to 1,600 mg/day (based upon a 70 kg adult, this dosage ranged from ~ 3-23 mg/kg/day). "**In general, acidosis was successfully managed with alkali treatment and dose reductions" (quoted statement by sponsor).**

Renal Events/Kidney Stones

In the double-blind (core) phase of TOPMAT-PEP-3001, renal events of interest were observed for 9 topiramate-treated subjects on topiramate and 1 placebo-treated subject, all of whom entered the open-label extension. Seven events were detected on renal ultrasound only, 2 as a TEAE only, and 1 was both a TEAE

event and a sonographic finding. The sponsor noted that none of the events reported on renal ultrasound were thought to be indicative of nephrolithiasis.

For the Integrated Open-Label Extension Safety Analysis Set, analysis includes the events observed in the placebo-controlled study and the PK study (1002). Clinical review was performed on the data from 63 subjects programmatically selected using criteria established for the special safety category of renal effects.

– Eleven subjects had renal TEAE alone, 23 had renal sonogram abnormalities alone, 29 had both, and 0 had renal lab abnormalities.
– Among the 40 subjects (14% overall) reporting renal TEAE(excluding urinary tract infections) the most frequent event was renal calculus (14 subjects).
– Among the 14 subjects (5% overall) with specificall "renal calculus," the event was mild, moderate, or severe in 11, 2, and 1 subject, respectively. It was considered by the study investigator to be probably or very likely related to study medication for 10 subjects. Treatment for renal calculi was rarely reported during the study, although 3 subjects with renal calculi had their topiramate dose adjusted and 2 subjects were discontinued from the study.
– The sponsor thought that overall mean increases in BUN or creatinine were small and not clinically relevant.
– The sponsor also noted that no shifts occurred in creatinine levels from low or normal at pretreatment baseline to high at open-label extension end point. Ten patients had a shift in BUN from low or normal to high.
– Markedly high BUN was observed in 2 patients.
– Review of the selected narratives by the sponsor suggest that nephrolithiasis was reported or detected in a total of 18 subjects, generally at Visit 10, approximately 4-5 months into the trial. All patients were believe to be asymptomatic and nephrolithiasis was detected by the routine study sonogram, except for one case where painful micturition was noted but no stone was reported on sonogram. Serum BUN and creatinine were usually normal throughout in subjects with nephrolithiasis. Nephrolithiasis was sometimes associated with nephrocalcinosis and/or hydronephrosis. **Five subjects with a TEAE of renal calculus also had metabolic acidosis**. In 11 subjects, the nephrolithiasis persisted at study end and in 6 subjects it resolved.
– An additional 9 subjects had isolated bladder stone, echos, sediment, or debris in bladder. These could be indicative of an undetected renal stone. It was believed that bladder calculi presumably reflected renal calculi that were detected in the bladder. Overall, the incidence of renal calculi (including renal and bladder calculi) was 7 %. All were detected on renal ultrasound testing and none were clinically symptomatic.
– Seven subjects had mild hydronephrosis detected on ultrasound, possibly indicating an occult stone. Nine subjects had nephrocalcinosis. Four subjects had echopositive signs which were not further described and one, with pre-existing tuberous sclerosis, had a renal cyst. Three subjects had a TEAE of pyelonephritis and 1 of isolated hematuria.
– Generally, nephrolithiasis was acutely asymptomatic and subjects continued in the study without treatment. There did not appear to be a clear effect on serum BUN or creatinine.

The sponsor noted that a total of 32/2,086 (1.5%) adults and children exposed to topiramate as adjunctive epilepsy therapy reported the occurrence of kidney stones. However, unlike the infant clinical program, these studies did not include systematic screening using renal sonograms. The sponsor thought that when renal sonograms are performed in studies of adult and pediatric subjects taking recommended dosages of topiramate, that the incidence of kidney stones appears to be similar to that observed in the integrated analysis set. The sponsor further noted that, the renal effects of topiramate in this study population appear consistent with those in older subjects when renal ultrasounds are used for assessment. Increased incidence of kidney stones has also been reported in the literature in connection with topiramate and metabolic acidosis.

Hepatic

In the double-blind (core) phase of Study TOPMAT-PEP-3001, 4 topiramate-treated subjects had hepatic events of interest (no cases were reported among placebo-treated subjects). Two were reported as TEAEs only and 2 met laboratory criteria only.

For the Integrated Open-Label Extension Safety Analysis Set, analysis includes events described in studies 3001 and 1002. Clinical review was performed on the data from 43 subjects programmatically selected using criteria established for the special safety category of hepatic effects, with results as follows:
– Twenty subjects had TEAEs only, 20 had abnormal lab parameters only, and 3 based on both.
– Among the twenty-three subjects (8%) with TEAEs, the most frequent events were GGT increased and SGOT increased (3% of subjects each). The event for SGOT was mild, moderate, or severe in 7, 1, and 1 subject, respectively. The event for GGT was mild or moderate in 7 and 2 subjects, respectively. One subject with SGOT increased had his or her topiramate dose adjusted; none had topiramate stopped temporarily or permanently. No adverse events of GGT increased resulted in action taken.
– The sponsor noted that mean ALT, AST, GGT, total bilirubin, and direct bilirubin levels changed slightly overall but were not considered clinically relevant.
– The sponsor also summarized that shifts in alkaline phosphatase, ALT, AST, or GGT from normal at pretreatment baseline to high at open-label extension end point were observed in 11, 2, 12, and 23 patients, respectively.
– One subject had a shift in direct bilirubin levels from normal at pretreatment baseline to high at open-label extension end point. One subject had a shift in total bilirubin levels from low at pretreatment baseline to high at open-label extension end point.
– Markedly high ALT, AST, or GGT were observed in 2, 4, and 12 subjects, respectively. Markedly high direct bilirubin was observed in 18 subjects (6%) (the sponsor commented that many of these subjects had a poor quality sample).
– Review of the selected narratives by the sponsor showed that in 18 patients there were elevations in or TEAEs regarding AST and/or ALT with or without involvement of GGT or bilirubin. Elevations in liver function tests (LFTs) were generally not greatly increased over the upper limit of normal (ULN), and were transient. In one case where they persisted, the level was also high at baseline and returned to baseline levels. In all subjects the presence of other AEDs such as phenobarbital, carbamazepine, or VPA was a confounder and samples were sometimes old or hemolyzed. The larger elevations above the upper limit of normal were generally in the presence of acute infectious illnesses or in one case, an overdose of VPA.
– Fifteen subjects had isolated increases in total or direct bilirubin where other LFTs were normal or unremarkable. In 11 of these subjects the abnormal blood sample was hemolyzed and/or too old and the results are questionable. Other time points were normal. Of the remaining 4 subjects, in 3, the bilirubin normalized at the next time point and in the 4th, although there was no follow-up lab assessment, the abnormal results was only very slightly above the normal range and no adverse event was reported.
– Nine subjects had isolated increases in GGT. The increases were generally small and other LFTs remained normal. These subjects were all taking other AEDs and samples were noted sometimes to be hemolyzed.
– There was one case of hepatomegaly on the 5th day of treatment that the investigator believes was pre-existing. There was one case of hepatocellular damage with elevated LFTs in the context of enteroviral meningitis. There was one case of cholecystitis which the investigator considered mild and doubtfully related to study drug and for which no supporting evidence is documented.
– The sponsor noted that, overall, a review of narratives, TEAes and laboratory analysis results did not reveal evidence of a hepatic safety concern for topiramate in this population.

Hyperammonemia and Encephalopathy

In the double-blind (core) phase of Study TOPMAT-PEP-3001, hyperammonemia (serum ammonia 200 mmol/L) was reported for 1 subject (Subject 300276) who was treated with topiramate 15 mg/kg/d and VPA (360 mg/d). This patient was hospitalized on Day 18 following reports of treatment-emergent fever and a lower respiratory tract infection (considered by the investigator to be doubtfully related to the study drug). On Day 19, the subject was reported to have moderate hyperammonemia, which was serious, and led to the discontinuation of study treatment. Hyperammonemia was treated with oral lactulose and sodium benzoate, while valproate was reduced. The event resolved by Day 24, and the investigator considered it to be probably related to study treatment. There was no reported evidence of encephalopathy. This patient did not enter the open-label extension

For the Integrated Open-Label Extension Safety Analysis Set, analysis includes TEAEs described in studies 3001 and 1002 except for the 1 subject described above who did not enter the open-label extension. Clinical

review was performed on the data from 42 subjects programmatically selected according to criteria established for the special safety category of hyperammonemia. After exclusion of 1 subject by the project physician as a false positive, results of the review are as follows :
– Eighteen subjects had TEAEs alone, 12 had lab abnormalities alone, and 12 had both.
– Among the 30 subjects (11%) with TEAEs, 28 subjects (10%) reported TEAEs of hyperammonemia and 4 subjects (1%) reported encephalopathy. Hyperammonemia was mild, moderate, or severe in 15, 11, and 2 subjects, respectively. Four of these events were serious, 1 of which was associated with encephalopathy, and 3 of which were associated with VPA use. Eleven subjects with hyperammonemia had their topiramate dose adjusted; none had topiramate stopped temporarily or permanently. Encephalopathy was mild, moderate, or severe in 1, 2, and 1 subject, respectively. Two subjects with encephalopathy had their topiramate dose adjusted; none had topiramate stopped temporarily or permanently.
– Mean ammonia levels increased slightly overall (6.70 µmol/L) but the sponsor did not consider this change to be clinically relevant
– Twenty-four subjects had a shift in ammonia levels from normal at pretreatment baseline to high at open-label extension end point.
– The sponsor summarized that, overall, markedly high ammonia levels were observed in 24 subjects (8 %).
– Review of the selected narratives by the sponsor showed that thirty of these subjects were also taking VPA at the time of the event. Encephalopathy was rarely reported and all cases were associated with VPA use. The sponsor further noted that ammonia elevations were sometimes in the context of a serious illness and samples were in some cases were thought to be hemolyzed or old, leading to spurious elevated ammonia levels.
– **Ten subjects who were not taking VPA at the time, but were on various other AEDs, had hyperammonemia.** None of the subjects had known underlying metabolic disturbances that may have led to hyperammonemia. The elevations in these patientts were transient, there were supposedgly no symptoms reported, and in general they were not treated. The sponsor commented that "the overall clinical significance of hyperammonemia in this setting is unclear but likely minimal."
– One subject had transient, mild encephalopathy lasting for 2 days, in the absence of any evidence of elevated ammonia or confounders such as concomitant medications, illnesses etc. The investigator considered the event non-serious, mild, and possibly related to topiramate. The subject was on VPA, phenobarbital, and clonazepam.
– The sponsor summarized that, overall, consistent with the known association of hyperammonemia with the concomitant use of VPA and topiramate, there are a number of cases of hyperammonemia in subjects using both medications.

The sponsor provided the following summary of data on ammonia levels in the studies. Mean ammonia levels increased by 6.70 µmol/L for the integrated analysis set. Baseline serum ammonia values were higher for subjects who were receiving VPA than for subjects receiving any concomitant AED other than VPA (median values 30.7 and 28.0 µmol/L, respectively). Median of change in serum ammonia from baseline to open-label extension end point was 9.0 µmol/L for subjects receiving VPA compared with 4.0 µmol/L for subjects receiving any concomitant AED other than VPA. During the double-blind (core) phase of Study TOPMAT-PEP-3001, the small mean increases in ammonia observed in the topiramate 15 and 25 mg/kg/d groups (2.45 and 3.90 µmol/L) were less than that observed in the placebo group (5.32 µmol/L). Mean change from baseline to **core phase end point** (reflecting short-term treatment) was 4.43 µmol/L for all topiramate-treated subjects receiving concomitant VPA compared with -2.81 µmol/L for those not receiving concomitant VPA. For the placebo group, mean change in serum ammonia was 4.20 µmol/L for those receiving concomitant VPA. Thus, in subjects receiving valproate without topiramate, mean increase in ammonia (4.20 µmol/L) was comparable to the mean increase observed in subjects who received valproate in combination with topiramate (4.43 µmol/L), whereas topiramate without concomitant treatment with valproate resulted in a decrease of -2.81 µmol/L.

Hyperammonemia with and without encephalopathy has been reported in topiramate-treated patients. The sponsor noted that "all cases in the Sponsor's database have been associated with valproate polytherapy or confounded by the presence of other concomitant therapies (including carbamazepine, lamotrigine, phenytoin, and phenobarbital) and background medical conditions." **In the integrated analysis set, although the majority of cases of hyperammonemia occurred in subjects using concomitant VPA and TPM, several cases of hyperammonemia occurred in patients taking topiramate without VPA. There were 10 subjects who had either markedly abnormal ammonia lab value or a TEAE of hyperammonemia in the absence of concomitant VPA use. The elevations in these 10 patientts, all of whom were receiving other concomitant**

AEDs in addition to topiramate, were transient, no symptoms were reported, and in general the subjects received no additional treatment. The sponsor also noted that assessment of hyperammonemia is complicated by the sensitivity of the laboratory assay to poor handling and preparation of the blood sample and to long delays in testing, all of which can contribute to falsely elevated results.

The sponsor concluded that the current studies support the association of hyperamonemia with the combination of topiramate andVPA. In the controlled, double-blind phase of TOPMAT-PEP-3001 mean ammonia decreased among subjects on topiramate and a concomitant AED excluding VPA. **The sponsor thought that "the clinical significance of the cases of hyperammonemia in the absence of valproic acid is unclear."** The postmarketing summary also describes 2 cases in which increased ammonia levels were found in the absence of concomitant treatment with VPA but the sponsor thought that these cases were confounded by other factors.

Cognitive/Neuropsychiatric Events

See also results on Vineland Adaptive Behavior Scales (results presented in section 7.1.12)

In the double-blind (core) phase of Study TOPMAT-PEP-3001, cognitive/neuropsychiatric adverse events present more frequently in the topiramate arms compared to placebo included ataxia (3% vs. 0), nervousness (6% vs. 0), and somnolence (15% vs. 8%). None of these events were treatment limiting or serious.

In the Integrated Open-Label Extension Safety Analysis Set, analysis includes events described in studies 3001 and 1002 except for the 1 subject who did not enter the open-label extension. A total of 147 subjects (52%) had cognitive/neuropsychiatric TEAEs. The most common events included anorexia (35%), somnolence (27%), nervousness (13%), and insomnia (7%). All other cognitive/neuropsychiatric adverse events had an incidence of < 3%.
– The majority of these events were mild or moderate in severity.
– A total of 11 subjects had events of clinical interest that were serious (somnolence, n=4; anorexia, n=2; somnolence and anorexia, n=1; somnolence and fatigue, n=1; dizziness, n=1; ataxia, n=1; psychomotor development impaired, n=1).
– Thirty-eight subjects with anorexia had their topiramate dose adjusted, 1 subject had topiramate stopped temporarily, and 2 subjects (with mild or moderate anorexia) were discontinued from the study.
– Thirty subjects with somnolence had their topiramate dose adjusted; one had topiramate stopped permanently. Most events were considered by the investigator to be related to study medication.
– Seven subjects with nervousness had their topiramate dose adjusted; none had topiramate stopped temporarily or permanently.
– Five subjects with insomnia had their topiramate dose adjusted, 1 had topiramate stopped temporarily, and none were discontinued from the study.
– There was 1 subject with infantile autism who had a TE-SAE of psychomotor development impaired. This subject had a pre-existing language delay at enrollment. The investigator documented regression of social and communication skills in this subject as the study progressed. The subject discontinued due to calcinosis, and the symptoms of developmental regression persisted after topiramate was stopped.

Ocular

In the double-blind (core) phase of Study TOPMAT-PEP-3001, the TEAE of conjunctivitis was reported for 1 topiramate-treated subject and 1 placebo-treated subject.

In the Integrated Open-Label Extension Safety Analysis Set, 25 subjects (9%) were selected programmatically for the ocular special safety category, all due to TEAEs. Clinical review of these 25 subjects showed the following :
– Nineteen subjects had conjunctivitis, blepharitis or stye, and in all cases the events were mild, judged not related by the investigator, did not lead to dose adjustment, appeared to be infectious in nature, and were transient.

– The remaining events included optic atrophy, photophobia, anisocoria, strabismus, not focusing, vision abnormal, and conjunctival hemorrhage. All cases were mild in severity (except for 1 case of moderate photophobia), did not lead to dose adjustment, and were judged not or doubtfully related by the investigator.
– In no case was there evidence of glaucoma or increased intraocular pressure.

Growth

See also data on Effects on Growth (results presented in section 7.1.15).

In the double-blind (core) phase of Study TOPMAT-PEP-3001, the TEAE weight decrease was reported for 7 subjects who received topiramate (2 subjects in the 15 mg/kg/d group and 5 subjects in the 25 mg/kg/d group) and 1 subject who received placebo (6% vs. 3%). No subject had a decrease from baseline in weight-for-age z-score of 1 or more.

In the Integrated Open-Label Extension Safety Analysis Set, mean body weight, body length, and head circumference increased overall. Clinical review was performed on the data from 155 subjects programmatically selected according to criteria established for the special safety category of growth (i.e., 1-unit z-score decrease from baseline at any 2 consecutive postbaseline visits or endpoint, and/or TEAEs of weight decrease, growth retarded, or cachexia. Results of the review are as follows :
– Thirty-two subjects were selected based on growth-related TEAE alone, 84 were selected based on laboratory parameters alone, and 39 had both.
– Among the 71 subjects (25%) with TEAEs, the most frequent event was weight decreased (64 subjects, 23% overall). TEAEs of weight decreased were generally mild in severity and did not lead to dose adjustment. These events were considered by the investigator to be probably or very likely related to study medication for 33 subjects.
– Review of selected narratives showed that in many subjects the pattern of decrease is one of a decrease in z-score followed by a stabilization or slow increase in z-score (although generally not to baseline levels). The decrease generally occurred in the first 4 months of the trial, though it also happened later.
– In 47 subjects there was a decrease in weight z-score of 2 units at 2 consecutive visits or endpoint. These are considered clinically meaningful decreases. Many of these subjects showed the same pattern of initial decrease followed by stabilization as described above here.
– Body weight z-score continued to decrease throughout the trial for 25 of these 47 subjects (9%).
– Fifteen subjects (5%) were given nutritional supplements and 7 subjects (2%) received gastric feeding tubes. When such treatment was reported, it was effective in increasing weight. Study drug dose reduction was sometimes effective and sometimes not. In a few subjects there is clear correlation between a serious illness and body weight z-score decrease.
– Changes in body length z-score were much more gradual and smaller than those in body weight z-score and when they occurred were small, steady decreases over many months. No correlations with other factors, such as dose, acute illness, or acidosis, are apparent. In the 16 subjects with a decrease in length z-score of at least 2 units at 2 consecutive visits or endpoint, approximately half had severe neurological impairment at baseline.
– Many of the subjects were microcephalic at baseline and head circumference z-score tended to decrease over the course of the trial.
– There is a significant mean decrease in body weight z-score and a smaller decrease in body length z score over the course of the trial. In addition 15% and 4% of subjects, respectively, had a clinically significant decrease of at least 2 z-scores in body weight or length during the trial.
– There were 3 major patterns of change in weight z-score observed: Slightly fewer than half the patients' weight z-scores increased, were stable, or decreased less than 1 z-score over the course of the trial. Of the remaining subjects whose weight z-scores decreased 1, or even 2, units at 2 consecutive visits or endpoint, most showed an initial decrease followed by a stabilization or improvement. Finally, among the subjects with a decrease of 2 units, 25 subjects (9% of the overall study population) steadily decreased in weight z-score throughout the trial.
– There were 2 major patterns of change in length z-score observed: Almost two-thirds of subjects' length z-scores increased, were stable, or decreased less than 1 z-score over the course of the trial. The remaining subjects showed a gradual decline in length z-score throughout the trial, most between 1-2 units and very few (11 subjects, 4% of total population) of greater than 2 units.

The sponsor noted that, overall, decreases in mean z-scores (from pre-treatment baseline to the final study visit) were observed for body weight (-0.82), length (-0.45), and head circumference (-0.36) among subjects in the integrated analysis set. The weight loss was consistent with the recognized effect of topiramate on weight in older pediatric and adult patients. The effect of topiramate on length has been only sporadically evaluated, and head circumference has never before been systematically measured in topiramate clinical trials. Overall, 17%, 6%, and 4% of subjects, respectively, had a decrease of at least 2 z-scores in weight, length, or head circumference. **Among subjects with persistent metabolic acidosis (serum bicarbonate values < 20 mmol/L at 2 or more visits), mean changes in weight and length z-scores (from baseline to the final visit) were –1.0 and –0.6, respectively, compared with -0.5 and -0.1 for subjects who did not meet these criteria.**

There were 3 major patterns of change in weight z-score observed: Slightly fewer than half the subjects' weight z-scores increased, were stable, or decreased less than 1 z-score over the course of the trial. Of the remaining subjects whose weight z-scores decreased 1, or even 2, units at 2 consecutive visits or endpoint, most showed an initial decrease followed by a stabilization or improvement. Finally, among the subjects with a decrease of 2 units, 25 subjects (9% of the overall study population) steadily decreased in weight z-score throughout the trial.

There were 2 major patterns of change in length z-score observed :
- Almost two-thirds of subjects' length z-scores increased, were stable, or decreased less than 1 z-score over the course of the trial.
- The remaining subjects showed a gradual decline in length z-score throughout the trial, most between 1-2 units and very few (11 subjects, 4% of total population) of greater than 2 units.

The sponsor noted that there were growth data from older children include study TOPMAT-EPMN-106, a double-blind, randomized monotherapy study of newly diagnosed epilepsy patients followed by an open-label extension period. This study included 151 pediatric subjects aged 6 to 15 years who received topiramate at dosages ranging from 50 to 400 mg/d. **However, it was not clear (and I believe that it is unlikely) that this study had prospectively employed careful, specifically outlined procedures for measuring height as had been done for these infant/toddler studies.** Eighty-six subjects had baseline and 12-month data (46 M/40 F; mean age 11 years [range: 6 to 15]). At 12 months the mean height z-score change from baseline was -0.079 (-0.97 to 1.97).

The sponsor also noted that in a separate, open-label adjunctive treatment study in pediatric subjects with refractory epilepsy ages 1 to 18 years (Study TOPMAT-EPPD-002) evaluation of the height data provided 12-month data on 173 subjects of the 554 subjects enrolled. **However, it was not clear (and I believe that it is unlikely) that this study had prospectively employed careful, specifically outlined procedures for measuring height as had been done for these infant/toddler studies.** The 173 pediatric subjects (92 M/81 F; mean age 9.26 years [range: 2 to 18 years]) with 12-month data had a mean change in height z-score from baseline of -0.191 (range:–1.76 to 1.55). The median weight-adjusted average daily dose in this study was 5.0 mg/kg/d for subjects weighing < 25 kg and 4.0 mg/kg/d for subjects weighing ≥ 25 kg, with a maximum allowable dose of 24 mg/kg/d. In addition, Morita, Glauser et al., in a retrospective chart review, identified a slight slowing of weight gain but no signficant effect of topiramate on height changes over time in children aged 3 to 24 years treated with typical, clinical doses of topiramate for refractory partial onset seizures for a mean duration of 21 months compared to age- and disease-matched controls.

Publications identified in the literature review were generally consistent in showing a small decrease in body weight and no effect on height with topiramate therapy, including a controlled investigation of the long-term effects of topiramate on body weight, height, and head circumference in infants and toddlers. In this study, 100 children from China aged 3 to 21 months with various forms of epilepsy were treated with topiramate (titrated from starting dose of 0.5 or 1 mg/kg/d to a target dose of 4 to 6 mg/kg/d) for up to 12 months, and their growth was compared with an age- and sex-matched control group. The effects of topiramate on body weight were most evident during the first 3 months of treatment, after which time body weight tended to normalize in all age subgroups. While mean body weight was statistically significantly lower at 3, 6, and 12 months in the topiramate-treated group compared with controls for each of the 5 age subgroups, the mean body weight change was statistically significantly less on topiramate for each age subgroup only at Month 3. With longer topiramate use, the inhibitory effects of topiramate on body weight gradually lessened, such that by Month 12 the mean

body weight change in the topiramate group did not differ significantly from that of the control group for any age subgroup. No significant differences between the topiramate and age- and sex-matched controls were seen in the changes in body length/height or head circumference at any time point for any age subgroup.

The differences in the effects on growth in this open-label extension study compared to those in older children and also to those in infants on lower doses are likely attributable to the higher doses of topiramate administered to this infant population, possibly mediated, at least in part, through the metabolic acidosis. The findings in this open-label integrated dataset are, however, limited by the absence of a control group and the background of poor growth in children with refractory epilepsy.

Clinically Relevant Rashes

In the double-blind (core) phase of Study TOPMAT-PEP-3001, 3 topiramate-treated subjects (3%) and 2 placebo-treated subjects (5%) had rash that was considered by the Sponsor to be possibly clinically relevant. One of these subjects did not enter the open-label extension: Subject 300290 (topiramate 15 mg/kg/d) had moderate rash that resulted in study discontinuation, although the investigator considered the event unrelated to study drug.

In the Integrated Open-Label Extension Safety Analysis Set, analysis included the events described in studies 3001 and 1002 except for the 2 subjects who did not enter the open-label extension. Rash and dermatitis were predominantly those typical of infancy. Clinical review identified 24 subjects (9%) who had rash that was not clearly infectious, irritant, or eczematous in nature.
– In 22 of these subjects, the rashes were mild (except for 1 case that was of moderate severity), sometimes coincided with infections, were predominantly considered not related to study drug, and generally resolved with only typical treatments for infant rashes. Rashes did not lead to discontinuation. Even those rashes which were considered related to study drug appeared typical of infant rashes.
– The first of the remaining 2 subjects, Subject 300394, developed a pink, evanescent rash with irregular rashes immediately upon being changed from liquid formulation to sprinkle formulation. When she was switched back to liquid formulation after 4 days, the rash resolved. The rash was moderate in severity and the investigator attributed it to a component of the sprinkle formulation.
– The second subject, Subject 300636, had an erythematous maculopapular rash all over his body that started while the subject was on liquid formulation, was temporally related to each day's dose, and was diagnosed as a drug-induced rash. The rash was moderate in severity and led to discontinuation from the study. The rash resolved shortly after discontinuation of study medication. However, the rash began while the subject was on placebo and was not reported to change upon transition to open-label topiramate.
The sponsor noted that, overall, there was no evidence reported of any drug-associated bullous rashes or rashes such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

7.1.4 Other Search Strategies

Based upon my request, the sponsor conducted and submitted additional subgroup analyses of all TEAEs observed in the placebo-controlled study with regard to the presence or absence of metabolic acidosis (e.g., a post-treatment serum bicarbonate of < 20 mEq/L). The incidence of TEAEs associated with or without metabolic acidosis were assessed by calculating the relative risk (incidence of each specific PT TEAE **with metabolic acidosis**/ incidence of each specific PT TEAE w**ithout metabolic acidosis**). I focused my review on TEAEs that were increased with topiramate treatment vs placebo and presumably suggested a causal role of topiramate.

Certain TEAEs (i.e., ataxia, weight decrease, bronchospasm, dermatitis) that showed an increased occurrence during topiramate treatment (vs placebo) were found to occur more frequently in association with laboratory diagnosed metabolic acidosis in the placebo-controlled study based upon analyses showing the relative risk of the specific TEAE in patients with metabolic acidosis vs those without metabolic acidosis. These increased frequencies suggested the possibility that metabolic acidosis may have contributed to the risk of occurrence of these adverse reactions.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

All adverse events that occurred between the first and the last study-related procedure were reported. These were assessed at each study visit as well as through the subject take-home records in which adverse events seen and action taken were described by the subject's parent (or legally acceptable representative). Information recorded for each adverse event included description, dates of onset and resolution (if applicable), investigator's assessment of severity (mild, moderate, or severe), investigator's assessment of relationship to the study medication (not related, doubtful, possible, probable, or very likely), and whether or not the adverse event was serious or treatment limiting. A treatment-emergent adverse event was any adverse event that was new (i.e., after first dose date) in onset or was aggravated in severity or
frequency following treatment.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor noted that an adverse event was defined as any untoward medical occurrence, such as intercurrent illness or injury, which occurred during the study. Adverse events (verbatim terms) were coded using the TWA92 dictionary, a modified version of the World Health Organization Adverse Reaction Terminology (WHOART) dictionary.

Based upon my previous experience with an NDA of infants 1-24 months, it was clearly apparent that many TEAEs (particularly those related to symptoms that are subjective assessments by the patient) that had been coded to certain preferred terms may not necessarily have reflected what was actually the adverse reaction experienced by the infant/toddler. This is a potentially major problematic issue that is relevant to all studies of very young pediatric patients who are not able to communicate symptoms at all or not very well or precisely. Thus, one approach that I have developed is to try to categorize a variety of verbatim and preferred terms to certain basic behavioral changes (i.e., irritability, crying, changes in crawling/walking, changes in feeding, changes in sleeping) that may be occurring and reflecting an adverse reaction associated with experimental drug treatment.

The sponsor was asked to conduct such analyses as described above prior to NDA submission and complied with our request to do this. Thus TEAEs were also categorized by verbatim/preferred term into 'change in behavior' groupings.;The incidence table for these change of behavior groupings contained both incidence count by subject, treatment group and topiramate total and total number of events by each 'change in behavior' grouping (counted by onset date) by treatment group and topiramate total.

Change in Behavior Grouping Categories according to various Verbatim/Preferred Terms

Crying-Irritable : Aggressive Reaction, Agitation, Restlessness Marked, Excitability, Irritability, Nervousness

Crawl-Walk : Weakness Generalized, Astasia, Ataxia, Balance Difficulty, Incoordination, Gait Abnormal, Gait Disturbance

Feeding : Anorexia, Appetite Decreased, Appetite Lost, Cachexia, Dehydration, Swallowing Difficult, Swallowing Impaired, Growth Retarded, Urine Volume Deficient, Weight Decrease

Sleeping : Insomnia, Sleep Decreased, Sleep Difficult, Sleep Disturbed, Sleep Restless

Crying : All verbatim terms to be searched for 'crying'

The following are the sponsor's summaries of the findings in each of the 3 studies using the approach that the DNP recommended and discussed with the sponsor.

Study TOPMAT-PEP-1002 Open-Label Treatment (Core) Phase

Overall, 10 behavioral events were reported for 9 subjects (16%). Nine of the events were in the feeding category: 1 report for 1 subject in each of the 3, 5, and 15 mg/kg/d treatment groups, and 6 reports for 5 subjects in the 25 mg/kg/d group. The 1 other event was in the sleeping category, for a subject in the 3 mg/kg/d group.

No events were reported in the other behavior categories of crying/irritability, crying, or crawling/walking.

Study TOPMAT-PEP-3001 Double-Blind (Core) Phase

Forty behavioral events were reported for 22 topiramate-treated subjects (20%), compared with 5 events in 4 (11%) placebo-treated subjects. The frequency of subjects reporting these events as well as the number of events reported appeared to be dose related: 11 events in 5 (13%) subjects in the 5 mg/kg/d group, 14 events in 7 (19%) subjects in the 15 mg/kg/d group, and 15 events in 10 subjects (27%) in the 25 mg/kg/d group. This pattern was most evident for feeding-related events, which was the most commonly reported behavior category (8%, 11%, 11%, and 27% of subjects in the placebo, 5, 15, and 25 mg/kg/d groups, respectively).

More topiramate-treated subjects than placebo-treated subjects reported events categorized as crying/irritability (6% vs. 3%) and crawling/walking (4% vs. 0). No subject had an event reported for the category of isolated crying.

Studies TOPMAT-PEP-1002 and -3001 Integrated Open-Label Extension

Overall, 314 events describing a behavioral change were reported for 138 subjects (49%). Feeding-related events were most common, with a total of 226 events reported for 125 subjects (44%), followed by crying/irritability-related events (48 events for 31 subjects, 11%), and sleeping-related events (21 events for 17 subjects, 6%). Three subjects (1%) had an event in the category of crying.

• Overall, a higher percentage of subjects reported behavioral events while receiving topiramate in the 20 40 mg/kg/d dose range (38%) than in the <20 mg/kg/d range (27%) or >40 mg/kg/d range (23%). However, the number of events reported was greater while subjects were receiving topiramate at dosages in the lowest dose range category: 165 events in the <20 mg/kg/d range, 129 events in the 20-40 mg/kg/d range, and 20 events in the >40 mg/kg/d dose range. The exception to this pattern was the feeding category, in which 94 events were reported in the <20 mg/kg/d range, 115 events in the 20-40 mg/kg/d range, and 17 events in the >40 mg/kg/d dose range.

Reviewer Comment

- Overall, the overwhelming majority of TEAEs seemed to be reasonable PTs that seemed to reflect observable findings rather than subjective symptoms (that one would predict would be difficult for these very young pediatric patients to communicate appropriately or precisely.

- Of interest, the placebo-controlled study suggested that topiramate produced an increased risk for changes in the composite of these altered behaviors ((11%, 13%, 19%, and 27% of subjects in the placebo, 5, 15, and 25 mg/kg/d groups, respectively). More specifically, topiramate produced an increase risk for changes in feeding behavior (8%, 11%, 11%, and 27% of subjects in the placebo, 5, 15, and 25 mg/kg/d groups, respectively) changes in crying irritability (topiramate 6 % vs placebo 3 %), and changes in crawling/walking (topiramate 4% vs placebo 0 %).

7.1.5.3 Incidence of common adverse events

Only adverse events that were treatment-emergent (i.e., new or aggravated in severity or frequency following treatment) known as TEAEs are summarized.

Study TOPMAT-PEP-3001 Double-Blind (Core) Phase

The following table shows the incidence of TEAEs in the placebo-controlled trial.

Table 7: Incidence of Treatment-Emergent Adverse Events in ≥5% of Subjects in Any Treatment Group By Body System and Preferred Term During Double Blind Phase (Study TOPMAT-PEP-3001: Safety Analysis Set)

WHO Body System WHO Preferred Term	Placebo (N=37) n (%)	TPM 5 mg/kg/d (N=38) n (%)	TPM 15 mg/kg/d (N=37) n (%)	TPM 25 mg/kg/d (N=37) n (%)	All TPM (N=112) n (%)
Total no. subjects with AE	19 (51)	30 (79)	27 (73)	34 (92)	91 (81)
Body as a Whole - General Disorders	5 (14)	12 (32)	7 (19)	8 (22)	27 (24)
Fever	4 (11)	11 (29)	7 (19)	7 (19)	25 (22)
Central & Peripheral Nervous System Disorders	3 (8)	4 (11)	5 (14)	1 (3)	10 (9)
Ataxia	0	1 (3)	2 (5)	0	3 (3)
Convulsions Aggravated	2 (5)	2 (5)	1 (3)	1 (3)	4 (4)
Gastro-intestinal System Disorders	5 (14)	12 (32)	6 (16)	11 (30)	29 (26)
Diarrhoea	0	1 (3)	4 (11)	3 (8)	8 (7)
Mouth Dry	0	0	0	2 (5)	2 (2)
Saliva Increased	1 (3)	0	0	2 (5)	2 (2)
Vomiting	2 (5)	7 (18)	3 (8)	6 (16)	16 (14)
Metabolic and Nutritional Disorders	1 (3)	2 (5)	5 (14)	6 (16)	13 (12)
Acidosis	0	0	2 (5)	1 (3)	3 (3)
Weight Decrease	1 (3)	0	2 (5)	5 (14)	7 (6)
Psychiatric Disorders	5 (14)	7 (18)	10 (27)	9 (24)	26 (23)
Anorexia	2 (5)	4 (11)	4 (11)	6 (16)	14 (13)
Nervousness	0	3 (8)	3 (8)	1 (3)	7 (6)
Somnolence	3 (8)	3 (8)	8 (22)	6 (16)	17 (15)
Resistance Mechanism Disorders	0	7 (18)	0	6 (16)	13 (12)
Infection Viral	0	5 (13)	0	3 (8)	8 (7)
Otitis Media	0	2 (5)	0	2 (5)	4 (4)
Respiratory System Disorders	6 (16)	17 (45)	12 (32)	16 (43)	45 (40)
Bronchitis	0	3 (8)	1 (3)	3 (8)	7 (6)
Bronchospasm	0	0	3 (8)	2 (5)	5 (4)
Coughing	2 (5)	2 (5)	0	4 (11)	6 (5)
Pharyngitis	0	2 (5)	0	1 (3)	3 (3)
Rhinitis	0	2 (5)	0	2 (5)	4 (4)
Upper Respiratory Tract Infection	5 (14)	8 (21)	8 (22)	8 (22)	24 (21)
Skin and Appendages Disorders	2 (5)	4 (11)	3 (8)	2 (5)	9 (8)
Dermatitis	0	1 (3)	2 (5)	0	3 (3)
Rash Maculo-papular	2 (5)	0	0	0	0
Skin Dry	0	2 (5)	0	0	2 (2)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
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Cross-reference: Mod5.3.5.1\TOPMAT-PEP-3001\Sec6.2.1\Table 15

• A larger proportion of subjects who received topiramate (91/112, 81%) than placebo (19/37, 51%) had a TEAE during the double-blind phase. (Table 7). TEAEsreported by ≥ 10% of all topiramate-treated or placebo-treated subjects, respectively, were fever (22% and 11%), vomiting (14% and 5%), anorexia (13% and 5%), somnolence (15% and 8%), and upper respiratory tract infection (21% and 14%).

• Events reported for a larger proportion of subjects who received topiramate than placebo (≥ 5 % treatment difference/effect after topiramate % - placebo %) included fever, diarrhea, vomiting, anorexia, nervousness, somnolence, infection viral, bronchitis, and upper respiratory tract infection.

• TEAEs of anorexia were more frequent among topiramate-treated subjects (13%) than among placebo-treated subjects (5%).

• Most TEAEs were considered by the investigator to be unrelated or of doubtful relation to study medication. TEAEs more often considered possibly, probably, or very likely related to study treatment were usually those previously associated with topiramate treatment and were most often in the psychiatric disorder body system, including anorexia, nervousness, and somnolence.

Reviewer Comment

- With the exception of saliva increased, and maculopapular rash, I consider all of the TEAEs shown in Table 7 to be related to topiramate treatment. I draw this conclusion based upon the observation that TEAEs that did not appear to be dose-related showed an overall greater incidence than in placebo patients, or that there was a suggestion of dose-relationship to topiramate and the incidence with the highest dose or doses was greater than the incidence in placebo.

- I consider that many of the TEAEs (i.e., diarrhea, mouth dry, vomiting, acidosis, weight decrease, anorexia, somnolence, bronchospasm, coughing) shown in Table 7 are dose-related to topiramate. I note that my consideration of a dose-relationship does not necessarily expect a progressive, monotonic increased incidence with progressively higher doses and does not view the incidence data as a precise point estimate.

Study TOPMAT-PEP-1002 Open-Label Treatment (Core) Phase

• Thirty-five (64%) of the 55 subjects experienced at least 1 TEAE during the open-label treatment (core) phase of Study TOPMAT-PEP-1002 TEAEs reported in ≥ 5% of all patients were upper respiratory tract infection (15%), fever (15%), vomiting (13%), somnolence (11%), anorexia (11%), diarrhea (9%), infection viral (7%), coughing (7%), rhinitis (7%), bronchitis (5%), and otitis media (5%).

• TEAEs that were reported more frequently for subjects in the higher dose groups included fever (7%, 15%, 0%, and 33% in the 3, 5, 15, and 25 mg/kg/d groups, respectively), diarrhea (0%, 8%, 0%, and 27%, respectively), vomiting (7%, 8%, 15%, and 20%, respectively), weight decrease (0%, 0%, 0%, and 13%, respectively), anorexia (7%, 8%, 8%, and 20%, respectively), somnolence (0%, 15%, 8%, and 20%, respectively), infection viral (0%, 0%, 23%, and 7%, respectively), otitis media (7%, 0%, 0%, and 13%, respectively), bronchitis (0%, 0%, 8%, and 13%, respectively), rhinitis (0%, 8%, 0%, and 20%, respectively), and upper respiratory tract infection (0%, 8%, 15%, and 33%, respectively).

• Most TEAEs were considered by the investigator to be unrelated or doubtfully related to study drug. In 4 of the 7 subjects with vomiting reported as an adverse event, the events were considered probably or very likely related to study drug. Other events considered at least possibly related to study drug were somnolence (6 subjects), anorexia (4 subjects), and diarrhea, gastrointestinal disorder NOS, weight decrease, dermatitis, rash maculo-papular, hyperammonemia, renal function abnormal, flushing, and vasospasm (1 subject each).

• All but 6 TEAEs were mild to moderate in severity. Events of severe intensity were upper respiratory tract infection, infection viral, bronchitis, convulsions aggravated, vomiting, and hepatomegaly (1 subject each). The subject with severe vomiting was in the 25 mg/kg/d group.

Studies TOPMAT-PEP-1002 and -3001 Integrated Open-Label Extension

The following table shows the incidence of TEAEs in the, open-label, extension trial .

Table 8: Treatment-Emergent Adverse Events in At Least 5% of Subjects in Any Analysis Category by Body System and Preferred Term - Core Phase and Open-Label Extension Phases Combined (TOPMAT-PEP-1002 and TOPMAT-PEP-3001 Integrated OL Extension: Safety Analysis Set)

WHO Body System WHO Preferred Term	PEP-1002 (N=50)	PEP-3001 PBO (N=36)	PEP-3001 TPM (N=108)	PEP-3001 Shunt (N=90)	Total (N=284)
Total no. subjects with adverse Events	50 (100)	34 (94)	107 (99)	86 (96)	277 (98)
Respiratory system disorders	37 (74)	28 (78)	75 (69)	68 (76)	208 (73)
Upper resp tract infection	24 (48)	16 (44)	52 (48)	52 (58)	144 (51)
Rhinitis	12 (24)	6 (17)	16 (15)	17 (19)	51 (18)
Coughing	9 (18)	4 (11)	20 (19)	14 (16)	47 (17)
Bronchitis	9 (18)	6 (17)	21 (19)	9 (10)	45 (16)
Pneumonia	5 (10)	6 (17)	10 (9)	14 (16)	35 (12)
Pharyngitis	7 (14)	8 (22)	8 (7)	11 (12)	34 (12)
Bronchospasm	5 (10)	1 (3)	8 (7)	7 (8)	21 (7)
Sinusitis	2 (4)	0	2 (2)	5 (6)	9 (3)
Respiratory disorder	1 (2)	2 (6)	1 (1)	3 (3)	7 (2)
Pneumonitis	0	2 (6)	2 (2)	1 (1)	5 (2)
Gastro-intestinal system disorders	28 (56)	23 (64)	63 (58)	56 (62)	170 (60)
Vomiting	17 (34)	13 (36)	34 (31)	16 (18)	80 (28)
Diarrhoea	14 (28)	8 (22)	25 (23)	22 (24)	69 (24)
Gastroenteritis	4 (8)	5 (14)	18 (17)	15 (17)	42 (15)
Constipation	7 (14)	3 (8)	10 (9)	8 (9)	28 (10)
Tooth disorder	6 (12)	3 (8)	0	10 (11)	19 (7)
Gastroesophageal reflux	0	2 (6)	1 (1)	3 (3)	6 (2)
Saliva increased	0	2 (6)	2 (2)	1 (1)	5 (2)
Body as a whole - general disorders	22 (44)	22 (61)	64 (59)	57 (63)	165 (58)
Fever	20 (40)	18 (50)	58 (54)	51 (57)	147 (52)
Injury	4 (8)	3 (8)	6 (6)	8 (9)	21 (7)
Metabolic and nutritional disorders	32 (64)	16 (44)	67 (62)	41 (46)	156 (55)
Acidosis	17 (34)	12 (33)	37 (34)	23 (26)	89 (31)
Weight decrease	17 (34)	5 (14)	31 (29)	11 (12)	64 (23)
Hyperammonaemia	13 (26)	2 (6)	10 (9)	3 (3)	28 (10)
Dehydration	5 (10)	1 (3)	6 (6)	4 (4)	16 (6)
Growth retarded	1 (2)	0	13 (12)	1 (1)	15 (5)
Hyperchloraemia	1 (2)	2 (6)	6 (6)	1 (1)	10 (4)

Psychiatric disorders	23 (46)	16 (44)	60 (56)	43 (48)	142 (50)
Anorexia	14 (28)	8 (22)	46 (43)	32 (36)	100 (35)
Somnolence	12 (24)	10 (28)	32 (30)	22 (24)	76 (27)
Nervousness	5 (10)	4 (11)	12 (11)	15 (17)	36 (13)
Insomnia	2 (4)	2 (6)	6 (6)	10 (11)	20 (7)
Resistance mechanism disorders	23 (46)	15 (42)	42 (39)	40 (44)	120 (42)
Infection viral	14 (28)	10 (28)	27 (25)	24 (27)	75 (26)
Otitis media	12 (24)	2 (6)	11 (10)	18 (20)	43 (15)
Infection	4 (8)	3 (8)	7 (6)	2 (2)	16 (6)
Sepsis	0	2 (6)	0	1 (1)	3 (1)

Table 8 (Continued)

Table 8: Treatment-Emergent Adverse Events in At Least 5% of Subjects in Any Analysis Category by Body System and Preferred Term - Core Phase and Open-Label Extension Phases Combined (Continued)
(TOPMAT-PEP-1002 and TOPMAT-PEP-3001 Integrated OL Extension: Safety Analysis Set)

WHO Body System WHO Preferred Term	PEP-1002 (N=50)	PEP-3001 PBO (N=36)	PEP-3001 TPM (N=108)	PEP-3001 Shunt (N=90)	Total (N=284)
Centr & periph nerv syst disorders	11 (22)	8 (22)	40 (37)	26 (29)	85 (30)
Convulsions aggravated	4 (8)	7 (19)	30 (28)	16 (18)	57 (20)
Convulsions grand mal	3 (6)	2 (6)	1 (1)	3 (3)	9 (3)
Skin and appendages disorders	13 (26)	7 (19)	32 (30)	27 (30)	79 (28)
Dermatitis	2 (4)	2 (6)	9 (8)	7 (8)	20 (7)
Rash	2 (4)	1 (3)	9 (8)	5 (6)	17 (6)
Sweating decreased	6 (12)	0	5 (5)	5 (6)	16 (6)
Eczema	3 (6)	2 (6)	3 (3)	3 (3)	11 (4)
Skin dry	2 (4)	1 (3)	5 (5)	0	8 (3)
Dermatitis contact	1 (2)	2 (6)	1 (1)	3 (3)	7 (2)
Rash maculo-papular	0	2 (6)	5 (5)	0	7 (2)
Urinary system disorders	12 (24)	3 (8)	15 (14)	16 (18)	46 (16)
Urinary tract infection	4 (8)	0	5 (5)	7 (8)	16 (6)
Renal calculus	3 (6)	1 (3)	5 (5)	5 (6)	14 (5)
Bladder calculus	3 (6)	0	1 (1)	2 (2)	6 (2)
Vision disorders	1 (2)	2 (6)	11 (10)	10 (11)	24 (8)
Conjunctivitis	0	2 (6)	7 (6)	8 (9)	17 (6)
Liver and biliary system disorders	8 (16)	2 (6)	7 (6)	6 (7)	23 (8)
Gamma-GT increased	2 (4)	1 (3)	5 (5)	1 (1)	9 (3)

SGOT increased	4 (8)	1 (3)	1 (1)	3 (3)	9 (3)
Red blood cell disorders	3 (6)	2 (6)	7 (6)	6 (7)	18 (6)
Anaemia	2 (4)	2 (6)	6 (6)	6 (7)	16 (6)
Neonatal and infancy disorders	3 (6)	1 (3)	2 (2)	2 (2)	8 (3)
Psychomotor development impaired	3 (6)	1 (3)	2 (2)	2 (2)	8 (3)
Reproductive disorders, female	0	2 (6)	0	0	2 (1)
Vaginitis	0	2 (6)	0	0	2 (1)

Note: Incidence is based on the number of subjects, not the number of events.
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Table 8 presents TEAEs reported by ≥ 5% of subjects in any analysis category for the Integrated Open-Label Extension Safety Analysis Set for the core phases and open-label extensions of Studies TOPMAT-PEP-1002 and TOPMAT-PEP-3001.

• Overall, 98% of subjects had at least 1 TEAE. The most frequently reported TEAEs were fever (52% of subjects) and upper respiratory tract infection (51% of subjects). Most events were mild (57%) to moderate (34%) in intensity.

• TEAEs rated as severe by the investigator were reported for 120 subjects. These events included convulsions aggravated (20 subjects), pneumonia (14 subjects), bronchitis (8 subjects), convulsions grand mal (7 subjects), infection viral (6 subjects), gastroenteritis (6 subjects), dehydration (6 subjects), fever (5 subjects), upper respiratory infection (5 subjects), bronchospasm (4 subjects), and somnolence (4 subjects).

• Most TEAEs were considered by the investigator to be unrelated (53%) or of doubtful (13%) relation to study medication. Events considered by the investigator to be possibly, probably, or very likely related to study treatment were usually those previously associated with topiramate treatment in older populations and were most often metabolic and nutritional disorders (mainly metabolic acidosis, weight loss, and hyperammonemia) or psychiatric disorders (mainly anorexia, nervousness, and somnolence).

• Most TEAEs required no action taken. TEAEs most commonly leading to action taken included psychiatric disorders (in 67 of 142 cases), metabolic and nutritional disorders (in 59 of 156 cases), and central and peripheral nervous system disorders (in 40 of 85 cases).

The action taken for the majority of these events was dose reduction.

Reviewer Comment

- Overall, the profile of the specific PT TEAEs was quite similar to the profiles describing the incidence of specific TEAEs with topiramate treatment in many other randomized, double-blind, controlled studies (including many placebo-controlled studies).

- It is remarkable that the frequency of TEAEs in 2 organ system classes (i.e., respiratory and resistance mechanism-indicating infections) were notably increased with topiramate treatment (vs placebo). These very young pediatric patients appeared to experience an increased risk/frequency of resistance mechanism disorders (any topiramate dose 12 %, placebo 0 %) and of respiratory system disorders (any topiramate dose 40 %, placebo 16 %).

The following summarizes TEAEs occurring in these 2 organs systems. A closer analysis (from the placebo-controlled trial) of TEAEs from these 2 organ systems suggested an increased risk/occurrence of a novel TEAE (i.e., bronchospasm) and that a few other TEAEs (i.e., otitis media, upper respiratory infection, cough) appeared to occur more frequently than previously recognized in controlled studies of older pediatric patients or adults for various indications. The incidence of bronchospasm was 0 % for placebo and 5 mg/kg/d, 8 % for 15 mg/kg/d, 5 % for 25 mg/kg/d, and 4 % for any topiramate dose. Other increased frequency TEAEs (i.e, infection viral, bronchitis, pharyngitis, rhinitis) occurring within these 2 organs systems appeared to occur with a relatively similar frequency as has been observed in other controlled topiramate trials.

7.1.5.4 Common adverse event tables

See section 7.1.5.3.

7.1.5.5 Identifying common and drug-related adverse events

Events were primarily considered as drug-related when the frequency occurring with topiramate treatment was greater than that with placebo treatment, and especially when there was a moderately increased treatment difference/effect (e.g., $\geq$ 3 %). See the analyses and presentations of TOPMAT-PEP-3001 in section 7.1.5.3.

7.1.5.6 Additional analyses and explorations

- See sections 7.1.4 and 7.1.5.2
- See section 7.1.5

7.1.6 Less Common Adverse Events

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Most of this reviewer's attention on clinical laboratory results focused on the results from the randomized, double-blind, placebo-controlled study that was conducted over a period of up to 20 days. Nevertheless, some summary findings are also presented from the PK study (3002) and also the open-label extension study.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

See section 7.1.7.1. Analyses were conducted investigating clinical laboratory analytes changes in absolute values over time, changes from baseline over time, and outlier analyses for abnormal results

(relative to "normal" reference range) over time, and markedly abnormal results (relative to sponsor and/or DNP recommended markedly abnormal criteria) over time. Some analyses were conducted assessing the incidence of certain abnormal outliers (e.g., abnormal relative to the " normal" reference range and markedly abnormal criteria) at any time during the study and/or at the final visit. Many various detailed analyses were conducted relative to changes in serum bicarbonate.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

The sponsor noted that it considered that key findings based on laboratory evaluations in the all 3 studies were as follows :

• An overall mean decrease in serum bicarbonate of 3.40 mmol/L (i.e., 3.40 mEq/L) from the pretreatment baseline to open-label extension end point was observed in the *integrated analysis set*. As observed from shift analyses, when metabolic acidosis occurred, it was usually but not always early in the course of treatment. During the *double-blind (core) phase* of Study TOPMAT-PEP-3001, decrease in serum bicarbonate appeared to be dose related with mean changes of 0.72, -3.31, -4.07, and -5.15 mmol/L observed for the placebo, 5, 15, and 25 mg/kg/d groups, respectively.

• Mean ammonia levels increased by 6.70 µmol/L for the open-label *integrated analysis set*, and markedly high ammonia was observed in 8% of subjects. Elevated serum ammonia values occurred with markedly greater frequency in subjects who were receiving concomitant VPA. During the *double-blind (core) phase* of Study TOPMAT-PEP-3001, the small mean increases in ammonia observed in the topiramate 15 and 25 mg/kg/d groups were less than that observed in the placebo group.

• Mean changes in other laboratory assessments were not considered clinically relevant or were consistent with the increasing age of the subjects during the study. Most laboratory values remained stable for most subjects, and in general, the small shifts from pretreatment baseline observed in other laboratory values were not considered clinically relevant..

Clinical laboratory evaluations were examined for changes from baseline over time (descriptive statistics).

Study TOPMAT-PEP-1002 Open-Label Treatment (Core) Phase

• On average, mean serum bicarbonate decreased from pretreatment baseline to end point more in subjects in the 25 mg/kg/d group (-6.33 mmol/L) than subjects in the other 3 groups (-2.21, -1.36 and -3.64 mmol/L for the 3, 5, and 15 mg/kg/d groups, respectively).

• The sponsor noted that there were no apparent dosage-related changes in liver function test results or serum ammonia.

Study TOPMAT-PEP-3001 Double-Blind (Core) Phase

• A mean decrease in serum bicarbonate was associated with topiramate treatment. The decrease appeared to be dose related with mean changes of 0.72, -3.31, -4.07, and -5.15 mmol/L observed for the placebo, 5, 15, and 25 mg/kg/d groups, respectively.

• Mean serum chloride levels increased in topiramate patients and these increments appeared to be dose-related.

• The sponsor commented that there were no clinically meaningful mean changes in liver transaminases were observed in any treatment group. The sponsor also noted that the small changes in total and direct bilirubin observed with topiramate treatment were not dose related nor considered clinically relevant.

• The mean increases in alkaline phosphatase observed in the 3 topiramate groups (109.01 to 269.80 nkat/L) were greater than was observed in the placebo group (2.10 nkat/L). The sponsor did not consider that the increases appeared to be dose related. However, I believe that they are dose-related because I do not necessarily expect progressive, monotonic increases but rather view the changes as occurring over a range and not as precise point estimates. The sponsor further commented that these small changes were not considered clinically relevant.

• The small mean increases in ammonia observed in the topiramate 15 and 25 mg/kg/d groups were less than that observed in the placebo group.

• Small mean increases in creatinine were observed in the 3 topiramate groups compared with a small mean decrease in the placebo group. Although the sponsor did not consider the increase to be dose-related, I believe that they are dose-related because the greatest increment occurred with the highest dose (25 mg/kg/d) and I do not necessarily expect progressive, monotonic increases but rather view the changes as occurring over a range and not as precise point estimates. The sponsor also commented that these small changes were not considered clinically relevant.

• A small mean decrease in potassium was observed in the 3 topiramate groups, but not in the placebo group. The sponsor commented that these changes were not considered clinically relevant.

• A mean decrease in platelets was observed with topiramate 5 and 25 mg/kg/d, but not at the 15 mg/kg/d dosage. The sponsor commented that these small changes were not considered clinically relevant.

The following table shows results for the mean baseline and mean change from baseline for selected clinical chemistry and hematology analyses.

A notable dose-related increase in mean serum protein from baseline occurred during the DB trial but was not shown in the following table of selected analytes. Iin this study, the mean change was approximately + 0.9, 2.7. 3.1, and 4.5 g/L for placebo, 5, 15, and 25 mg/kg/day respectively. The mean serum protein in all treatment groups was approximately 69 g/L.

Table 11: Selected Clinical Laboratory Analytes: Change From Baseline to End Point - Double-Blind (Core) Phase (Study TOPMAT-PEP-3001: Safety Analysis Set)

	Placebo (N=37)	TPM 5 mg/kg/d (N=38)	TPM 15 mg/kg/d (N=37)	TPM 25 mg/kg/d (N=37)
Chemistry				
Alkaline phosphatase (nkat/l)				
N	24	26	27	27
Mean baseline	3597.95	3584.05	3474.16	3774.21
Mean change (SD)	2.10 (784.588)	109.01 (854.916)	269.80 (850.428)	193.87 (524.804)
Alanine aminotransferase (U/L)				
N	25	27	23	24
Mean baseline	24.48	32.89	23.61	25.21
Mean change (SD)	5.56 (18.337)	-3.33 (15.123)	1.13 (11.307)	-1.92 (11.847)
Aspartate aminotransferase (U/L)				
N	25	26	27	27
Mean baseline	39.08	57.88	40.15	50.89
Mean change (SD)	5.60 (21.109)	-3.96 (46.066)	-1.74 (25.765)	1.89 (36.262)
Bilirubin (umol/l)				
N	24	26	25	26
Mean baseline	2.70	2.68	3.21	2.88
Mean change (SD)	-0.71 (2.139)	1.12 (9.090)	-1.24 (3.935)	0.79 (8.011)
Direct bilirubin (umol/l)				
N	24	25	26	25
Mean baseline	0.50	0.96	0.98	0.54
Mean change (SD)	-0.14 (1.219)	0.55 (7.418)	-0.59 (2.858)	1.37 (6.731)
Ammonia (umol/l)				
N	19	22	20	21
Mean baseline	26.47	40.95	36.05	39.67
Mean change (SD)	5.32 (17.830)	-1.82 (27.550)	2.45 (28.489)	3.90 (23.694)
Carbon dioxide (mmol/L)				
N	25	26	27	27
Mean baseline	23.68	23.92	23.00	24.22
Mean change (SD)	0.72 (5.712)	-3.31 (2.739)	-4.07 (3.951)	-5.15 (5.044)
Chloride (mmol/L)				
N	25	27	27	25
Mean baseline	105.64	105.33	105.04	106.00
Mean change (SD)	-0.64 (3.850)	2.11 (3.262)	5.37 (5.256)	3.96 (4.458)

Sodium (mmol/L)				
N	25	27	27	25
Mean baseline	138.44	137.96	139.48	138.60
Mean change (SD)	-0.52 (3.653)	0.81 (3.259)	-0.33 (12.869)	0.48 (3.687)
Potassium (mmol/L)				
N	24	26	27	24
Mean baseline	4.64	4.75	4.71	4.72
Mean change (SD)	0.00 (0.563)	-0.21 (0.889)	-0.35 (0.643)	-0.42 (0.478)
Urea nitrogen (mmol/L)				
N	25	27	27	25
Mean baseline	3.67	3.99	3.20	3.01
Mean change (SD)	-0.43 (1.814)	-0.21 (1.225)	0.25 (1.192)	0.59 (1.294)
Creatinine (umol/l)				
N	25	27	27	27
Mean baseline	27.93	27.83	28.49	27.84
Mean change (SD)	-1.06 (6.910)	5.58 (5.575)	3.94 (5.117)	6.55 (6.300)
Hematology				
WBC (giga/l)				
N	20	23	25	23
Mean baseline	11.21	10.36	10.60	12.12
Mean change (SD)	-0.61 (2.446)	0.50 (2.900)	1.00 (3.571)	0.50 (3.980)
Hematocrit (vol-%)				
N	20	23	25	23
Mean baseline	35.22	37.29	36.21	36.79
Mean change (SD)	1.39 (2.823)	1.84 (3.784)	0.58 (2.937)	1.13 (4.730)
Hemoglobin (g/L)				
N	20	23	25	23
Mean baseline	112.75	120.13	115.12	118.83
Mean change (SD)	3.45 (8.281)	4.22 (12.098)	1.12 (8.487)	4.65 (14.380)
Platelets (giga/l)				
N	16	18	19	13
Mean baseline	300.31	329.28	341.11	314.69
Mean change (SD)	21.19 (171.040)	-23.17 (129.174)	7.37 (132.898)	-71.77 (97.428)

tlab01.rtf generated by tlab01.sas.
Cross-reference: Mod5.3.5.1\TOPMAT-PEP-3001\Sec6.2.1\Table 18

Reviewer Comment

- There were changes in several clinical laboratory analytes in these very young pediatric patients that were remarkable, especially because most of them appeared to be novel and had not previously been described or noted in placebo-controlled studies of older pediatric or adults. Most of the notable observations relative to clinical laboratory analytes were derived from the placebo-controlled study. Topiramate produced notable changes in mean change from baseline or outliers in several clinical laboratory analytes (serum potassium, creatinine, BUN, total protein, alkaline phosphatase, bicarbonate, chloride, total eosinophil count) during the placebo-controlled study.

- Mean change from baseline was dose-related for all these analytes. The mean treatment difference/effect (25 mg/kg/d topiramate – placebo) was - 5.9 mEq/L for bicarbonate, + 4.6 mEq/L for chloride, - 0.4 mmol/L for potassium, + 1 mmol/L for BUN, + 7.7 mmol/L for creatinine, + 3.6 g/L for protein, and + 191 nkat/L for alkaline phosphatase.

- I consider that the mean change from baseline for all these analytes (except total eosinophil count) were dose-related. In considering the existence of a dose-relationship, I do not consider the mean changes as precise point estimates and do not require observing a progressive monotonic increased change with each higher dose that is greater than the immediately preceding lower dose and that all are drug doses are greater than that with placebo. I consider "adjacent" doses to represent potentially a range of values.

- Although the decrease in serum bicarbonate and increase in serum chloride are commonly recognized effects of topiramate in producing non-anion gap, hyperchloremic metabolic

acidosis, the magnitude (- 5..9 mEq/L for serum bicarbonate) and severity of these changes of metabolic acidosis (serum bicarbonate ≤ 20 mEq/L) are notably greater than that (mean serum bicarbonate treatment difference effect = - 3.6 mEq/L) observed previously in a controlled trial of in older children (2-16 years), who were treated with a target topiramate dose of ~ 6 mg/kg/d.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The following table shows the incidence of treatment-emergent abnormal (relative to the reference range) clinical laboratory values at the endpoint/final visit of the placebo-controlled phase (Study 3001).

Table 3001_ab1: Number and Percentage of Subjects with Treatment-Emergent Abnormal Clinical Laboratory Values at End Point Based on Normal Reference Range - Double-Blind Phase (TOPMAT-PEP-3001: Safety Analysis Set)

Lab Type Lab Test Name Abnormal High/Low	Placebo (N=37) n/N (%)	TPM 5 mg/kg/d (N=38) n/N (%)	TPM 15 mg/kg/d (N=37) n/N (%)	TPM 25 mg/kg/d (N=37) n/N (%)	Total TPM (N=112) n/N (%)
Chemistry					
Albumin					
Abnormal High	0	2/30 (7)	0	0	2/86 (2)
Abnormal Low	1/26 (4)	0	1/29 (3)	1/27 (4)	2/86 (2)
Alkaline Phosphatase					
Abnormal High	0	0	1/29 (3)	0	1/86 (1)
ALT (SGPT)					
Abnormal Low	0	0	0	1/25 (4)	1/81 (1)
Ammonia					
Abnormal High	1/26 (4)	3/27 (11)	1/27 (4)	2/23 (9)	6/77 (8)
Abnormal Low	0	1/27 (4)	0	1/23 (4)	2/77 (3)
AST (SGOT)					
Abnormal High	1/26 (4)	3/30 (10)	1/29 (3)	2/28 (7)	6/87 (7)
Bilirubin					
Abnormal High	0	1/30 (3)	0	1/28 (4)	2/85 (2)
Abnormal Low	5/26 (19)	3/30 (10)	8/27 (30)	4/28 (14)	15/85 (18)
Calcium					
Abnormal High	4/26 (15)	2/28 (7)	1/29 (3)	2/25 (8)	5/82 (6)
Carbon Dioxide					
Abnormal High	3/26 (12)	0	0	1/28 (4)	1/87 (1)
Abnormal Low	0	4/30 (13)	7/29 (24)	6/28 (21)	17/87 (20)
Chloride					
Abnormal High	2/26 (8)	9/29 (31)	15/29 (52)	14/26 (54)	38/84 (45)
Creatinine					
Abnormal High	0	2/30 (7)	1/29 (3)	1/27 (4)	4/86 (5)
Direct Bilirubin					
Abnormal High	0	1/29 (3)	0	1/28 (4)	2/86 (2)
GGT					
Abnormal High	0	0	0	1/24 (4)	1/82 (1)
Glucose					
Abnormal High	0	1/30 (3)	0	0	1/86 (1)
LDH					
Abnormal High	0	1/27 (4)	0	1/22 (5)	2/74 (3)
Abnormal Low	2/26 (8)	5/27 (19)	5/25 (20)	4/22 (18)	14/74 (19)

Phosphorus					
Abnormal High	1/26 (4)	4/29 (14)	1/29 (3)	0	5/85 (6)
Potassium					
Abnormal High	0	1/28 (4)	0	0	1/83 (1)
Abnormal Low	0	2/28 (7)	1/29 (3)	2/26 (8)	5/83 (6)
Protein					
Abnormal High	1/26 (4)	8/30 (27)	6/29 (21)	9/26 (35)	23/85 (27)
Sodium					
Abnormal High	0	0	1/29 (3)	0	1/84 (1)
Abnormal Low	2/26 (8)	1/29 (3)	1/29 (3)	0	2/84 (2)
Urea Nitrogen					
Abnormal High	0	1/30 (3)	1/29 (3)	0	2/85 (2)
Abnormal Low	0	0	0	1/26 (4)	1/85 (1)
Uric Acid					
Abnormal High	1/26 (4)	0	0	0	0
Abnormal Low	0	1/30 (3)	0	2/27 (7)	3/86 (3)

Abnormal Low = end point measurement < lower limit of the normal reference range for a subject whose baseline measurement was ≥ lower limit of the normal reference range.
Abnormal High = end point measurement > upper limit of the normal reference range for a subject whose baseline measurement was ≤ upper limit of the normal reference range.
The percentages (%)are computed as 100 x n/N. The numerators (n) represent the number of subjects with an Abnormal Low or Abnormal High value. The denominators (N) represent the number of subjects in the treatment group, and who had a measurement for the particular laboratory test. Subjects must have both a baseline and an end point measurement for the given laboratory test to be included in the percentage calculations.

Table 3001_ab1: Number and Percentage of Subjects with Treatment-Emergent Abnormal Clinical Laboratory Values Based on Normal Reference Range - Double-Blind Phase
(TOPMAT-PEP-3001: Safety Analysis Set)

Lab Type	Placebo	TPM 5 mg/kg/d	TPM 15 mg/kg/d	TPM 25 mg/kg/d	Total TPM
Lab Test Name	(N=37)	(N=38)	(N=37)	(N=37)	(N=112)
Upper Normal High/low	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Hematology					
Basophils					
Abnormal High	0	4/24 (17)	2/25 (8)	1/22 (5)	7/71 (10)
Eosinophils					
Abnormal High	1/21 (5)	4/26 (15)	3/28 (11)	3/26 (12)	10/80 (13)
Abnormal Low	2/21 (10)	0	1/28 (4)	0	1/80 (1)
Granulocytes					
Abnormal High	0	1/22 (5)	2/24 (8)	2/22 (9)	5/68 (7)
Abnormal Low	1/16 (6)	0	2/24 (8)	1/22 (5)	3/68 (4)
Hematocrit					
Abnormal High	3/21 (14)	7/28 (25)	5/28 (18)	5/26 (19)	17/82 (21)
Abnormal Low	0	1/28 (4)	1/28 (4)	0	2/82 (2)
Hemoglobin					
Abnormal High	2/21 (10)	3/28 (11)	0	3/26 (12)	6/82 (7)
Abnormal Low	0	1/28 (4)	4/28 (14)	0	5/82 (6)
Lymphocytes					
Abnormal High	0	1/27 (4)	0	2/26 (8)	3/81 (4)

Abnormal Low	0	1/27 (4)	2/28 (7)	2/26 (8)	5/81 (6)
Monocytes					
Abnormal High	2/21 (10)	3/27 (11)	3/27 (11)	6/26 (23)	12/80 (15)
Abnormal Low	0	0	0	1/26 (4)	1/80 (1)
Nonsegm Neutrophils					
Abnormal Low	1/3 (33)	0	1/2 (50)	0	1/3 (33)
Platelets					
Abnormal High	2/17 (12)	1/23 (4)	2/23 (9)	0	3/63 (5)
Abnormal Low	1/17 (6)	1/23 (4)	1/23 (4)	0	2/63 (3)
RBC					
Abnormal High	0	1/28 (4)	1/28 (4)	5/26 (19)	7/82 (9)
Abnormal Low	0	2/28 (7)	1/28 (4)	1/26 (4)	4/82 (5)
Segm Neutrophils					
Abnormal High	1/5 (20)	0	1/4 (25)	0	1/13 (8)
Abnormal Low	0	1/5 (20)	1/4 (25)	1/4 (25)	3/13 (23)
Total Eosinophils					
Abnormal High	1/21 (5)	2/26 (8)	2/28 (7)	3/26 (12)	7/80 (9)
WBC					
Abnormal High	0	1/28 (4)	0	2/26 (8)	3/82 (4)
Urinalysis					
U Renal Tub Cells					
Abnormal High	1/10 (10)	0	0	0	0
U Sp Gravity					
Abnormal High	1/18 (6)	0	0	2/26 (8)	2/76 (3)
Abnormal Low	2/18 (11)	4/27 (15)	3/23 (13)	3/26 (12)	10/76 (13)
Urine RBC					
Abnormal High	1/8 (13)	1/16 (6)	0	0	1/38 (3)
Urine WBC					
Abnormal High	1/9 (11)	0	0	0	0

See footnotes on the first page of the table.
3001_ab1.rtf generated by 3001_ab1.sas.

In response to a DNP request because these data had not been submitted, the sponsor submitted shift data for total eosinophils controlled study 3001 showing the shifts from low, normal, or high at baseline to low, normal, or high at the end of treatment (20 days). **These data showed that topiramate treatment produced a noteworthy dose-related increase in the % of patients who had a shift from normal at baseline to high/increased (above the normal reference range) in total eosinophils at the end of treatment. Results were 6 % for placebo, 10 % for 5 mg/kg/d, 9 % for 15 mg/kg/d, 14 % for 25 mg/kg/d, and 11% for any topiramate dose.**

Reviewer Comment

- The incidence of metabolic acidosis (when baseline serum bicarbonate was $\geq$ 20 mEq/L) was 0 % for placebo, 30 % for 5 mg/kg/d, 50 % for 15 mg/kg/d, and 45 % for 25 mg/kg/d. The incidence of "markedly abnormal changes" (< 17 mEq/L and > 5 mEq/L decrease from baseline of $\geq$ 20) was 0 % for placebo, 4% for 5 mg/kg/d, 5 % for 15 mg/kg/d, and 5 % for 25 mg/kg/d.

- Notable changes in outliers (relative to the reference range) for the analytes that showed remarkable mean topiramate-induced changes from baseline (vs placebo) were observed for serum creatinine, BUN, total protein, and potassium. Topiramate treatment resulted in an increased incidence of patients with increased creatinine (any topiramate dose 5 %, placebo 0

%), BUN (any topiramate dose 3 %, placebo 0 %), and protein (any topiramate dose 34 %, placebo 6 %), and an increased incidence of decreased potassium (any topiramate dose 7 %, placebo 0 %). These increased frequencies of abnormal values did not appear to be dose-related. Of potential relevance, the current topiramate labeling notes an increased incidence of hypokalemia with topiramate treatment (0.4 %) vs placebo (0.1 %.

Topiramate treatment also produced a noteworthy dose-related increase in the percentage of patients who had a shift from normal at baseline to high/increased (above the normal reference range) in total eosinophil count at the end of treatment. The incidence of these abnormal shifts was 6 % for placebo, 10 % for 5 mg/kg/d, 9 % for 15 mg/kg/d, 14 % for 25 mg/kg/d, and 11% for any topiramate dose.

Outliers for Open-Label, Extension Study

The immediately following table shows the incidence of abnormal clinical laboratory analytes (relative to the reference range) **at ANY time** during the long-term, open-label, extension study. The subsequent table shows the incidence of abnormal clinical laboratory analytes (relative to the reference range) **at the FINAL visit** during the long-term, open-label, extension.

Table OL_ABN1: Number and Percentage of Subjects with Treatment-Emergent Abnormal Clinical Laboratory Values Based on Normal Reference Range at Any Time during the Combined Core and Open-Label Extension Phases (TOPMAT-PEP-1002 and TOPMAT-PEP-3001 Integrated OL Extension: Safety Analysis Set)

Lab Type: CHEMISTRY

Parameter Abnormal High/Low	<20 mg/kg/day (N=273) n/N (%)	20-40 mg/kg/day (N=215) n/N (%)	>40 mg/kg/day (N=69) n/N (%)	Any Dose (N=284) n/N (%)
ALBUMIN (g/L)				
Abnormal High	2/186(1)	0	0	2/273(1)
Abnormal Low	13/186(7)	12/196(6)	5/57 (9)	25/273(9)
ALKALINE PHOSPHATASE (nkat/l)				
Abnormal High	17/186(9)	13/195(7)	4/57 (7)	32/273(12)
ALT (SGPT) (U/L)				
Abnormal High	1/183(1)	5/193(3)	0	6/272(2)
Abnormal Low	8/183(4)	7/193(4)	3/57 (5)	18/272(7)
AMMONIA (umol/l)				
Abnormal High	17/178(10)	52/193(27)	16/57 (28)	69/273(25)
Abnormal Low	12/178(7)	4/193(2)	0	15/273(5)
AST (SGOT) (U/L)				
Abnormal High	15/187(8)	22/196(11)	9/57 (16)	38/273(14)
BILIRUBIN (umol/l)				
Abnormal High	2/187(1)	5/195(3)	0	7/273(3)
Abnormal Low	57/187(30)	70/195(36)	23/57 (40)	122/273(45)
CALCIUM (mmol/L)				
Abnormal High	18/184(10)	20/193(10)	5/56 (9)	39/273(14)
CARBON DIOXIDE (mmol/L)				
Abnormal High	20/186(11)	14/196(7)	2/57 (4)	34/273(12)
Abnormal Low	54/186(29)	93/196(47)	25/57 (44)	136/273(50)
CHLORIDE (mmol/L)				
Abnormal High	101/185(55)	104/194(54)	26/57 (46)	149/273(55)
Abnormal Low	2/185(1)	0	0	2/273(1)
CREATININE (umol/l)				
Abnormal High	10/186(5)	11/196(6)	3/57 (5)	22/273(8)
Abnormal Low	0	1/196(1)	0	1/273(<1)
DIRECT BILIRUBIN (umol/l)				
Abnormal High	4/187(2)	6/195(3)	0	10/273(4)
GGT (U/L)				
Abnormal High	23/184(13)	29/193(15)	10/57 (18)	50/273(18)
Abnormal Low	3/184(2)	0	0	3/273(1)
GLUCOSE (mmol/L)				
Abnormal High	13/186(7)	16/196(8)	5/56 (9)	32/273(12)
Abnormal Low	5/186(3)	3/196(2)	0	8/273(3)
LDH (U/L)				
Abnormal High	7/179(4)	13/191(7)	4/57 (7)	23/273(8)
Abnormal Low	35/179(20)	51/191(27)	13/57 (23)	78/273(29)
PHOSPHORUS (mmol/L)				
Abnormal High	12/185(6)	16/196(8)	4/57 (7)	27/273(10)
Abnormal Low	16/185(9)	12/196(6)	6/57 (11)	32/273(12)
POTASSIUM (mmol/L)				
Abnormal High	4/184(2)	7/193(4)	0	11/273(4)
Abnormal Low	35/184(19)	42/193(22)	8/57 (14)	73/273(27)
PROTEIN (g/L)				
Abnormal High	56/186(30)	56/196(29)	14/57 (25)	97/273(36)
Abnormal Low	2/186(1)	0	1/57 (2)	3/273(1)
SODIUM (mmol/L)				
Abnormal High	11/184(6)	19/193(10)	3/57 (5)	30/273(11)
Abnormal Low	16/184(9)	15/193(8)	3/57 (5)	32/273(12)
UREA NITROGEN (mmol/L)				
Abnormal High	18/186(10)	9/196(5)	2/57 (4)	26/273(10)
Abnormal Low	9/186(5)	15/196(8)	2/57 (4)	25/273(9)
URIC ACID (umol/l)				
Abnormal High	3/186(2)	2/196(1)	0	4/273(1)
Abnormal Low	26/186(14)	34/196(17)	12/57 (21)	58/273(21)

In the column headings, (N=xxx) represents the number of subjects who received a dose in the given topiramate dose range at any time during the open-label extension. A subject may therefore be in more than one topiramate dose range.
[Yrs Exp] = subject years of exposure for the given dose range.
Abnormal Low = post-baseline measurement < lower limit of the normal reference range for a subject whose baseline measurement was ≥ lower limit of the normal reference range.
Abnormal High = post-baseline measurement > upper limit of the normal reference range for a subject whose baseline measurement was ≤ upper limit of the normal reference range.
The percentages (%) are computed as 100 x n/N. The numerators (n) represent the number of subjects with an Abnormal Low or Abnormal High value. The denominators (N) represent the number of subjects who received a dose in the given range, and who had a measurement for the particular laboratory test. Subjects must have both a baseline and a post-baseline measurement for the given laboratory test to be included in the percentage calculations.

Table OL_ABN1: Number and Percentage of Subjects with Treatment-Emergent Abnormal Clinical Laboratory Values Based on Normal Reference Range at Any Time during the Combined Core and Open-Label Extension Phases (TOPMAT-PEP-1002 and TOPMAT-PEP-3001 Integrated OL Extension: Safety Analysis Set)

Lab Type: HEMATOLOGY

Parameter Abnormal High/low	<20 mg/kg/day (N=272) n/N (%)	20-40 mg/kg/day (N=215) n/N (%)	>40 mg/kg/day (N=69) n/N (%)	Any Dose (N=284) n/N (%)
BASOPHILS (%)				
Abnormal High	23/150(15)	24/170(14)	5/48 (10)	44/245(18)
EOSINOPHILS (%)				
Abnormal High	31/176(18)	49/189(26)	12/51 (24)	81/270(30)
Abnormal Low	10/176(6)	24/189(13)	4/51 (8)	34/270(13)
HEMATOCRIT (vol-%)				
Abnormal High	42/178(24)	55/190(29)	12/52 (23)	95/272(35)
Abnormal Low	25/178(14)	27/190(14)	4/52 (8)	47/272(17)
HEMOGLOBIN (g/L)				
Abnormal High	20/178(11)	26/190(14)	9/52 (17)	44/272(16)
Abnormal Low	23/178(13)	29/190(15)	9/52 (17)	50/272(18)
LYMPHOCYTES (%)				
Abnormal High	22/178(12)	18/190(9)	1/52 (2)	37/272(14)
Abnormal Low	30/178(17)	49/190(26)	6/52 (12)	77/272(28)
MONOCYTES (%)				
Abnormal High	40/178(22)	42/189(22)	13/52 (25)	81/272(30)
Abnormal Low	8/178(4)	2/189(1)	2/52 (4)	12/272(4)
NEUTROPHILS (%)				
Abnormal High	16/135(12)	27/162(17)	1/44 (2)	42/222(19)
Abnormal Low	24/135(18)	40/162(25)	7/44 (16)	61/222(27)
NONSEGM NEUTROPHILS (%)				
Abnormal High	1/41 (2)	0	0	1/61 (2)
Abnormal Low	2/41 (5)	4/25 (16)	1/8 (13)	5/61 (8)
PLATELETS (giga/l)				
Abnormal High	26/159(16)	24/175(14)	5/46 (11)	51/256(20)
Abnormal Low	15/159(9)	15/175(9)	5/46 (11)	33/256(13)
RBC (tera/l)				
Abnormal High	23/178(13)	22/190(12)	4/52 (8)	44/272(16)
Abnormal Low	9/178(5)	11/190(6)	1/52 (2)	20/272(7)
SEGM NEUTROPHILS (%)				
Abnormal High	13/53 (25)	12/39 (31)	1/9 (11)	22/75 (29)
Abnormal Low	9/53 (17)	2/39 (5)	3/9 (33)	14/75 (19)
TOTAL EOSINOPHILS				
Abnormal High	24/176(14)	32/189(17)	6/51 (12)	53/270(20)
WBC (giga/l)				
Abnormal High	7/178(4)	19/190(10)	1/52 (2)	27/272(10)
Abnormal Low	13/178(7)	17/190(9)	3/52 (6)	31/272(11)

U RENAL TUB CELLS (/HPF)				
Abnormal High	5/141(4)	9/141(6)	0	14/240(6)
U SP GRAVITY (g/ml)				
Abnormal High	6/177(3)	3/180(2)	1/47 (2)	10/264(4)
Abnormal Low	38/177(21)	29/180(16)	4/47 (9)	63/264(24)
U TRANS EPI CELLS (/HPF)				
Abnormal High	4/140(3)	4/142(3)	0	8/238(3)
URINE HYALINE CASTS (/LPF)				
Abnormal High	3/142(2)	5/144(3)	0	8/241(3)
URINE PH				
Abnormal High	13/177(7)	12/180(7)	5/47 (11)	29/264(11)
URINE RBC (/HPF)				
Abnormal High	3/124(2)	9/128(7)	1/34 (3)	13/221(6)
URINE UROBILINOGEN (umol/l)				
Abnormal High	2/176(1)	3/180(2)	0	5/264(2)
URINE WBC (/HPF)				
Abnormal High	5/128(4)	11/139(8)	1/33 (3)	17/227(7)

See footnotes on the first page of the table.
ol_abn1_t1.rtf generated by ol_abn1.sas.

Table OL_ABN1: Number and Percentage of Subjects with Treatment-Emergent Abnormal Clinical Laboratory Values Based on Normal Reference Range at the Final Visit During the Open-Label Extension Phase (TOPMAT-PEP-1002 and TOPMAT-PEP-3001 Integrated OL Extension)

Lab Type: CHEMISTRY

Parameter Abnormal High/low	<20 mg/kg/day (N=273) n/N (%)	20-40 mg/kg/day (N=215) n/N (%)	>40 mg/kg/day (N=69) n/N (%)	Any Dose (N=284) n/N (%)
ALBUMIN (g/L)				
Abnormal High	1/114(1)	0	0	1/233(<1)
Abnormal Low	7/114(6)	0	1/28 (4)	8/233(3)
ALKALINE PHOSPHATASE (nkat/l)				
Abnormal High	5/114(4)	2/91 (2)	1/28 (4)	8/233(3)
ALT (SGPT) (U/L)				
Abnormal High	0	2/90 (2)	0	2/232(1)
Abnormal Low	1/113(1)	1/90 (1)	1/29 (3)	3/232(1)
AMMONIA (umol/l)				
Abnormal High	4/108(4)	10/99 (10)	10/29 (34)	24/236(10)
Abnormal Low	3/108(3)	1/99 (1)	0	4/236(2)
AST (SGOT) (U/L)				
Abnormal High	3/114(3)	5/90 (6)	4/28 (14)	12/232(5)
BILIRUBIN (umol/l)				
Abnormal High	0	1/91 (1)	0	1/234(<1)
Abnormal Low	23/115(20)	26/91 (29)	5/28 (18)	54/234(23)
CALCIUM (mmol/L)				
Abnormal High	2/115(2)	5/91 (5)	0	7/234(3)
CARBON DIOXIDE (mmol/L)				
Abnormal High	8/113(7)	4/91 (4)	1/28 (4)	13/232(6)
Abnormal Low	9/113(8)	24/91 (26)	8/28 (29)	41/232(18)
CHLORIDE (mmol/L)				
Abnormal High	54/114(47)	40/91 (44)	12/29 (41)	106/234(45)
DIRECT BILIRUBIN (umol/l)				
Abnormal High	0	1/91 (1)	0	1/234(<1)
GGT (U/L)				
Abnormal High	6/113(5)	9/91 (10)	6/29 (21)	21/233(9)
GLUCOSE (mmol/L)				
Abnormal High	3/113(3)	1/92 (1)	3/27 (11)	7/232(3)
Abnormal Low	1/113(1)	0	0	1/232(<1)

LDH (U/L)				
Abnormal High	1/111(1)	2/96 (2)	2/29 (7)	5/236(2)
Abnormal Low	4/111(4)	15/96 (16)	6/29 (21)	25/236(11)
PHOSPHORUS (mmol/L)				
Abnormal High	5/114(4)	1/92 (1)	2/28 (7)	8/234(3)
Abnormal Low	8/114(7)	2/92 (2)	2/28 (7)	12/234(5)
POTASSIUM (mmol/L)				
Abnormal High	0	2/91 (2)	0	2/234(1)
Abnormal Low	7/114(6)	6/91 (7)	0	13/234(6)
PROTEIN (g/L)				
Abnormal High	19/113(17)	14/91 (15)	4/28 (14)	37/232(16)
SODIUM (mmol/L)				
Abnormal High	2/114(2)	3/91 (3)	0	5/234(2)
Abnormal Low	1/114(1)	1/91 (1)	1/29 (3)	3/234(1)
UREA NITROGEN (mmol/L)				
Abnormal High	6/113(5)	0	1/28 (4)	7/232(3)
Abnormal Low	2/113(2)	1/91 (1)	0	3/232(1)
URIC ACID (umol/l)				
Abnormal Low	13/114(11)	13/91 (14)	4/28 (14)	30/233(13)

In the column headings, (N=xxx) represents the number of subjects who received a dose in the given topiramate dose range at any time during the open-label extension. A subject may therefore be in more than one topiramate dose range.
[Yrs Exp] = subject years of exposure for the given dose range.
Abnormal Low = final visit measurement < lower limit of the normal reference range for a subject whose baseline measurement was ≥ lower limit of the normal reference range.
Abnormal High = final visit measurement > upper limit of the normal reference range for a subject whose baseline measurement was ≤ upper limit of the normal reference range.
The percentages (%) are computed as 100 x n/N. The numerators (n) represent the number of subjects with an Abnormal Low or Abnormal High value. The denominators (N) represent the number of subjects who received a dose in the given range, and who had a measurement for the particular laboratory test. Subjects must have both a baseline and a final visit measurement for the given laboratory test to be included in the percentage calculations.

Table OL_ABN1: Number and Percentage of Subjects with Treatment-Emergent Abnormal Clinical Laboratory Values Based on Normal Reference Range at the Final Visit During the Open-Label Extension Phase(continued)
(TOPMAT-PEP-1002 and TOPMAT-PEP-3001 Integrated OL Extension)

Lab Type: HEMATOLOGY

Parameter Abnormal High/low	<20 mg/kg/day (N=272) n/N (%)	20-40 mg/kg/day (N=215) n/N (%)	>40 mg/kg/day (N=69) n/N (%)	Any Dose (N=284) n/N (%)
BASOPHILS (%)				
Abnormal High	6/97 (6)	6/94 (6)	0	12/217(6)
EOSINOPHILS (%)				
Abnormal High	12/115(10)	11/93 (12)	2/27 (7)	25/235(11)
Abnormal Low	4/115(3)	8/93 (9)	2/27 (7)	14/235(6)
HEMATOCRIT (vol-%)				
Abnormal High	19/116(16)	14/93 (15)	5/27 (19)	38/236(16)
Abnormal Low	4/116(3)	5/93 (5)	2/27 (7)	11/236(5)
HEMOGLOBIN (g/L)				
Abnormal High	11/116(9)	6/93 (6)	3/27 (11)	20/236(8)
Abnormal Low	10/116(9)	12/93 (13)	3/27 (11)	25/236(11)
LYMPHOCYTES (%)				
Abnormal High	5/116(4)	3/93 (3)	1/27 (4)	9/236(4)
Abnormal Low	12/116(10)	7/93 (8)	2/27 (7)	21/236(9)
MONOCYTES (%)				
Abnormal High	12/116(10)	5/93 (5)	4/27 (15)	21/236(9)
Abnormal Low	1/116(1)	1/93 (1)	0	2/236(1)
NEUTROPHILS (%)				
Abnormal High	5/84 (6)	7/90 (8)	0	12/196(6)
Abnormal Low	9/84 (11)	11/90 (12)	1/22 (5)	21/196(11)
NONSEGM NEUTROPHILS (%)				
Abnormal Low	2/37 (5)	1/16 (6)	0	3/59 (5)
PLATELETS (giga/l)				
Abnormal High	9/108(8)	8/96 (8)	3/26 (12)	20/230(9)
Abnormal Low	1/108(1)	4/96 (4)	1/26 (4)	6/230(3)
RBC (tera/l)				
Abnormal High	9/116(8)	5/93 (5)	1/27 (4)	15/236(6)
Abnormal Low	3/116(3)	1/93 (1)	1/27 (4)	5/236(2)
SEGM NEUTROPHILS (%)				
Abnormal High	7/45 (16)	3/17 (18)	0	10/69 (14)
Abnormal Low	4/45 (9)	2/17 (12)	0	6/69 (9)
TOTAL EOSINOPHILS				
Abnormal High	8/109(7)	6/92 (7)	2/26 (8)	16/227(7)
WBC (giga/l)				
Abnormal High	3/116(3)	3/93 (3)	1/27 (4)	7/236(3)
Abnormal Low	2/116(2)	4/93 (4)	0	6/236(3)

U RENAL TUB CELLS (/HPF)				
Abnormal High	3/102(3)	1/97 (1)	0	4/226(2)
U SP GRAVITY (g/ml)				
Abnormal High	3/116(3)	0	0	3/230(1)
Abnormal Low	12/116(10)	9/82 (11)	1/32 (3)	22/230(10)
U TRANS EPI CELLS (/HPF)				
Abnormal High	2/100(2)	1/97 (1)	0	3/224(1)
URINE HYALINE CASTS (/LPF)				
Abnormal High	0	1/97 (1)	0	1/226(<1)
URINE PH				
Abnormal High	4/116(3)	3/82 (4)	1/32 (3)	8/230(3)
URINE RBC (/HPF)				
Abnormal High	1/94 (1)	2/90 (2)	1/24 (4)	4/208(2)
URINE UROBILINOGEN (umol/l)				
Abnormal High	0	1/83 (1)	0	1/230(<1)
URINE WBC (/HPF)				
Abnormal High	1/94 (1)	5/97 (5)	0	6/214(3)

See footnotes on the first page of the table.
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Sponsor's Summary of Outlier Results

Study TOPMAT-PEP-1002 Open-Label Treatment (Core) Phase

• The laboratory profiles for most subjects remained stable or normalized during the core phase.

Study TOPMAT-PEP-3001 Double-Blind (Core) Phase

• A larger proportion of subjects treated with topiramate compared with placebo had a shift in serum bicarbonate from normal at baseline to below the normal range at the end of double-blind treatment (26% vs. 0) and in serum chloride from normal at baseline to above the normal range at the end of double-blind treatment (71% vs. 15%.

• A larger proportion of subjects treated with topiramate than placebo had a shift from normal at baseline to above the normal range at the end of double-blind treatment in serum protein (34% vs. 6%). The individual elevations in serum protein were not clinically significant.

• Most laboratory values remained stable for most subjects, and the small differences between treatments in shifts from baseline observed in other laboratory values were not considered clinically relevant.

Studies TOPMAT-PEP-1002 and -3001 Integrated Open-Label Extension

• Forty-six subjects (18%) had a shift in CO_2 from normal or high at pretreatment baseline to below the normal range at open-label extension end point, and 125 subjects (44%) had a shift in serum chloride from low or normal at baseline to above the normal range at open-label extension end point. . Generally metabolic acidosis occurred early during treatment, although cases occurred at any time.

• Shifts in alkaline phosphatase, ALT, AST, or GGT from normal at pretreatment baseline to high at open-label extension end point were observed in 11, 2, 12, and 23 subjects, respectively. There were no shifts from low to high.

• One subject had a shift in direct bilirubin levels from normal at pretreatment baseline to high at open-label extension end point. There were no shifts from low to high. One subject had a shift in total bilirubin levels from low at pretreatment baseline to high at open-label extension end point.

• Twenty-four (8%) subjects had a shift in ammonia levels from normal at pretreatment baseline to high at open-label extension end point (see also Section 2.1.5.5). There were no shifts from low to high.

• No shifts occurred in creatinine levels from low or normal at pretreatment baseline to high at open-label extension end point. Ten subjects had a shift in BUN from low or normal to high and 5 subjects had a shift from normal to low.

• Most laboratory values remained stable for most subjects, and in general, the small shifts from pretreatment baseline observed in other laboratory values were not considered clinically relevant.

Reviewer Comment

- In the open-label, long-term extension study, there were some outlier results occurring at ANY time in the study that I consider notetworthy.
    - Ammonia levels showed a dose-related increased incidence of elevated values at the 2 highest dose ranges (20-40 mg/kg/g 27 %, > 40 mg/kg/d 28 %) vs the lowest dose range (< 20 mg/kg/d 10 %).
    - Serum bicarbonate showed a dose-related increased incidence at the 2 highest dose ranges (20-40 mg/kg/g 47 %, > 40 mg/kg/d 48 %) vs the lowest dose range (< 20 mg/kg/d 29 %).
    - Serum creatinine for all dose ranges that had a similar incidence showed an overall incidence of increased values of 8 %.
    - The overall incidence of decreased and increased serum phosphorus values were similar for all doses at 12 %, and 10 %, respectively.
    - The incidence of increased serum total protein levels was similar for all dose ranges and the overall incidence for all doses was relatively high at 36 %, an incidence similar to that at the end of the placebo-controlled study.
    - Total eosinophils showed a dose-related increased incidence at the 2 highest dose ranges (20-40 mg/kg/g 26 %, > 40 mg/kg/d 24 %) vs the lowest dose range (< 20 mg/kg/d 18 %).

- In the open-label, long-term extension study, there were some outlier results occurring at the FINAL visit in the study that I consider notetworthy.
    - Overall, not unexpectedly, the incidence of abnormally increased or decreased values for all analytes was lower at the final visit incidence analyses compared to the any visit incidence analyes.
    - Ammonia levels showed a dose-related increased incidence of elevated values with the greatest incidence occurring at the highest dose range (> 40 mg/kg/d 34 %) vs the lower dose ranges (< 20 mg/kg/d 4 %, 20-40 mg/kg/g 10 %,).
    - Serum bicarbonate showed a dose-related increased incidence at the 2 highest dose ranges (20-40 mg/kg/g 26 %, > 40 mg/kg/d 29 %) vs the lowest dose range (< 20 mg/kg/d 8 %).
    - The incidence of increased serum total protein levels was similar for all dose ranges and the overall incidence for all doses was still relatively notably high at 16 % %.

Other Data Sources (Randomized, double-blinded, placebo-controlled study MIGR-3006 for adolescents 12-16 year for topiramate treatment as migraine prophylaxis)

- The final study report for the above study of adolescent administering topiramate as migraine prophylaxis showed that there was a dose-related increased incidence shift for serum creatinine from normal at baseline to elevated values at 4 months for topiramate (placebo 4 %, 50 mg/d 4 %, 100 mg/d 18 %, any topiramate dose 11%). There was no notable changes from baseline in mean serum creatinine or BUN and no noteworthy shift in BUN to increased values. This increased incidence of outliers for increased creatinine provides additional support to the observations noted in infants/toddlers regarding an increase of creatinine.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

The analyses described below are based on criteria for treatment-emergent markedly abnormal values that were defined in the study protocols.

Study TOPMAT-PEP-1002 Open-Label Treatment (Core) Phase

• The incidences of all protocol-defined markedly abnormal clinical laboratory values except low serum CO_2 were <5%.

• Six (11%) subjects had treatment-emergent markedly abnormal low serum CO_2 level during the core phase. In no case was the serum CO_2 level decreased to below 10 mmol/L (the lowest level of serum CO_2 measured in these 6 subjects was 12 mmol/L). Four of the 6 cases were coincident with infectious diseases or associated with poor quality of blood samples. In 3 of the 6 subjects, a serum CO_2 level below 17 mmol/L was first detected on the last day of the core phase. In the other 3 subjects, serum CO_2 levels had recovered from the lowest level by the end of the core phase. Four of the 6 subjects were in the highest dosage (25 mg/kg/d) group. Metabolic acidosis was reported in 1 of the 6 subjects. There was no change in the study treatment in any of the 6 subjects as a result of a decreased serum CO_2 level. None of the subjects required any alkali treatment.

• Subject 101033 had a markedly abnormally high serum ammonia level (145 mmol/L, normal: 10-64) on the last day of the core phase (Visit 5). Subject 101053 had a higher than normal serum ammonia level (74 mmol/L) at Visit 4, which was reported as mild hyperammonemia. There was no change in study treatment in either case. In both cases, topiramate was taken as add-on therapy to VPA, which is known to cause hyperammonemia. Also the poor quality of blood samples has rendered the test results in both cases questionable.

• One subject (Subject 101016) had a markedly abnormal total bilirubin level (46.17 mmol/L, normal: 1.71-17.1) at the last day of the core phase (Visit 5).

• One subject (Subject 101008) had a markedly abnormal high direct bilirubin level (15.39 mmol/L; normal: 0-8.55) at the last day of the core phase (Visit 5).

Study TOPMAT-PEP-3001 Double-Blind (Core) Phase

• No placebo-treated subjects had a protocol-defined treatment-emergent markedly abnormal clinical chemistry value; all abnormalities were observed for topiramate-treated subjects.

• Seven subjects had a markedly low bicarbonate value (300245, 300263, 300282, 300294, 300457, 300619, and 300689). Abnormally high total and direct bilirubin was observed in 2 subjects (300378 and 300702).

Studies TOPMAT-PEP-1002 and -3001 Integrated Open-Label Extension

• Markedly low platelet count (≤$80x10^3/mm^3$) was observed in 26 subjects (9%). Many of these subjects had clumped samples, which can give an erroneously low reading. Thrombocytopenia resolved at later visits for all except 2 subjects (300415 and 300645) who had low counts at open-label extension end point. Markedly high WBC count (≥$20.0x10^3/mm^3$) was observed in 25 subjects (9%), although 9 of these subjects had recent adverse events of infections prior to their high WBC count. Markedly low hemoglobin was observed in 8 subjects (3%).

• The most frequent protocol-defined abnormal values were markedly low CO_2 (defined as <17 mmol/L and a decrease of >5 mmol/L), observed in 115 subjects (40% overall). Sixty-six subjects (23%) had persistent treatment-emergent decreases (defined as <17 mmol/L at 2 consecutive visits) in serum CO_2 values..

• Markedly high chloride was observed in 3 subjects.

• Markedly high ALT, AST, or GGT were observed in 2, 4, and 12 subjects, respectively. Markedly high direct bilirubin (≥0.6 mg/dL) was observed in 18 subjects (6%), although the sponsor noted that many of these subjects had a poor quality sample.

• Markedly high ammonia [≥128 µmol/L (and ≥1.5x baseline, if available)] was observed in 24 subjects (8%).
• Markedly high BUN or high uric acid was observed in 2 and 1 subject, respectively.

The following table shows the incidence of markedly abnormal results in the placebo-controlled study (3001).

TOPMAT-PEP-3001 Additional Safety Request FDA July 2007

Output DLAB11: Number of Subjects with DNP Defined Treatment-Emergent Markedly Abnormal Clinical Laboratory Values - Double Blind Phase

Analysis Set: Safety

Lab Type Lab Test Name Indicator	Placebo (N=37) n (%)	TPM 5 mg/kg/d (N=38) n (%)	TPM 15 mg/kg/d (N=37) n (%)	TPM 25 mg/kg/d (N=37) n (%)	All TPM (N=112) n (%)
Chemistry					
Alkaline Phosphatase	0	1 (3)	0	0	1 (1)
Markedly Abnormal High	0	1 (3)	0	0	1 (1)
Ammonia	0	0	1 (3)	2 (5)	3 (3)
Markedly Abnormal High	0	0	1 (3)	2 (5)	3 (3)
Bilirubin	0	1 (3)	0	1 (3)	2 (2)
Markedly Abnormal High	0	1 (3)	0	1 (3)	2 (2)
Calcium	0	2 (5)	1 (3)	0	3 (3)
Markedly Abnormal Low	0	2 (5)	1 (3)	0	3 (3)
Carbon Dioxide	1 (3)	10 (26)	17 (46)	19 (51)	46 (41)
Markedly Abnormal Low: <=20	0	8 (21)	14 (38)	16 (43)	38 (34)
Markedly Abnormal Low: <=17	0	4 (11)	7 (19)	7 (19)	18 (16)
Markedly Abnormal Low: <17 and Change >5	0	2 (5)	2 (5)	3 (8)	7 (6)
Markedly Abnormal Low: <=15	1 (3)	1 (3)	3 (8)	3 (8)	7 (6)
Chloride	2 (5)	7 (18)	15 (41)	12 (32)	34 (30)
Markedly Abnormal High	2 (5)	7 (18)	15 (41)	12 (32)	34 (30)
Creatinine	0	0	0	2 (5)	2 (2)
Markedly Abnormal High	0	0	0	2 (5)	2 (2)
Direct Bilirubin	0	1 (3)	0	1 (3)	2 (2)
Markedly Abnormal High	0	1 (3)	0	1 (3)	2 (2)
Potassium	0	2 (5)	0	0	2 (2)
Markedly Abnormal High	0	2 (5)	0	0	2 (2)
Protein	0	1 (3)	0	0	1 (1)
Markedly Abnormal High	0	1 (3)	0	0	1 (1)
Hematology					
Hematocrit	0	1 (3)	0	1 (3)	2 (2)
Markedly Abnormal High	0	1 (3)	0	1 (3)	2 (2)
Hemoglobin	0	0	1 (3)	0	1 (1)
Markedly Abnormal Low	0	0	1 (3)	0	1 (1)
Platelets	0	3 (8)	2 (5)	2 (5)	7 (6)
Markedly Abnormal High	0	2 (5)	2 (5)	1 (3)	5 (4)
Markedly Abnormal Low	0	1 (3)	0	1 (3)	2 (2)
Total Eosinophils*	1 (3)	1 (3)	1 (3)	1 (3)	3 (3)
Markedly Abnormal High	1 (3)	1 (3)	1 (3)	1 (3)	3 (3)
Total Granulocytes*	0	0	0	2 (5)	2 (2)
Markedly Abnormal High	0	0	0	2 (5)	2 (2)
WBC	0	0	0	1 (3)	1 (1)
Markedly Abnormal High	0	0	0	1 (3)	1 (1)

Note: Percentages calculated with the number of subjects in each group as denominator.
A Subject may be in more than one category.
*Absolute values calculated from total WBC and respective %.
The test called 'total granulocytes' is actually 'total neutrophils'. It does not include eosinophils and basophils.

Reviewer Comment

Placebo-Controlled Study 3001 (see immediately preceding table)

- Ammonia levels showed a dose-related increased incidence 0 % for placebo and 5 mg/kg/d, 3 % for 15 mg/kg/d, and 5 % for 25 mg/kg/d.

- Creatinine showed a noteworthy, dose-related increased incidence (topiramate 25 mg/kg/d 5 %, placebo 0 %) of a markedly abnormal change (an increase) in the controlled study (3001).

- Not surprisingly, there was a dose-related increased incidence of "markedly abnormal" values for various threshold decreases of serum bicarbonate. As the threshold decrease to be considered markedly abnormally low became more severe, the incidence of these markedly abnormal values decreased.

- Not surprisingly, there was a dose-related increased incidence of "markedly abnormal" serum chloride values, reflecting the changes occurring with metabolic acidosis.

Overall Reviewer Comment for Laboratory Findings

- (b) (5) **.** Of potential interest, topiramate treatment of older pediatric patients (e.g., adolescents, 12-16 years) for migraine prophylaxis treatment produced a dose-related increased shift in serum creatinine from normal at baseline to an increased value at the end of 4 months treatment in adolescent patients. The incidence of these abnormal shifts was 4 % for placebo, 4 % for 50 mg, 18 % for 100 mg, and 11% for any topiramate dose.

- (b) (5) **. Of potential interest, the investigators found the metabolic acidosis to be of sufficient concern to administer alkali treatment in ~ 23 % of all the patients (N=284) in the open-label extension study (usually in the open-label, extension study.**

- (b) (5) **.** Although there were no clear changes in serum phosphorus in the placebo-controlled phase of the infant/toddler studies, there appears to be an increased incidence of hypophosphatemia with topiramate treatment. Results (shown in the DNDP Clinical Review by Dr. Cynthia McCormick) from topiramate treatment of adjunctive partial epilepsy in placebo-controlled trials in adults in the original NDA submission for initial topiramate approval showed an increased incidence (topiramate 6 %, placebo 2 %) of markedly abnormally decreased values for serum phosphorus and an increased incidence (topiramate 3 %, placebo 1 %) of markedly abnormally increased values for serum Alkaline phosphatase (b) (5)

  Of potential relevance, a dose-related increase in serum alkaline phosphatase occurred in the placebo-controlled study of infants/toddlers.

  The significance of these changes in serum phosphorus remain to be shown. However, considering that metabolic acidosis increases phosphate excretion, conceivably the development of metabolic acidosis could be at least partially contributing to the lowering of serum phosphorus. In addition, there is a theoretical risk of osteomalacia from metabolic acidosis and chronic hypophosphatemia can also result in osteomalacia, that can be associated with an increased serum alkaline phosphatase.

7.1.7.4 Additional analyses and explorations

As a result of DNP requests and the special interest in metabolic acidosis and hyperammonemia, the sponsor conducted and submitted various analyses of serum bicarbonate and ammonia levels.

Special Analyses Related to Metabolic Acidosis

My analyses presented here will focus primarily on results from the placebo-controlled study (3001) and the long-term, open-label , extension study.

Sponsor's Summary of Results

Study TOPMAT-PEP-3001 Double-Blind (Core) Phas

• Of the 52 topiramate-treated subjects with normal chloride values at baseline (note that 33% of subjects had above-normal chloride values at baseline), 37 shifted to above normal values at end point (9 subjects in the 5 mg/kg/d group, 14 in the 15 mg/kg/d group, and 14 in the 25 mg/kg/d group); 2 of 13 placebo-treated subjects shifted from normal to above normal values. Chloride values that met the FDA definition of markedly abnormal high (≥ 112 mmol/L for ages 0-1 year, ≥ 109 mmol/L for ages ≥ 2 years) were observed in 34 topiramate-treated subjects (30%) with 7, 15, and 12 subjects, respectively, in the 5, 15, and 25 mg/kg/d groups, compared with 2 subjects in the placebo group

• Of the 57 topiramate-treated subjects with normal bicarbonate values at baseline, 15 shifted to values below the normal range at end point (4 in the 5 mg/kg/d group, 6 in the 15 mg/kg/d group, and 5 in the 25 mg/kg/d group); 3 of 17 placebo-treated subjects shifted from normal to above normal values. Bicarbonate values that met the FDA definition of abnormal low (≤ 20 mmol/L) were observed in 46 (41%) subjects (10, 17, and 19 subjects, respectively, in the 5, 15, and 25 mg/kg/d groups). Of these, 7 subjects (6%) had values ≤15 mmol/L (1, 3, and 3 subjects, respectively, in the 5, 15, and 25 mg/kg/d groups). One placebo-treated subject had a value ≤15 mmol.

The following tables show the effects of topiramate on specific threshold abnormalities/changes based upon baseline/pre-treatment values of $\geq$ 20 mEq/L and $\geq$ 17 mEq/L in the randomized, double-blind, placebo-controlled study 3001.

output DLAB14: Incidence of Subjects Whose Baseline Serum Bicarbonate Was >= 20 mEq/L and Developed a Serum Bicarbonate < 20 mEq/L During Double Blind

Analysis Set: SAFETY

Serum Bicarbonate Value	Placebo (N) (%)	TPM 5 mg/kg/d (N) (%)	TPM 15 mg/kg/d (N) (%)	TPM 25 mg/kg/d (N) (%)	All TPM (N) (%)
BASELINE >= 20 mEq/L*	18/25 (72.0)	23/26 (88.5)	22/27 (81.5)	20/27 (74.1)	65/80 (81.3)
BASELINE < 20 mEq/L*	7/25 (28.0)	3/26 (11.5)	5/27 (18.5)	7/27 (25.9)	15/80 (18.8)
FINAL VISIT**	0/18	7/23 (30.4)	11/22 (50.0)	9/20 (45.0)	27/65 (41.5)

Output DLAB17: Incidence of Subjects Whose Baseline Serum Bicarbonate Was >= 20 mEq/L and Developed a Serum Bicarbonate (< 17 mEq/L and > 5 mEq/L decrease from Baseline) During Double Blind

Analysis Set: SAFETY

Serum Bicarbonate Value	Placebo (N) (%)	TPM 5 mg/kg/d (N) (%)	TPM 15 mg/kg/d (N) (%)	TPM 25 mg/kg/d (N) (%)	All TPM (N) (%)
BASELINE >= 20 mEq/L*	18/25 (72.0)	23/26 (88.5)	22/27 (81.5)	20/27 (74.1)	65/80 (81.3)
BASELINE < 20 mEq/L*	7/25 (28.0)	3/26 (11.5)	5/27 (18.5)	7/27 (25.9)	15/80 (18.8)
FINAL VISIT**	0/18	1/23 (4.3)	1/22 (4.5)	1/20 (5.0)	3/65 (4.6)

Output DLAB19: Incidence of Subjects Whose Baseline Serum Bicarbonate was >= 17 mEq/L and Developed a Serum Bicarbonate < 17 mEq/L During Double Blind

Analysis Set: SAFETY

Serum Bicarbonate Value	Placebo (a) (%)	TPM 5 mg/kg/d (a) (%)	TPM 15 mg/kg/d (a) (%)	TPM 25 mg/kg/d (a) (%)	All TPM (a) (%)
BASELINE >= 17 mEq/L*	22/25 (88.0)	25/26 (96.2)	24/27 (88.9)	26/27 (96.3)	75/80 (93.8)
BASELINE < 17 mEq/L*	3/25 (12.0)	1/26 (3.8)	3/27 (11.1)	1/27 (3.7)	5/80 (6.3)
FINAL VISIT**	0/22	3/25 (12.0)	5/24 (20.8)	4/26 (15.4)	12/75 (16.0)

Output DLAB20: Incidence of Subjects Whose Baseline Serum Bicarbonate was >= 17 mEq/L and Developed a Serum Bicarbonate (< 17 mEq/L and > 5 mEq/L decrease from Baseline) During Double Blind

Analysis Set: SAFETY

Serum Bicarbonate Value	Placebo (a) (%)	TPM 5 mg/kg/d (a) (%)	TPM 15 mg/kg/d (a) (%)	TPM 25 mg/kg/d (a) (%)	All TPM (a) (%)
BASELINE >= 17 mEq/L*	22/25 (88.0)	25/26 (96.2)	24/27 (88.9)	26/27 (96.3)	75/80 (93.8)
BASELINE < 17 mEq/L*	3/25 (12.0)	1/26 (3.8)	3/27 (11.1)	1/27 (3.7)	5/80 (6.3)
FINAL VISIT**	0/22	1/25 (4.0)	2/24 (8.3)	2/26 (7.7)	5/75 (6.7)

Output DLAB21: Incidence of Subjects Whose Baseline Serum Bicarbonate was >= 17 mEq/L and Developed a Serum Bicarbonate (< 15 mEq/L and > 5 mEq/L decrease from Baseline) During Double Blind

Analysis Set: SAFETY

Serum Bicarbonate Value	Placebo (a) (%)	TPM 5 mg/kg/d (a) (%)	TPM 15 mg/kg/d (a) (%)	TPM 25 mg/kg/d (a) (%)	All TPM (a) (%)
BASELINE >= 17 mEq/L*	22/25 (88.0)	25/26 (96.2)	24/27 (88.9)	26/27 (96.3)	75/80 (93.8)
BASELINE < 17 mEq/L*	3/25 (12.0)	1/26 (3.8)	3/27 (11.1)	1/27 (3.7)	5/80 (6.3)
FINAL VISIT**	0/22	0/25	1/24 (4.2)	1/26 (3.8)	2/75 (2.7)

The incidence of metabolic acidosis by timeframe (at baseline, at any visit, and at 2 consecutive visits or the final visit) and for varying serum CO_2 thresholds was presented for the double-blind phase. The percentages of subjects with baseline serum CO_2 values of ≥22 mmol/L, ≥20 mmol/L, ≥17 mmol/L, ≥15 mmol/L, and ≥12 mmol/L was also presented.

• Of the 65 subjects whose baseline serum bicarbonate value was ≥20 mmol/L, 27 subjects (42%) had a treatment-emergent serum value at the final visit of <20 mmol/L,6 subjects (9%) had a treatment-emergent serum value at the final visit of <17 mmol/L, and 3 subjects (5%) had a treatment-emergent serum bicarbonate at the final visit of <17 mmol/L and a >5 mmol/L decrease from baseline. None had a treatment-emergent serum bicarbonate at the final visit of <15 mmol/L . Of the 18 placebo-treated subjects whose baseline serum bicarbonate was ≥20 mmol/L, none met any of these criteria for metabolic acidosis.

Studies TOPMAT-PEP-1002 and -3001 Integrated Open-Label Extension

Individual Abnormal Values (FDA-Defined Criteria)

Shifts in clinical laboratory values from pretreatment baseline to open-label extension end point according to normal range were shown. The number of subjects with FDA-defined treatment-emergent markedly abnormal clinical laboratory values was summarized.

• Of the 200 subjects with normal bicarbonate values at baseline, 13 shifted to values below the normal range at end point (5 subjects in the <20 mg/kg/d dose range, 7 in the 20-40 mg/kg/d dose range, and 1 in the >40 mg/kg/d dose range). Bicarbonate values that met one of many FDA definitions of markedly abnormal low (≤20 mmol/L) were observed at the open-label extension end point in 95 (41%) subjects, 35 (31%) in the <20 mg/kg/d modal dose range, 45 (49%) in the 20-40 mg/kg/d modal dose range, and 15 (54%) in the >40 mg/kg/d modal dose range. Of these, 25 subjects (11%) had values below 15 mmol/L: 5 (4%) in the <20 mg/kg/d dose range, 10 (11%) in the 20-40 mg/kg/d dose range, and 10 (36%) in the >40 mg/kg/d dose range.

• The incidence of metabolic acidosis by timeframe (at baseline, at final visit, at any visit, and at 2 consecutive visits and/or the final visit) and for varying serum bicarbonate thresholds was presented. The percentages of subjects with baseline serum bicarbonate of ≥22 mmol/L, ≥20 mmol/L, ≥17 mmol/L, ≥15 mmol/L, and ≥12 mmol/L was also shown.

•Of the 217 subjects whose baseline serum bicarbonate value was ≥20 mmol/L, 174 subjects (80%) developed a treatment-emergent serum bicarbonate value at any visit (including the final visit) of <20 mmol/L91 (42%) subjects developed a treatment-emergent serum bicarbonate value at any visit of <17 mmol/L, 41 (19%) subjects developed a treatment-emergent serum bicarbonate at any visit of<15 mmol/L, and 83 (38%) subjects developed a treatment-emergent serum bicarbonate value at any visit of <17 mmol/L and a >5 mmol/L decrease from baseline.

• Of the 253 subjects whose baseline serum bicarbonate value was ≥17 mmol/L, 116 (46%) subjects developed a treatment-emergent serum bicarbonate at any visit of <17 mmol/L, 58 (23%) subjects developed a treatment-emergent serum bicarbonate at any visit of <15 mmol/L, 92 (36%) subjects developed a treatment-emergent serum bicarbonate at any visit of <17 mmol/L and >5 mmol/L decrease from baseline, and 50 (20%) subjects developed a treatment-emergent serum bicarbonate at any visit of <15 mmol/L and >5 mmol/L decrease from baseline.

Reviewer Comment

- Regardless of how serum bicarbonate was assessed with varying required "baselines" values and varying post-treatment thresholds for significant effects, one cannot escape the conclusion that metabolic acidosis is an extremely common event that develops and can be quite significant in magnitude regarding the reduction on bicarbonate. As expected, as one applies a different threshold the

associated % data change. Of relevance, even if one applies a relatively low threshold (i.e., ≥ 17) for considering the lower limit of normal for the reference bicarbonate range (as some have suggested with clear, and adequate validation), the incidence of metabolic acidosis and more severe levels of acidosis remain considerable and of clear clinical relevance and import.

Special Analyses of Ammonia Levels

Upon DNP requests, the sponsor conducted many various analyses (mean change, incidence at any visit, incidence at final visit, shift % over time for outliers above the reference range, and markedly abnormal outliers, and also performed many subgroup analyses of these analyse based upon concomitant AED and presence or absence of metabolic acidosis (based upon serum bicarbonate < 20 mEq/L in the placebo-controlled study and based upon > 2 serum bicarbonates values that were < 20 mEq/L) in the open-label, extension study. Many subgroup analyses of ammonia levels were performed by concomitant AED grouped subjects as follows: VPA, any AED excluding VPA, and any AED.

Mean Changes of Ammonia

There were no clear topiramate-induced mean changes from baseline for ammonia levels in the placebo-controlled study.

In the open-label study there were some interesting findings over time, especially relative to presence or absence of concomitant VPA use.

The following table of topiramate modal dose range shows the mean change in plasma ammonia over time in the open-label extension study according to topiramate modal dose and presence or absence of VPA as a concomitant AED. Data show that highest dose range topiramate appears to show increased mean changes of plasma ammonia from week 20 through week 52 or final visit (i.e., study endpoint) for patients on VPA or even without concomitant VPA compared to results for the 2 lower dose ranges..

Effect of Topiramate Modal Dose on Mean Change from Baseline for Mean Plasma Ammonia Over Time in Open_Label Extension Study According to VPA as C oncomitant AED

Timeframe		Modal Topiramate Dose (mg/kg/day)							
		< 20		20-40		> 40		Any Dose	
	Concomitant AED	VPA	Exclude VPA	VPA	Exclude VPA	VPA	Exclude VPA	VPA	Exclude VPA
Baseline	**Mean Plasma Ammonia* (µmol/L) (#Pts)**	**42**(39)	**32**(43)	**38**(57)	**36**(38)	**44**(21)	**31**(10)	**40**(117)	**33**(91)
	Mean Plasma Ammonia* (µmol/L) (#Pts) Change from Baseline								
Core		17(14)	1(16)	2(36)	-4(20)	22(14)	0(6)	9(64)	-2(42)
OLE Wk 2		4(31)	0(29)	12(41)	8(27)	17(20)	3(7)	10(92)	4(63)
OLE Wk 6		-1(26)	2(38)	12(43)	2(20)	22(18)	0(8)	10(87)	2(66)
OLE Wk 12		-12(22)	2(31)	19(43)	-5(20)	19(18)	-1(5)	11(83)	-1(56)
OLE Wk 20		-13 (14)	5(24)	10(43)	-3(24)	**18**(18)	**78**(6)	8(75)	10(54)
OLE Wk 28		-14(13)	-3(22)	-15(28)	-7(27)	**17**(13)	**86**(6)	8(54)	5(55)
OLE Wk 40		0(16)	-3(19)	2(23)	-5(19)	**20**(11)	**16**(7)	5(50)	-1(45)
OLE Wk 52		-21(8)	-3(16)	13(19)	-9(14)	**33**(10)	**8**(5)	11(37)	-4(35)
OLE "End"		4(28)	-4(31)	11(42)	-3(38)	**26**(18)	**63**(9)	12(88)	4(78)
	Mean Plasma Ammonia* (µmol/L) (#Pts)								
OLE Wk 52		38(8)	25(19)	47(24)	28(16)	65(16)	45(5)	52(48)	29(40)
OLE "End"		46(31)	30(37)	48(48)	33(48)	64(24)	92(10)	51(103)	38(95)

The following tabular outlier analyses show the incidence of increased plasma ammonia in various subgroup analyses with regard to presence of absence of VPA and low serum bicarbonate.

The incidence of hyperammonemia in the placebo-controlled study is shown in the following table including with subgroup analyses for VPA and metabolic acidosis (low bicarbonate). This table shows somewhat dose-related increase in the incidence of hyerpammonemia with VPA and with any AED but no clear effect of presence of absence of metabolic acidosis.

Table 3001_a4: Number of Subjects with Treatment-Emergent Abnormal Clinical Laboratory Values (Using Normal Range) for Ammonia (umol/L) by Concomitant Anti-Epileptic Group and Serum Bicarbonate Category - Double Blind Phase (TOPMAT-PEP-3001: Safety Analysis Set)

Indicator: Abnormal High (Baseline ≤ ULN and Value at Time Point>ULN)

Time Point Subgroup	Placebo (N=37) n/N (%)	TPM 5 mg/kg/d (N=38) n/N (%)	TPM 15 mg/kg/d (N=37) n/N (%)	TPM 25 mg/kg/d (N=37) n/N (%)	Total TPM (N=112) n/N (%)
END POINT					
VPA	0	2/17 (12)	1/14 (7)	2/12 (17)	5/57 (9)
VPA/LOW BICARB	0	2/6 (33)	1/10 (10)	1/5 (20)	4/22 (18)
VPA/NON-LOW BICARB	0	0	0	1/7 (14)	1/35 (3)
AED EXCL VPA	1/12 (8)	1/10 (10)	0	1/11 (9)	3/46 (7)
AED EXCL VPA/LOW BICARB	0	1/3 (33)	0	1/7 (14)	2/15 (13)
AED EXCL VPA/NON-LOW BICARB	1/11 (9)	0	0	0	1/31 (3)
ANY AED	1/26 (4)	3/27 (11)	1/27 (4)	3/23 (13)	8/103(8)
ANY AED/LOW BICARB	0	3/9 (33)	1/14 (7)	2/12 (17)	6/37 (16)
ANY AED/NON-LOW BICARB	1/24 (4)	0	0	1/11 (9)	2/66 (3)

VPA includes any usage of valproate either alone or with another AED.
Low bicarb = subjects with end point value of serum bicarbonate < 20 mEq/L. Non-Low bicarb = subjects not included in the Low bicarb category
For VPA, AED EXCL VPA and AED categories, the denominators represent the number of subjects in the safety analysis set, randomized to the corresponding treatment groups, who had a measurement for the selected laboratory test at the considered time point and took an AED in the particular concomitant AED group during the double-blind phase.
For VPA, AED EXCL VPA and AED categories, the denominators for the 'Low Bicarb' subgroups represent the number of subjects in the safety analysis set, randomized to the corresponding treatment groups, who had a measurement for the selected laboratory test at the considered time point, took an AED in the particular concomitant AED group during the double-blind phase and belonged to the 'Low Bicarb' category.
For VPA, AED EXCL VPA and AED categories, the denominators for the 'Non-Low Bicarb' subgroups represent the number of subjects in the safety analysis set, randomized to the corresponding treatment groups, who had a measurement for the selected laboratory test at the considered time point, took an AED in the particular concomitant AED group during the double-blind phase and belonged to the 'Non-Low Bicarb' category.
3001_a4.rtf generated by 3001_a4.sas.

The following table shows the incidence of hyperammonemia in the open-label extensions study at any visit including the VPA and bicarbonate subgroup analyses. The incidence of hyperammonemia is increased and dose-related for patients on VPA, patients on an AED excluding VPA, and any AED. The incidence of hyperammonemia is more frequent with VPA than for patients without VPA and there is no clear effect of bicarbonate.

Table OL_a4_a: Number of Subjects with DNP-Defined Treatment-Emergent Abnormal Clinical Laboratory Values (Using Normal Range) for Ammonia (umol/L) by Topiramate Dose Range at Measurement, Concomitant Anti-Epileptic Group and Serum Bicarbonate Category at Any Time During the Combined Core and Open-Label Extension Phases
(TOPMAT-PEP-1002 and TOPMAT-PEP-3001 Integrated OL Extension: Safety Analysis Set)

Indicator: Abnormal High (Baseline ≤ ULN and Value at Time Point>ULN)

Time Point Subgroup	<20 mg/kg/day [Yrs Exp=82.31] (N=272) n/N (%)	20-40 mg/kg/day [Yrs Exp=102.48] (N=215) n/N (%)	>40 mg/kg/day [Yrs Exp=25.22] (N=69) n/N (%)	Any Dose [Yrs Exp=210.01] (N=284) n/N (%)
ANY VISITS				
VPA	21/103(20)	42/103(41)	14/37 (38)	58/142(41)
VPA/LOW BICARB	15/74 (20)	31/79 (39)	11/28 (39)	44/103(43)
VPA/NON-LOW BICARB	6/29 (21)	11/29 (38)	4/10 (40)	15/45 (33)
AED EXCL VPA	2/91 (2)	11/70 (16)	5/13 (38)	17/120(14)
AED EXCL VPA/LOW BICARB	1/48 (2)	7/45 (16)	3/10 (30)	10/69 (14)
AED EXCL VPA/NON-LOW BICARB	1/45 (2)	4/32 (13)	3/5 (60)	8/62 (13)
ANY AED	23/185(12)	53/166(32)	18/48 (38)	73/242(30)
ANY AED/LOW BICARB	16/115(14)	38/120(32)	14/37 (38)	53/158(34)
ANY AED/NON-LOW BICARB	7/72 (10)	15/58 (26)	6/14 (43)	22/101(22)

The following table shows the incidence of hyperammonemia at 40, and 52 weeks, and at the final visit. In general, the findings regarding the incidence are similar to those described previously for the incidence of hyperammonemia at any visit.

Table OL_a4_1: Number of Subjects with Treatment-Emergent Abnormal Clinical Laboratory Values (Using Normal Range) for Ammonia (umol/L) Over Time by Topiramate Dose Range at Measurement, Concomitant Anti-Epileptic Group and Serum Bicarbonate Category - Open-Label Extension Phase (continued)
(TOPMAT-PEP-1002 and TOPMAT-PEP-3001 Integrated OL Extension: Safety Analysis Set)

Indicator: Abnormal High (Baseline ≤ ULN and Value at Time Point>ULN)

Time Point / Subgroup	<20 mg/kg/day [Yrs Exp=82.31] (N=272) n/N (%)	20-40 mg/kg/day [Yrs Exp=102.48] (N=215) n/N (%)	>40 mg/kg/day [Yrs Exp=25.22] (N=69) n/N (%)	Any Dose [Yrs Exp=210.01] (N=284) n/N (%)
OL EXT WEEK 40				
VPA	3/16 (19)	4/30 (13)	5/13 (38)	12/59 (20)
VPA/LOW BICARB	2/12 (17)	2/25 (8)	5/11 (45)	9/48 (19)
VPA/NON-LOW BICARB	1/4 (25)	2/5 (40)	0	3/11 (27)
AED EXCL VPA	0	0	2/6 (33)	2/47 (4)
AED EXCL VPA/LOW BICARB	0	0	2/4 (50)	2/27 (7)
AED EXCL VPA/NON-LOW BICARB	0	0	0	0
ANY AED	3/39 (8)	4/48 (8)	7/19 (37)	14/106(13)
ANY AED/LOW BICARB	2/24 (8)	2/36 (6)	7/15 (47)	11/75 (15)
ANY AED/NON-LOW BICARB	1/15 (7)	2/12 (17)	0	3/31 (10)
OL EXT WEEK 52				
VPA	0	3/20 (15)	5/13 (38)	8/41 (20)
VPA/LOW BICARB	0	3/18 (17)	5/10 (50)	8/35 (23)
VPA/NON-LOW BICARB	0	0	0	0
AED EXCL VPA	0	0	0	0
AED EXCL VPA/LOW BICARB	0	0	0	0
AED EXCL VPA/NON-LOW BICARB	0	0	0	0
ANY AED	0	3/31 (10)	5/15 (33)	8/74 (11)
ANY AED/LOW BICARB	0	3/27 (11)	5/11 (45)	8/57 (14)
ANY AED/NON-LOW BICARB	0	0	0	0
OL EXT ENDPOINT				
VPA	3/31 (10)	8/44 (18)	8/16 (50)	19/91 (21)
VPA/LOW BICARB	2/22 (9)	6/32 (19)	6/11 (55)	14/65 (22)
VPA/NON-LOW BICARB	1/9 (11)	2/12 (17)	2/5 (40)	5/26 (19)
AED EXCL VPA	0	0	2/7 (29)	2/80 (3)
AED EXCL VPA/LOW BICARB	0	0	0	0
AED EXCL VPA/NON-LOW BICARB	0	0	2/4 (50)	2/39 (5)
ANY AED	3/74 (4)	8/74 (11)	10/23 (43)	21/171(12)
ANY AED/LOW BICARB	2/42 (5)	6/50 (12)	6/14 (43)	14/106(13)
ANY AED/NON-LOW BICARB	1/32 (3)	2/24 (8)	4/9 (44)	7/65 (11)

See footnotes on the first page of the table.
ol_a4_1.rtf generated by ol_a4_1.sas

The incidence of markedly abnormal hyperammonemia is shown in the following table for the placebo-controlled study. A dose-related increased incidence is noted for patients on VPA, not on VPA , and on any AED without a clear effect of low bicarbonate.

Table 3001_a3: Number of Subjects with DNP-Defined Treatment-Emergent Markedly Abnormal Clinical Laboratory Values for Ammonia (umol/L) by Concomitant Anti-Epileptic Group and Serum Bicarbonate Category - Double Blind Phase
(TOPMAT-PEP-3001: Safety Analysis Set)

Indicator: Markedly Abnormal High (≥ 96 umol/L)

Time Point Subgroup	Placebo (N=37) n/N (%)	TPM 5 mg/kg/d (N=38) n/N (%)	TPM 15 mg/kg/d (N=37) n/N (%)	TPM 25 mg/kg/d (N=37) n/N (%)	Total TPM (N=112) n/N (%)
END POINT					
VPA	0	0	1/14 (7)	1/12 (8)	2/57 (4)
VPA/LOW BICARB	0	0	1/10 (10)	1/5 (20)	2/22 (9)
VPA/NON-LOW BICARB	0	0	0	0	0
AED EXCL VPA	0	0	0	1/11 (9)	1/46 (2)
AED EXCL VPA/LOW BICARB	0	0	0	1/7 (14)	1/15 (7)
AED EXCL VPA/NON-LOW BICARB	0	0	0	0	0
ANY AED	0	0	1/27 (4)	2/23 (9)	3/103(3)
ANY AED/LOW BICARB	0	0	1/14 (7)	2/12 (17)	3/37 (8)
ANY AED/NON-LOW BICARB	0	0	0	0	0

VPA includes any usage of valproate either alone or with another AED.
Low bicarb = subjects with end point value of serum bicarbonate < 20 mEq/L. Non-Low bicarb = subjects not included in the Low bicarb category
For VPA, AED EXCL VPA and AED categories, the denominators represent the number of subjects in the safety analysis set, randomized to the corresponding treatment groups, who had a measurement for the selected laboratory test at the considered time point and took an AED in the particular concomitant AED group during the double-blind phase.
For VPA, AED EXCL VPA and AED categories, the denominators for the 'Low Bicarb' subgroups represent the number of subjects in the safety analysis set, randomized to the corresponding treatment groups, who had a measurement for the selected laboratory test at the considered time point, took an AED in the particular concomitant AED group during the double-blind phase and belonged to the 'Low Bicarb' category.
For VPA, AED EXCL VPA and AED categories, the denominators for the 'Non-Low Bicarb' subgroups represent the number of subjects in the safety analysis set, randomized to the corresponding treatment groups, who had a measurement for the selected laboratory test at the considered time point, took an AED in the particular concomitant AED group during the double-blind phase and belonged to the 'Non-Low Bicarb' category.
3001_a3.rtf generated by 3001_a3.sas.

The next table shows the incidence of markedly abnormal hyperammonemia at any visit in the open-label, extension study. In general, there are dose-related increases in all thre subgroups (with and without VPA and with any AED) and no clear effect of low bicarbonate. The incidence is greater with VPA than without VPA.

Table OL_a3_2: Number of Subjects with DNP-Defined Treatment-Emergent Markedly Abnormal Clinical Laboratory Values for Ammonia (umol/L) by Topiramate Dose Range at Measurement, Concomitant Anti-Epileptic Group and Serum Bicarbonate Category at Any Time During the Combined Core and Open-Label Extension Phases
(TOPMAT-PEP-1002 and TOPMAT-PEP-3001 Integrated OL Extension: Safety Analysis Set)

Indicator: Markedly Abnormal High (≥ 96 umol/L)

Time Point Subgroup	<20 mg/kg/day [Yrs Exp=82.31] (N=272) n/N (%)	20-40 mg/kg/day [Yrs Exp=102.48] (N=215) n/N (%)	>40 mg/kg/day [Yrs Exp=25.22] (N=69) n/N (%)	Any Dose [Yrs Exp=210.01] (N=284) n/N (%)
ANY VISITS				
VPA	9/103(9)	18/103(17)	5/37 (14)	29/142(20)
VPA/LOW BICARB	7/74 (9)	12/79 (15)	4/28 (14)	21/103(20)
VPA/NON-LOW BICARB	2/29 (7)	6/29 (21)	1/10 (10)	8/45 (18)
AED EXCL VPA	0	5/70 (7)	4/13 (31)	9/120(8)
AED EXCL VPA/LOW BICARB	0	3/45 (7)	2/10 (20)	5/69 (7)
AED EXCL VPA/NON-LOW BICARB	0	2/32 (6)	2/5 (40)	4/62 (6)
ANY AED	9/185(5)	23/166(14)	8/48 (17)	37/242(15)
ANY AED/LOW BICARB	7/115(6)	15/120(13)	6/37 (16)	26/158(16)
ANY AED/NON-LOW BICARB	2/72 (3)	8/58 (14)	2/14 (14)	11/101(11)

The following table show the incidence of hyperammonemia and markedly increased hyperammonemia with respect to the previously described bicarbonate subgroups at any visit and at the final visit for older pediatric patients (12-16 yrs) treated in a placebo-controlled study for migraine prophylaxis. These patients were prohibited from using any anticonvulsant (including no VPA) during the study. Thus, these data are not confounded by concomitant VPA.These data were accessed from a final study report previously submitted by the sponsor.

Table 3006_a3_2_new: Number of Subjects with Treatment-Emergent Abnormal Values (Using the Normal Range) for Ammonia by Serum Bicarbonate Category **at Any Time AND At the Final Visit** During the Double-Blind Phase
(Study TOPMAT-MIG-3006: Safety Analysis Set)

Indicator: Abnormal High (measurement > ULN for a subject whose baseline measurement was ≤ ULN)

Time Point / Subgroup	Placebo (N=33) n/N (%)	TPM 50 mg/day (N=35) n/N (%)	TPM 100 mg/day (N=35) n/N (%)	Total TPM (N=70) n/N (%)
ANY VISITS				
ANY BICARBONATE	7/32(**22**)	9/34(**26**)	13/32(**41**)	22/66(**33**)
LOW BICARBONATE		2/7 (29)	2/5 (40)	4/12(33)
NON-LOW BICARBONATE	7/32(22)	7/27(26)	11/27(41)	18/54(33)
END POINT				
ANY BICARBONATE	**0**	5/34(**15**)	2/32(**6**)	7/66(**11**)
LOW BICARBONATE		1/7 (14)	0	1/12(8)
NON-LOW BICARBONATE	0	4/27(15)	2/27(7)	6/54(11)

Low bicarbonate = subjects with at least 2 values of serum bicarbonate < 20 mEq/L in the double-blind phase
Non-Low bicarbonate = subjects not included in the Low bicarb category
3006_a3_2_new.rtf generated by 3006_a3_new.sas.

Table 3006_a5_2_new: Number of Subjects with Treatment-Emergent Markedly Abnormal Values for Ammonia by Serum Bicarbonate Category **at Any Time AND At the Final Visit** During the Double-Blind Phase
(Study TOPMAT-MIG-3006: Safety Analysis Set)

Indicator: Abnormal High (measurement > ULN for a subject whose baseline measurement was ≤ ULN)

Time Point / Subgroup	Placebo (N=33) n/N (%)	TPM 50 mg/day (N=35) n/N (%)	TPM 100 mg/day (N=35) n/N (%)	Total TPM (N=70) n/N (%)
ANY VISITS				
ANY BICARBONATE	2/33(**6**)	2/34(**6**)	3/4 (**12**)	26/68(**9**)
LOW BICARBONATE		1/7 (14)	2/6 (33)	3/13(23)
NON-LOW BICARBONATE	2/33(6)	1/27(4)	2/28(7)	3/55(5)
END POINT				
ANY BICARBONATE	**0**	1/34(**3**)	1/34(**3**)	2/68(**3**)
LOW BICARBONATE		1/7 (14)	1/6(17)	2/13(15)
NON-LOW BICARBONATE	0	0	0	0

Low bicarbonate = subjects with at least 2 values of serum bicarbonate < 20 mEq/L in the double-blind phase
Non-Low bicarbonate = subjects not included in the Low bicarb category
3006_a3_2_new.rtf generated by 3006_a3_new.sas.

These results show that topiramate increased the risk for hyperammonemia without VPA, that this risk is dose-related, and that there is no clear effect of metabolic acidosis from low bicarbonate. Also, as expected the incidence is greater at any visit vs the final visit (at 4 months in most cases).

To further support the possibility that topiramate without VPA can cause hyperammonemia, I provide a case report showing this phenomenon. There are several other somewhat similar reports in AERs.

Case of Hyperammonemia with TPM but no note of concomitant VPA

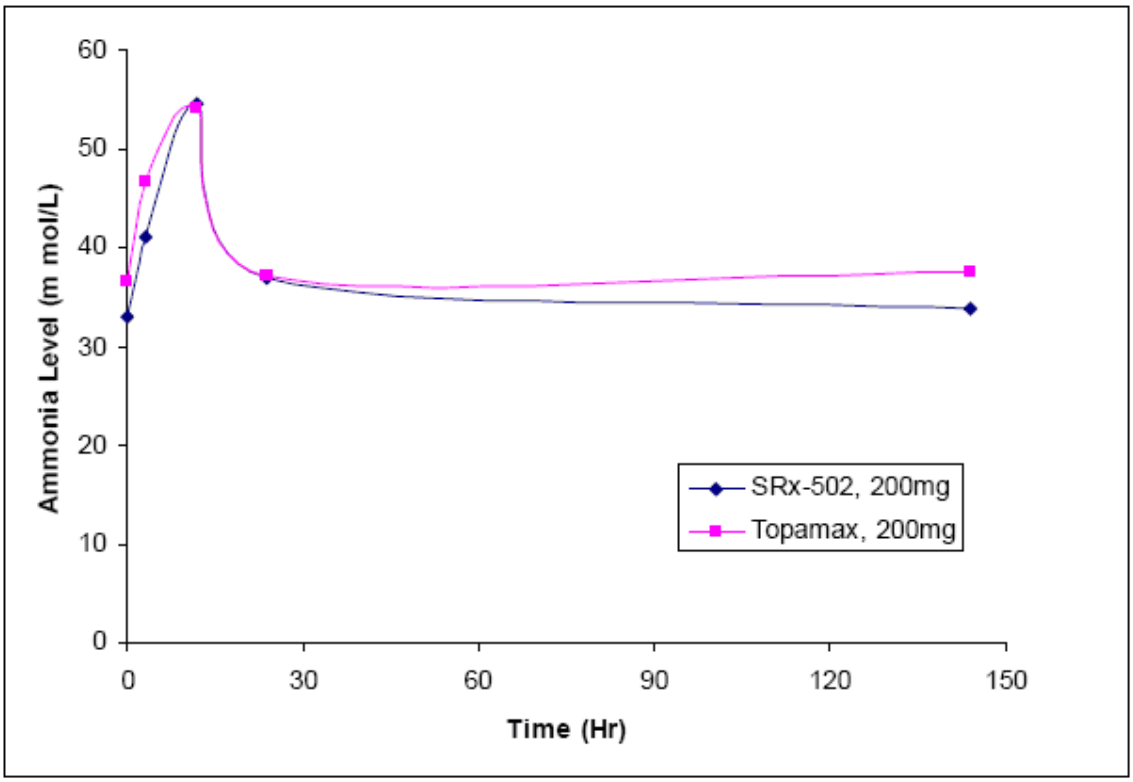
A post-marketing case report (NSADSS2003018598-1) has been reclassified (received by manufacturer 10/21/03) as serious based upon additional information. The patient's initials were (b) (6). Her date of birth was (b) (6) She weighed 10 kg and was 67.3 cm in height. The patient's medical history included nephrotoxicity secondary to vancomycin and respiratory failure (requiring prolonged intubation and tracheostomy). On 11-Mar-03 she was placed on therapy with topiramate (sprinkle formulation) 50 mg/three times a day (via a nasojejunal tube) for the treatment of seizures. **Concomitant medication includes acyclovir, epoetin alfa, phenobarbital sodium, phenytoin, ranitidine and "carmabatol and pyrixidene."** It was reported that the dose had been titrating upward due to poor seizure control. Concomitant therapy included pyridoxine 100mg/day and lorazepam, intravenous (IV) 1mg/once daily at bedtime. The patient had also been treated previously with paracetamol for fever but had received no doses for at least 7 days prior to the onset of the adverse event. **On 29-Mar-03 19 days after being placed on therapy with topiramate, the patient developed an elevated serum ammonia level. There were no other symptoms reported. Ammonia levels (normal range 21-50) were as follows: 29-Mar-03- 102, 31-Mar-03- 184, 01-Apr- 03- 59, 02-Apr-03- 100, 03-Apr-03- 61, 04-Apr-03- 87, 05-Apr-03- 40, 06-Apr- 03- 43, 07-Apr-03- 25, 08-Apr-03- 43, 09-Apr-03- 59, 10-Apr-03- 55, 11-Apr- 03- 39, 13-Apr-03- 57, 18-Apr-03- 56 and 24-Apr-03- 48. It was also reported that the patient had mild elevation of serum transaminases but a normal bilirubin and prothrombin time. To bring the ammonia levels down to normal, the patient was treated with lactulose and neomycin. The event resolved after discontinuation of topiramate (on 04-Apr-03) and other antiepileptic drugs (therapy with phenobarbital was continued).** Hepatitis A, B, and C serology performed on 18-Apr-03 was negative.

A search of AERS recently showed a data mining score (EB05) of 17 for hyperammonemia and 6 for increased ammoni associated with topiramate treatment. A review of these cases revealed that several of these reports occurred in patient taking topiramate without VPA..

Pharmacologic Evidence of Increase of Ammonia Levels by Topiramate

Acute treatment with topiramate (in an IND, Spherics = sponsor; in the DNP) increases serum/plasma ammonia by ~ 50 % from baseline/pre-treatment and many of these subjects developed ammonia levels above the upper limit of normal.

See figure below and table with ammonia levels with Topamax and an extended release formulation of topiramate under investigation



C. 1: Summary of volunteers' Ammonia levels according to treatment

	Volunteers Ammonia levels during treatment A					Volunteers Ammonia levels during treatment B				
	Predose	3.0	12.0	24.0	144.0	Predose	3.0	12.0	24.0	144.0
0120701	(b) (4)									
0120702										
0120703										
0120704										
0120705										
0120706										
0120707										
0120708										
0120709										
0120710										
0120711										
0120712										
0120713										
0120714										

0120715	(b) (4)									
0120716										
0120717										
0120718										
0120719										
0120720										
0120721										
0120722										
0120723										
0120724										
n	24	24	24	24	22	24	24	23	23	20
Mean	32.95	41.16	54.65	36.89	33.75	36.44	46.62	54.15	37.10	37.48
SD	6.84	12.86	15.94	10.72	7.09	9.96	12.60	13.02	6.98	18.38
Minimum	(b) (4)									
Maximum										

Notes:
NA=Not Available

Reviewer Comment

- I interpret these data to suggest that topirmate without concomitant VPA has the potential to increase ammonia levels and produce hyperammonemia with or without encephalopathic symptoms. However, I believe that the risk for developing hyperammonemia is greater when topiramate is used along with VPA.

- I believe that there are other sources of data information that support the possibility that topiramate treatment without VPA can increase the risk for hypermmonemias. First, topiramate monotherapy (up to 4 months in patients who were prohibited from using any concomitant antiepileptic drug) of adolescent pediatric patients (12-16 years) as migraine prophylaxis increased plasma ammonia levels (i.e., hyperammonemia) to levels above the normal reference range and to markedly abnormally increased levels (with and without encephalopathic symptoms). The incidence of these increased values (above the reference range) at any visit was 22 % for placebo, 26 % for 50 mg/day, 41 % for 100 mg/day, and 33 % for any topiramate dose. The incidence of hypermmonemia at the final visit was 0 % for placebo, 15 % for 50 mg/day, 6 % for 100 mg/day, and 11 % for any topiramate dose. The incidence of hyperammonemia to markedly abnormally increased values at any visit was 6 % for placebo, 6 % for 50 mg/day, 12 % for 100 mg/day, and 9 % for any topiramate dose. 6 % for 100 mg/day, and 11 % for any topiramate dose. The incidence of hyperammonemia to markedly abnormally increased values at the final visit was 0 % for placebo, 3 % for 50 mg/day, 3 % for 100 mg/day, and 3 % for any topiramate dose.

  Second, there are several AERS post-marketing reports of hyperammonemia in patients who were taking topiramate without VPA.

Third, an acute pharmacological effect of topiramate (with TOPAMAX and similarly also with an (b) (4)) increased plasma ammonia ~ 50 % above baseline and several pts developed hyperammonemia (increased above reference range).

- (b) (5)

7.1.7.5 Special assessments

- Not applicable

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

The main analyses presented here are those for vital signs (VS), pulse and blood pressure, temperature, and ventilation/respiratory rate.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Although results are presented for all 3 studies, I focused my interest on the placebo-controlled study.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Study TOPMAT-PEP-3001 Double-Blind (Core) Phase

• Mean changes in systolic blood pressure, pulse rate, respiration rate, and tympanic temperature were small, similar in all treatment groups, and not considered to be clinically relevant.

• There were small, dose-related mean increases in diastolic blood pressure,

Study TOPMAT-PEP-1002 Open-Label Treatment (Core) Phase

• The vital sign results were comparable in all dosage groups.

Studies TOPMAT-PEP-1002 and -3001 Integrated Open-Label Extension

• Mean changes in blood pressure, pulse rate, respiration rate, and tympanic temperature were small and not considered to be clinically meaningful. Decreases in pulse and respiration rate were consistent with the increasing age of the subjects.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

DNP provided outlier thresholds for blood pressure and pulse and the sponsor conducted analyses for these.

Study TOPMAT-PEP-3001 Double-Blind (Core) Phase

There was no clear abnormalities of clear significance.

Study TOPMAT-PEP-1002 Open-Label Treatment (Core) Phase

• The vital sign results were comparable in all dosage groups .

Studies TOPMAT-PEP-1002 and -3001 Integrated Open-Label Extension

• Systolic and diastolic blood pressure were above normal range for at least 1 time point in 26% and 38% of all subjects, respectively. Pulse rate was below normal range for at least 1 time point in 55% of all subjects. Respiration rate was below normal range for at least 1 time point in 35% of all subjects and above normal range for at least 1 time point in 74% of all subjects.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Study TOPMAT-PEP-3001 Double-Blind (Core) Phase

• Based on the protocol-defined criteria for markedly abnormal values, 3 subjects (2 in the topiramate 5 mg/kg/d group and 1 in the 25 mg/kg/d group) had a treatment-emergent markedly high systolic pressure (>134 mmHg). These were not reported as adverse events. No subject had a markedly abnormal diastolic pressure (<25 or >96 mmHg).

Study TOPMAT-PEP-1002 Open-Label Treatment (Core) Phase

• Based on the protocol-defined criteria for markedly abnormal values, there were no clinically noteworthy changes in systolic blood pressure, diastolic blood pressure, pulse rate, respiration rate, or tympanic temperature during the study, with 1 exception: Subject 101140 had a treatment-emergent markedly abnormal blood pressure value, with a systolic blood pressure reading of 139 mmHg (markedly abnormal: above 134 mmHg) on Day 5 (Visit 4). Her blood pressure was normal at all other visits including Visit 5 (99 mmHg on Day 7).

Studies TOPMAT-PEP-1002 and -3001 Integrated Open-Label Extension

• Based on the study-defined criteria for markedly abnormal values, 14 subjects had a treatment-emergent markedly high systolic pressure (>134 mmHg) and 1 subject had a markedly low systolic pressure (<56 mmHg). All but 3 of these systolic measurements normalized at later visits. Three subjects had a treatment-emergent markedly high diastolic pressure (>96 mmHg) and 1 subject had a markedly low diastolic pressure (<25 mmHg). All of these markedly abnormal measurements normalized at later visits during the open-label extension phase. Multiple additional recordings at the same time were not obtained and condition of the subjects at the time was not recorded.

• One subject (101143) with treatment-emergent markedly high systolic pressure reported an adverse event of hypertension (highest measurement, 141 mmHg) that was moderate in severity but resolved. Another subject (300651) reported an adverse event of hypertension that was mild in severity and resolved. Both events were considered by the investigator to be unrelated to study medication and no action was taken for either subject.

7.1.8.4 Additional analyses and explorations

There did not appear to be abnormalities of outliers based upon the DNP supplied outlier thresholds that appeared to be of concern.

Reviewer Comment

- There did not appear to be topirmate-related changes of significant concerns regarding VS.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

The sponsor conducted ECGs in patients and presented the results.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

I focused my concern on the placebo-controlled trial and especially QTc.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Study TOPMAT-PEP-3001 Double-Blind (Core) Phase

• No clinically meaningful changes in mean parameter values or mean parameter changes from baseline were noted among treatment groups in ECG parameters over the 20-day double-blind phase.

Study TOPMAT-PEP-1002 Open-Label Treatment (Core) Phase

• Small differences were noted across treatment groups in the mean change from baseline to end point for several ECG parameters, but none were clinically meaningful. No dose-dependent effects of topiramate were observed on mean ECG values over time.

• Mean changes in quantitative ECG variables over time were small and similar in all treatment groups. The 95% confidence intervals from the exploratory ANOVA showed no differences between topiramate and placebo or between any of the topiramate dose groups for any of the quantitative ECG variables.

• Overall, mean changes in ECG parameters from baseline over time to the open-label extension end point were small and not clinically significant.

• Mean change in QTcLD at open-label extension end point was 0.7 ms (median change, 2.0 ms; n=80), 2.6 ms (median change, 4.0 ms; n=107), and 6.1 ms (median change, 5.5 ms; n=28) for the <20, 20-40, and >40 mg/kg/d groups, respectively.

Studies TOPMAT-PEP-1002 and -3001 Integrated Open-Label Extension

• Mean changes in quantitative ECG variables were small and similar in all analysis Categories. Heart rate decreased in all analysis categories, as would be expected for babies as they mature.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Study TOPMAT-PEP-3001 Double-Blind (Core) Phase

• Using the linear-derived method for correcting the QT interval, QTc was within the normal range both at baseline and at the end of the double-blind treatment phase for all subjects. Most changes from baseline were <30 ms, but 6 subjects on topiramate (none on placebo) had an increase in QTc of 30 to <45 ms while remaining within the normal range.

• Most subjects had normal QTcLD interval values. Borderline (440-<470 ms) QTcLD values were recorded in 5% of subjects at any time point. One subject (300703) in the PEP-3001 TPM analysis category had a prolonged QTcLD interval of 472 ms; however, the ECG was of very poor quality. No subject had a QTcLD value of 500 ms or greater.

• Most changes from pretreatment baseline in QTcLD were <30 ms. Overall, 9% of subjects had changes of 30-<45 ms; 3% had changes of 45-<60 ms, and 1% of subjects had changes recorded of ≥60 ms.

• A shift in heart rate from normal at pretreatment baseline to low or high at open-label extension end point occurred in 15 and 5 subjects, respectively. The only QTc shift from pretreatment baseline to open-label extension end point occurred in a subject who's linear derived QTc interval shifted from normal to high.

• A change from normal to a clinically significant abnormal ECG (as assessed by the central reader) occurred in 10 subjects. One subject had a change from abnormal, not clinically significant ECG to a clinically significant abnormal ECG. One subject was not examined at pretreatment baseline, and 1 subject had a missing evaluation at pretreatment baseline. For all 13 of these subjects, ECGs were found to be not clinically significant when assessed locally, repeated, or evaluated by a cardiologist, or were consistent with a known preexisting cardiac condition.

• One subject had a QTc value (by any correction method) of ≥500 ms: Subject 300270 (15 mg/kg/d group) had a QTcB interval on Day –5 of 525 ms (QTcLD=492); on Day 21, QTcB was 402 ms (QTcLD=408).

• A QTcLD value of ≥450 ms was observed for 1 subject (300703) in the 25 mg/kg/d group and 1 subject (300063) in the placebo group.

• One subject had a change in QTc (by any correction method) of ≥60 ms: Subject 300261 (15 mg/kg/d group) had a baseline QTcB interval of 376 ms (QTcLD=389 ms); on Day 20 the QTcB was 439 ms (QTcLD=429 ms).

• A change from baseline in QTcLD of ≥30 ms was observed for 6 topiramate-treated subjects (8%), 2 in each topiramate treatment group; no placebo-treated subjects had a QTcLD change ≥30 ms.

Study TOPMAT-PEP-1002 Open-Label Treatment (Core) Phase

• No subjects with a normal ECG at baseline developed clinically significant abnormal ECG at the end of the core phase .

• No dose-related ECG parameter changes were observed during the core phase.

Studies TOPMAT-PEP-1002 and -3001 Integrated Open-Label Extension

• Most subjects had normal QTcLD interval values. Borderline (440-<470 ms) QTcLD values were recorded in 5% of subjects at any time point. One subject (300703) in the PEP-3001 TPM analysis category had a prolonged QTcLD interval of 472 ms; however, the ECG was of very poor quality. No subject had a QTcLD value of 500 ms or greater.

• Most changes from pretreatment baseline in QTcLD were <30 ms. Overall, 9% of subjects had changes of 30-<45 ms; 3% had changes of 45-<60 ms, and 1% of subjects had changes recorded of ≥60 ms.

• A shift in heart rate from normal at pretreatment baseline to low or high at open-label extension end point occurred in 15 and 5 subjects, respectively. The only QTc shift from pretreatment baseline to open-label extension end point occurred in a subject who's linear derived QTc interval shifted from normal to high.

• A change from normal to a clinically significant abnormal ECG (as assessed by the central reader) occurred in 10 subjects. One subject had a change from abnormal, not clinically significant ECG to a clinically significant abnormal ECG. One subject was not examined at pretreatment baseline, and 1 subject had a missing evaluation at pretreatment baseline. For all 13 of these subjects, ECGs were found to be not clinically significant when assessed locally, repeated, or evaluated by a cardiologist, or were consistent with a known preexisting cardiac condition.

• No subjects had a QTc value (by any correction method) >500 ms. At the open-label extension end point, 2 subjects (1%) had QTcLD values ≥450 ms.

• One subject had a change from baseline QTcLD value of ≥60 ms: Subject 300648 had a QTc of 390 ms at baseline and 459 ms at Week 20, concurrent with hospitalization for pneumonia; the subject died on Day 200.

• At the open-label extension end point, 15 subjects (8%) had change from baseline QTcLD of ≥30 ms.

Reviewer Comment

- I did not have any significant concerns about ECG results.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Outlier results were presented in section 7.1.9.3.3

7.1.9.4 Additional analyses and explorations

- Not applicable

7.1.10 Immunogenicity

- Not applicable

7.1.11 Human Carcinogenicity

- Not applicable

7.1.12 Special Safety Studies

Testing of behavior was conducted (during the randomized, double-blinded, placebo-controlled study and also during the open-label extension study) with the Vineland Adaptive Behavior test to assess the effect of topiramate on specific domains (socialization, communication, daily living skills, motor skills) and the Adaptive Baehavior composite of these domains

Core results reflect those at the end of the controlled study 3001 and 1002 (PK study conducted over a few weeks).

Vineland testing for all 4 domains and the composite Adaptive behavior was conducted at pre-treatment/baseline and at the end of the study in the placebo-controlled study and PK study. There were no apparent, noteworthy treatment effects of topiramate (vs placebo) in either study 3001 or 1002 (in regard to change from baseline).

The following tables show results over the open-label extension according to topiramate dose ranges for all domains separately and the composite score. Mean scores at baseline were decreased and more so in patients on concomitant VPA than in those without VPA. There did not appear to be an effect of VPA or low bicarbonate based upon subgroup analyses of these data.

Over 5 2 weeks treatment mean scores for all testing was ~ 18-23 % reduced from baseline and showed deteriorating behavioral functioning.

Change from Baseline for Mean Adaptive Behavior Composite Score (Vineland) (# Pts) Over Time According to Topiramate Dose Range and Concomitant AED

		Modal Topiramate Dose (mg/kg/day)							
		< 20		20-40		> 40		Any Dose	
Timeframe	Concomitant AED	VPA	Exclude VPA	VPA	Exclude VPA	VPA	Exclude VPA	VPA	Exclude VPA
Pre-treatment / Baseline	**Mean Adaptive Behavior Vineland) * (# Pts)**	72 (36)	78 (41)	68 (56)	77 (350	69 (21)	80 (9)	69 (113)	78 (85)
Core	**Mean Adaptive Behavior Composite Score (Vineland) * Change from Baseline (# Pts)**	-1 (14)	-2 (17)	-2 (40)	-1 (25)	-2 (16)	-4 (5)	-2 (70)	-2 (47)
OLE Wk 20		-10 (15)	-9 (26)	-10 (48)	-8 (30)	-9 (23)	-7 (7)	-9 (86)	-8 (63)
OLE Wk 52		-13 (7)	-16 (18)	-14 (24)	-21 (16)	-15 (16)	-31 (5)	-14 (47)	-20 (39)
OLE "End"		-14 (26)	-13 (35)	-14 (46)	-15 (44)	-16 (24)	-23 (9)	-15 (96)	-15 (88)
OLE Wk 52	**Mean Adaptive Behavior Composite Score (Vineland) * (# Pts)**	58 (8)	63 (18)	50 (24)	60 (16)	49 (16)	57 (5)	51 (48)	61 (39)
OLE "End"		60 (27)	64 (36)	54 (46)	62 (44)	53 (24)	55 (9)	56 (97)	62 (89)

* Scores are rounded off to integers
VPA = VPA at least 1 concomitant AED
Exclude VPA = VPA is excluded from Concomitant AEDs

Change from Baseline for Mean Communication Score (Vineland) (# Pts) Over Time According to Topiramate Dose Range and Concomitant AED

		Modal Topiramate Dose (mg/kg/day)							
		< 20		20-40		> 40		Any Dose	
Timeframe	Concomitant AED	VPA	Exclude VPA	VPA	Exclude VPA	VPA	Exclude VPA	VPA	Exclude VPA
Pre-treatment / Baseline	**Mean Communication Score (Vineland) * (# Pts)**	76 (36)	82 (41)	74 (56)	82 (35)	74 (21)	84 (9)	74 (113)	82 (85)
Core	**Mean Communication Score (Vineland) * Change from Baseline (# Pts)**	0 (14)	-2 (17)	- 1 (40)	-1 (25)	0 (16)	-2 (5)	-1 (70)	-1 (47)
OLE Wk 20		-9 (15)	-8 (26)	-8 (48)	-7 (30)	-8 (23)	-4 (7)	-8 (86)	-7 (63)
OLE Wk 52		-15 (7)	-16 (18)	- 14 (24)	-21 (16)	-15 (16)	-25 (5)	-14 (47)	-19 (39)
OLE "End"		-13 (26)	-12 (36)	-13 (46)	-14 (44)	-15 (24)	-19 (9)	-14 (96)	-14 (89)
OLE Wk 52	**Mean Communication Score (Vineland) * (# Pts)**	59 (8)	66 (18)	56 (24)	66 (15)	56 (16)	64 (5)	57 (48)	66 (39)
OLE "End"		65 (27)	68 (36)	61 (46)	68 (44)	60 (24)	61 (9)	62 (97)	67 (89)

***** Scores are rounded off to integers
VPA = VPA at least 1 concomitant AED

Change from Baseline for Mean Motor Skills Score (Vineland) (# Pts) Over Time According to Topiramate Dose Range and Concomitant AED

		Modal Topiramate Dose (mg/kg/day)							
		< 20		20-40		> 40		Any Dose	
Timeframe	Concomitant AED	VPA	Exclude VPA	VPA	Exclude VPA	VPA	Exclude VPA	VPA	Exclude VPA
Pre-treatment / Baseline	**Mean Motor Skills Score (Vineland) * (# Pts)**	75 (36)	77 (41)	69 (56)	77 (35)	70 (21)	80 (9)	71 (113)	77 (85)
Core	**Mean Motor Skills Score (Vineland) * Change from Baseline (# Pts)**	-1 (14)	-2 (17)	-1 (40)	-1 (25)	-2 (16)	-6 (5)	-1 (70)	-2 (47)
OLE Wk 20		-8 (15)	-8 (26)	-9 (48)	-8 (30)	-10 (23)	-9 (7)	-9 (86)	-8 (63)
OLE Wk 52		-16 (7)	-13 (18)	-15 (24)	-18 (36)	-17 (16)	-30 (5)	-16 (47)	-17 (39)
OLE "End"		-14 (26)	-11 (36)	-15 (46)	-15 (44)	-17 (24)	-23 (9)	-15 (96)	-14 (89)
OLE Wk 52	**Mean Motor Skill Score (Vineland) * (# Pts)**	67 (8)	65 (18)	48 (24)	61 (16)	47 (16)	59 (5)	51 (48)	63 (39)
OLE "End"		64 (27)	65 (36)	55 (46)	61 (44)	51 (24)	55 (9)	57 (97)	62 (89)

* Scores are rounded off to integers
VPA = VPA at least 1 concomitant AED
Exclude VPA = VPA is excluded from Concomitant AEDs

Change from Baseline for Mean Daily Living Skills Score (Vineland) (# Pts) Over Time According to Topiramate Dose Range and Concomitant AED

		Modal Topiramate Dose (mg/kg/day)							
		< 20		20-40		> 40		Any Dose	
Timeframe	Concomitant AED	VPA	Exclude VPA	VPA	Exclude VPA	VPA	Exclude VPA	VPA	Exclude VPA
Pre-treatment / Baseline	**Mean Daily Living Skills Score (Vineland) * (# Pts)**	84 (36)	91 (41)	82 (56)	89 (35)	83 (21)	93 (9)	83 (113)	90 (85)
Core	**Mean Daily Living Skills Score (Vineland) * Change from Baseline (# Pts)**	-1 (14)	-2 (17)	-3 (40)	-1 (25)	-2 (16)	-3 (5)	-2 (70)	-2 (47)
OLE Wk 20		-11 (15)	-10 (26)	-12 (48)	-12 (30)	-14 (23)	-6 (7)	-12 (86)	-10 (63)
OLE Wk 52		-14 (7)	-21 (18)	-19 (24)	-26 (16)	-19 (16)	-34 (5)	-18 (47)	-25 (39)
OLE "End"		-16 (26)	-16 (36)	-19 (46)	-20 (44)	-21 (24)	-28 (9)	-18 (96)	-19 (89)
OLE Wk 52	**Mean Daily Living Skills Score (Vineland) * (#Pts)**	62 (8)	69 (18)	58 (24)	67 (16)	58 (16)	67 (5)	59 (48)	68 (39)
OLE "End"		68 (27)	72 (36)	63 (46)	69 (44)	62 (24)	63 (9)	64 (97)	69 (89)

***** Scores are rounded off to integers
VPA = VPA at least 1 concomitant AED
Exclude VPA = VPA is excluded from Concomitant AEDs

Change from Baseline for Mean Socialization Score (Vineland) (# Pts) Over Time According to Topiramate Dose Range and Concomitant AED

		Modal Topiramate Dose (mg/kg/day)							
		< 20		20-40		> 40		Any Dose	
Timeframe	Concomitant AED	VPA	Exclude VPA	VPA	Exclude VPA	VPA	Exclude VPA	VPA	Exclude VPA
Pre-treatment / Baseline	**Mean Socialization Score (Vineland) * (# Pts)**	73 (36)	81 (41)	68 (56)	79 (35)	69 (21)	79 (9)	70 (113)	80 (85)
Core	**Mean Socialization Score (Vineland) * Change from Baseline (# Pts)**	0 (14)	0 (17)	-2 (40)	-1 (25)	-2 (16)	-3 (5)	-1 (70)	-1 (47)
OLE Wk 20		-8 (15)	-8 (26)	-9 (48)	-5 (30)	-5 (23)	-7 (7)	-8 (86)	-6 (63)
OLE Wk 52		-10 (7)	-13 (18)	-12 (24)	-13 (16)	-11 (16)	-26 (5)	-11 (47)	-15 (39)
OLE "End"		-10 (26)	-9 (35)	-12 (46)	-11 (44)	-12 (24)	-19 (9)	-12 (96)	-11 (88)
OLE Wk 52	**Mean Socialization Score (Vineland) * (# Pts)**	63 (8)	-13 (18)	53 (24)	-13 (16)	54 (16)	-26 (5)	55 (48)	-15 (39)
OLE "End"		65 (27)	69 (36)	57 (46)	67 (44)	56 (24)	58 (9)	59 (97)	67 (89)

***** Scores are rounded off to integers
VPA = VPA at least 1 concomitant AED
Exclude VPA = VPA is excluded from Concomitant AEDs

Sponsor summary

Decreases in all domains of the Vineland Scales of Adaptive Behavior were seen across all treatment categories of the *integrated analysis set*, suggesting that the neurodevelopmental and adaptive functioning gap continued to increase between this study population and other children their age. These results are consistent with a previously reported study (Berg et al., Pediatrics, 2004) for children with newly diagnosed epilepsy. However, the mean changes that were reported to occur in this publication over 1 year were much less than those occurring in these patients treated with topiramate.

Reviewer Comment

- Whereas significant behavioral effects (as reflected by Vineland adaptive composite behavioral scale testing including the 4 domains noted) were not observed in a 20 day placebo-controlled study, they were observed in the long-term, open-label study of infant/toddlers with topiramate. There were noteworthy decreases (from pre-treatment/baseline) in all behavioral domains (i.e., communication, daily living skills, motor skills, socialization) and the composite adaptive behavior score ranging from 18 % to 24 % observed during treatment over 52 weeks/1 year. These decreases were progressive over 1 year.

- Because these results were not collected in a placebo-controlled study, and the study population consisted of many neurologically affected individuals, it is not possible to determine the unequivocal causality of topiramate. One published study of newly diagnosed young pediatric patients with epilepsy showed that there was progressive deterioration over time (along with various anticonvulsant therapy) but the magnitude was not as great as that in the patients in these infant/toddler studies. However, it is likely that that the patients in the studies under review were more developmentally impaired and had a higher percentage of neurological abnormalities than the patients in the published study who likely represented a an overall less impaired population of patients.

- Nevertheless, despite the above caveat and limitations of the data, I believe that least some, significant portion of these changes (e.g., deterioriation of scores) were likely due to topiramate. I have this belief because of the magnitude (~ 18-23 % decrease from baseline) marked reductions in all scores associated with chronic topiramate treatment over a relatively limited period of time (many weeks up to 52 weeks/1 year) and the well known fact that topiramate treatment produces cognitive dysfunction. Longer term (than 20 days), topiramate treatment (ideally with several fixed doses of topiramate) under placebo-controlled conditions are needed to establish clearly whether topiramate is causal in these adverse changes.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

- Not applicable

7.1.14 Human Reproduction and Pregnancy Data

A consult was made to the Maternal Fetal Health group about the possible deleterious effects of chronic, metabolic acidosis in the pregnant mother on the fetus. The following is a summary of the consult recommendations.

EXECUTIVE SUMMARY
In January 2005, Johnson & Johnson responded to a November 2004 FDA Division of Metabolic and Endocrinology Products request by submitting an analysis of pregnancy outcomes in patients taking topiramate[1]. The analysis was requested because of increasing topiramate monotherapy indications, the known teratogenic effects of several other anti-epileptic drugs, and positive findings in pre-clinical topiramate teratogenicity studies. The FDA Pregnancy and Lactation Team (PLT) reviewed the Sponsor submission as well as anti-epileptic drug (AED) pregnancy
registry data, and relevant medical literature[2]. In concluding his analysis of the PLT review, Dr. Len Kapcala, Medical Officer in the FDA Division of Neurology Products (DNP), recommended (b) (5) and requested the Division of Adverse Event Analysis (DAEA) to review the AERS database for cases reporting findings in pregnancies in women exposed to topiramate[3].This review discusses 153 AERS topiramate cases of which 123 mentioned concomitant product use. However, 38 AERS cases did not report use of a concomitant AED. The most frequent adverse event in these 38 cases was spontaneous abortion, reported 20 times. The other adverse events reported more than once in the 38 cases were hydrocephaly (3), cleft lip (2), and cleft lip and palate (2). Data mining scores for cleft lip alone and for cleft lip and palate for topiramate stood out from scores for these adverse events with other AEDs. Because these particular adverse pregnancy outcomes are not highly unusual, assessing their relatedness to topiramate will require other survey methods. Spontaneous reporting systems, like FDA's MedWatch program, are designed to detect rare and serious drug-associated adverse events not expected in the background
of the patient population being analyzed.

We agree with Dr. Kapcala's recommendation tha (b) (5). Pregnancy registry data will complement AERS data by offering a source of prospectively defined cases of topiramate exposure.

CONCLUSION
The primary values of spontaneous adverse event reports are to find safety signals for further evaluation and to characterize adverse events. AERS data can support drug-event associations for events that are commonly drug-induced or for which the background rate is low. Also, detailed AERS cases can support drug-event associations when other explanations for the adverse event can be excluded or when the adverse event subsides and recurs with drug discontinuation and reinstitution, respectively. However, adverse pregnancy outcomes are common, have many

possible causes, and are not subject to de- and rechallenges with drug. Thus, no conclusions about the relatedness of the adverse pregnancy outcomes in this review and topiramate exposure in utero can be drawn.

RECOMMENDATIONS
We agree with the recommendations of DNP that the sponsor continue monitoring pregnancy exposure to topiramate and tha (b) (5)

7.1.15 Assessment of Effect on Growth

Growth (weight, length and head circumference were measure over all the studies and length was systematically evaluated according to specified procedures.

The following are results from the growth data and an Endocrine Consult conclusions regarding the possible effects of topiramate on growth.

Mean Z score changes from baseline for head circumference showed a mild decrease over 52 weeks (- 0.3 for any topiramate dose) and no apparent dose-relationship for dose ranges < 20 mg/kg/d, 20-40 mg/kg/d, and > 40 mg/kg/d) and no apparent relationship to low serum bicarbonate (i.e., metabolic acidosis). This mean decrease was progressive from baseline up to 20 weeks and then appeared to stabilize over weeks 20 to 52.

Table Effect of Topiramate Dose on WEIGHT Z Score Change from Baseline Over Time in Open- Label Extension Study

Timeframe	Serum Bicarbonate Category	Modal Topiramate Dose (mg/kg/day)			
		< 20	20-40	> 40	Any Dose
	Mean Z Score				
Baseline	Low	-0.9	-1.0	-1.2	-1.0
	Not Low	-1.0	-1.1	-0.7	-1.0
	Low and Not Low	-1.0	-1.1	-1.1	-1.0
	Mean Z Score Change from Baseline				
Core	Low	-0.1	-0.1	-0.2	-0.1
	Not Low	-0.2	-0	-0.1	-0.1
	Low and Not Low	-0.1	-0	-0.1	-0.1
OLE Wk 1	Low	-0	-0.1	-0.2	-0.1
	Not Low	-0.1	-0	-0.1	-0
	Low and Not Low	-0.1	-0	-0.1	-0.1
OLE Wk 2	Low	-0.1	-0.2	-0.2	-0.2
	Not Low	-0.2	-0	-0	-0.1
	Low and Not Low	-0.2	-0.1	-0.1	-0.2
OLE Wk 6	Low	-0.4	-0.4	-0.5	-0.4
	Not Low	-0.2	-0.1	-0.2	-0.2
	Low and Not Low	-0.3	-0.3	-0.4	-0.3
OLE Wk 12	Low	-0.6	-0.6	-0.7	-0.6
	Not Low	-0.3	-0.2	-0.4	-0.3

	Low and Not Low	-0.5	-0.5	-0.6	-0.5
OLE Wk 20	Low	-0.7	-0.8	-0.9	-0.8
	Not Low	-0.5	-0.6	-0.3	-0.5
	Low and Not Low	-0.6	-0.8	-0.7	-0.7
OLE Wk 28	Low	-1.0	-1.0	-1.1	-1.0
	Not Low	-0.6	-0.8	-0.5	-0.7
	Low and Not Low	-0.9	-1.0	-0.9	-0.9
OLE Wk 40	Low	-1.0	-1.1	-1.2	-1.1
	Not Low	-0.4	-0.9	-0.5	-0.6
	Low and Not Low	-0.8	-1.1	-1.0	-1.0
OLE Wk 52	Low	**-1.2**	**-1.1**	**-1.5**	**-1.2**
	Not Low	**-0.5**	**-1.1**	**-0.4**	**-0.6**
	Low and Not Low	**-0.9**	**-1.1**	**-1.1**	**-1.1**
OLE "End"	Low	**-0.9**	**-1.0**	**-1.2**	**-1.0**
	Not Low	**-0.4**	**-0.7**	**-0.5**	**-0.5**
	Low and Not Low	**-0.6**	**-0.9**	**-1.0**	**-0.8**
	Mean Z Score				
OLE "End"	Low	**-1.8**	**-2.0**	**-2.4**	**-2.0**
	Not Low	**-1.2**	**-1.8**	**-1.2**	**-1.5**
	Low and Not Low	**-1.6**	**-2.0**	**-2.0**	**-1.8**

Table Effect of Topiramate Dose on LENGTH Z Score Change from Baseline Over Time in Open- Label Extension Study

Timeframe	Serum Bicarbonate Category	Modal Topiramate Dose (mg/kg/day)			
		< 20	20-40	> 40	Any Dose
	Mean Z Score				
Baseline	Low	-0.4	-0.4	-0.3	-0.4
	Not Low	-0.9	-0.4	-0.5	-0.7
	Low and Not Low	-0.7	-0.4	-0.4	-0.5
	Mean Z Score Change from Baseline				
Core	Low	-0.1	0	-0.2	-0.1
	Not Low	-0	0	-0.1	0
	Low and Not Low	-0.1	0	-0.1	-0.1
OLE Wk 6	Low	-0.3	-0.1	-0.1	-0.2
	Not Low	-0.3	0	0	0.2
	Low and Not Low	0	0.1	0	0
OLE Wk 12	Low	-0.3	0	-0.3	-0.1
	Not Low	-0.3	0.1	0	-0.1
	Low and Not Low	-0.3	0	-0.2	-0.1
OLE Wk 20	Low	-0.5	-0.2	-0.5	-0.3
	Not Low	-0.5	0	0	-0.2
	Low and Not Low	-0.5	-0.2	-0.3	-0.3
OLE Wk 28	Low	-0.6	-0.3	-0.6	-0.4
	Not Low	-0.4	0	-0.2	-0.2
	Low and Not Low	-0.5	-0.2	-0.5	-0.4

OLE Wk 40	Low	-0.7	-0.6	-0.9	-0.7
	Not Low	-0.6	0	-0.5	-0.4
	Low and Not Low	-0.6	-0.5	-0.8	-0.6
OLE Wk 52	Low	**-0.9**	**-0.8**	**-1.0**	**-0.8**
	Not Low	**-0.8**	**-0.2**	**-0.6**	**-0.6**
	Low and Not Low	**-0.9**	**-0.7**	**-0.9**	**-0.8**
OLE "End"	Low	**-0.8**	**-0.5**	**-0.9**	**-0.6**
	Not Low	**-0.1**	**-0.1**	**-0.2**	**-0.1**
	Low and Not Low	**-0.4**	**-0.4**	**-0.7**	**-0.5**
	Mean Z Score				
OLE "End"	Low	**-1.2**	**-0.9**	**-1.2**	**-1.0**
	Not Low	**-0.9**	**-0.4**	**-0.7**	**-0.7**
	Low and Not Low	**-1.1**	**-0.8**	**-1.0**	**-0.9**

- Reductions in length, weight, and head circumference were observed during long-term (up to 1 year) treatment in the open-label extension study of these infants/toddlers (1-24 months) with topiramate (from low doses < 5 mg/kg/day up to 60 mg/kg/day) based upon decreases from baseline in Z-scores. Z scores, which reflect the standard deviation from standardized data of expected height/length or weight during the whole spectrum of pediatric development, are derived from data from normal pediatric subjects and not from patients such as these with seizures, all of whom were also taking other anticonvulsants. Over 52 weeks of treatment (all topiramate doses), the mean Z score reduction from pre-treatment/baseline for weight (-0.8) and length (-0.8) was progressive and did not plateau or stabilize. Mean Z score reduction for weight and length were greater for patients with metabolic acidosis than for those without metabolic acidosis. The mean Z score reduction from baseline progressively decreased for head circumference up to week 20 (-0.3) and then appeared to stabilize up to week 52. There was no apparent correlation of metabolic acidosis on mean Z score for head circumference. Although there appeared to be a shallow dose-response curve for topiramate dose across a range of doses analyzed (up to 60 mg/kg/d) for the mean Z score reductions for weight and length, there did not appear to be dose-related effect of topiramate dose on Z score reduction for head circumference.

- The sponsor presented the following summary about growth :
  "The differences in the effects on growth in this open-label extension study compared to those in older children and also to those in infants on lower doses are likely attributable to the higher doses of topiramate administered to this infant population, possibly mediated, at least in part, through the metabolic acidosis. The findings in this open-label integrated dataset are, however, limited by the absence of a control group and the background of poor growth in children with refractory epilepsy."

The consult specifically asked the following questions :

1. Determine whether there is any evidence that topiramate treatment in infants (e.g., 1-24 months) slows/delays growth. The sponsor collected prospective data for height/length and weight measurements in a brief controlled study and in open-label, extension studies based upon specific procedures for measuring height/length. The sponsor has also collected weight data. Topiramate is clearly known to be associated with weight loss in patients of all ages.

2. Comment on the quality of these height/length and weight data collected and the sponsor's analyses of these data.

3. Determine whether there is any evidence that growth is delayed/slowed in infants who experience any metabolic acidosis (e.g., decrease in serum bicarbonate) and if so, whether there is a greater delay/slowing of growth in infants with patients experiencing metabolic acidosis compared to those who do not experience metabolic acidosis.

4. Please comment on whether the sponsor should collect additional clinical data in infants and/or in older pediatric patients treated with topiramate to assess whether topiramate treatment slows/delays growth. There are no known data indicating whether any pediatric patients who experience chronic, untreated metabolic acidosis during topiramate treatment also experience a slowing/delay of growth. However, in theory, we expect that topiramate treatment that produces metabolic acidosis would slow/delay growth as does metabolic acidosis from any cause.

Consult's table and figures :

Table 1: Change from baseline in weight and length at Week 52

	Weight N = 283	Length N=271
Baseline Z-score Mean (SD)	-1.01	-0.48
Change from baseline to Week 52 in Z-score Mean (SD)	-0.82 (1.185)	-0.45 (1.600)

Source: Table 13. Summary of Clinical Safety

Figure 1: Change from baseline in weight and length Z-scores over time

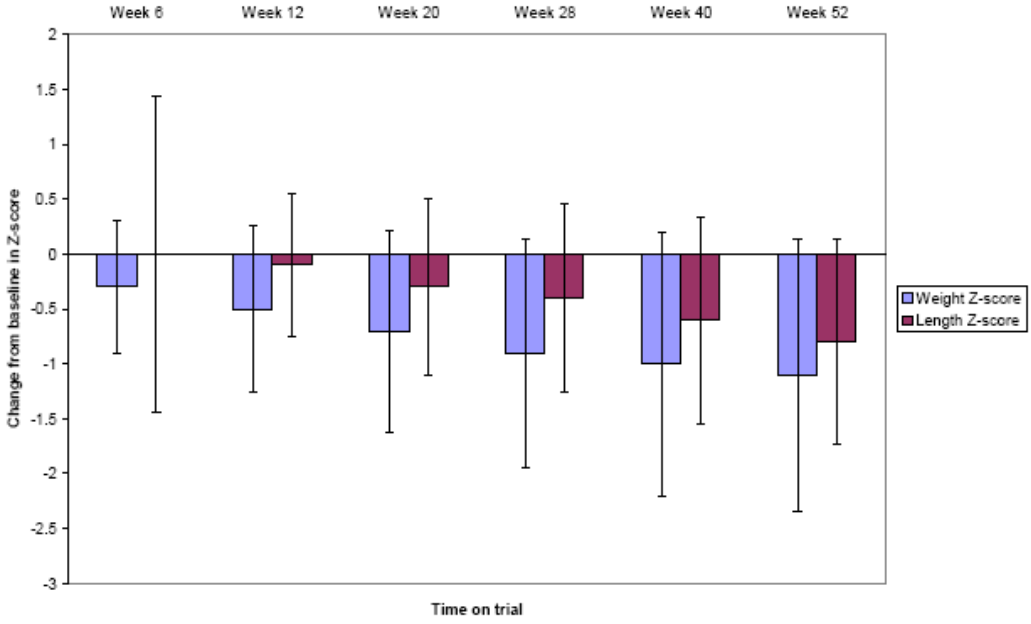


Figure 2: Change from baseline in mean weight Z-score by Topiramate modal dose

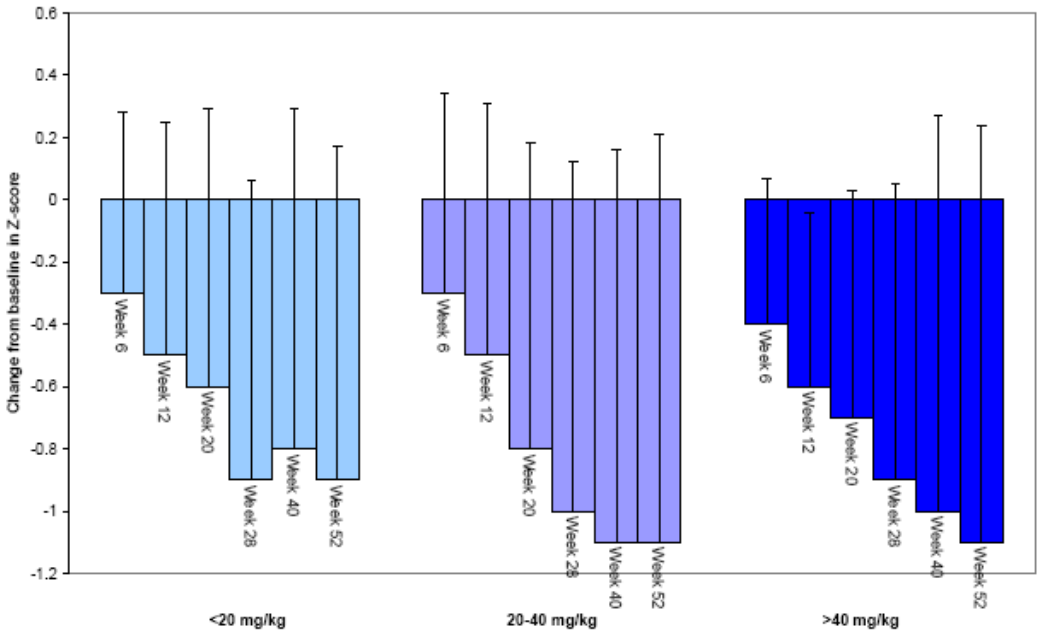


Figure 3: Change from baseline in length Z-score by Topiramate modal dose

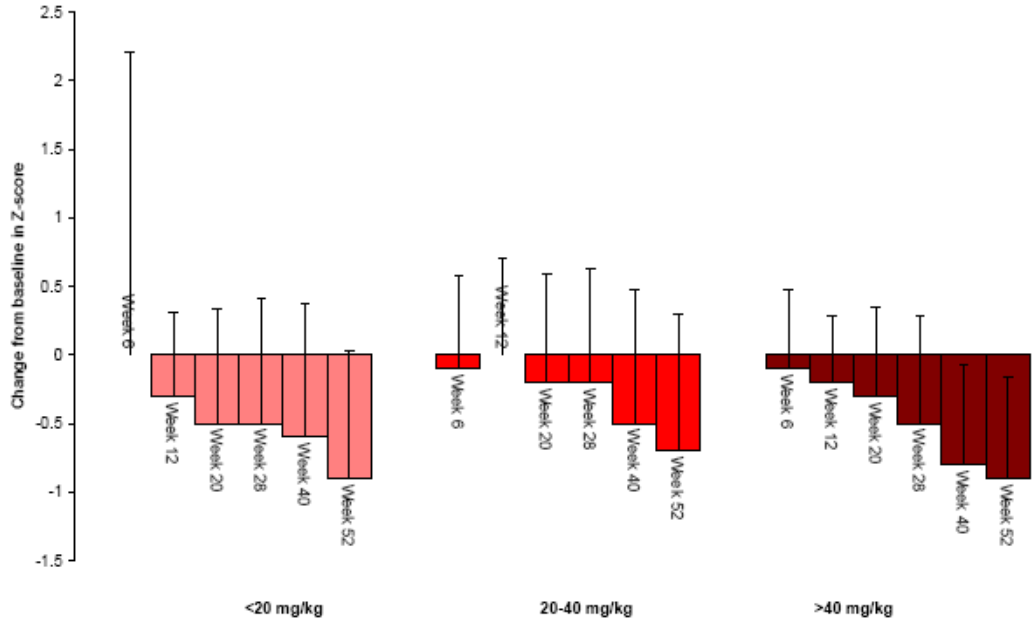


Figure 4: Change from baseline in weight Z-score in patients with and without acidosis

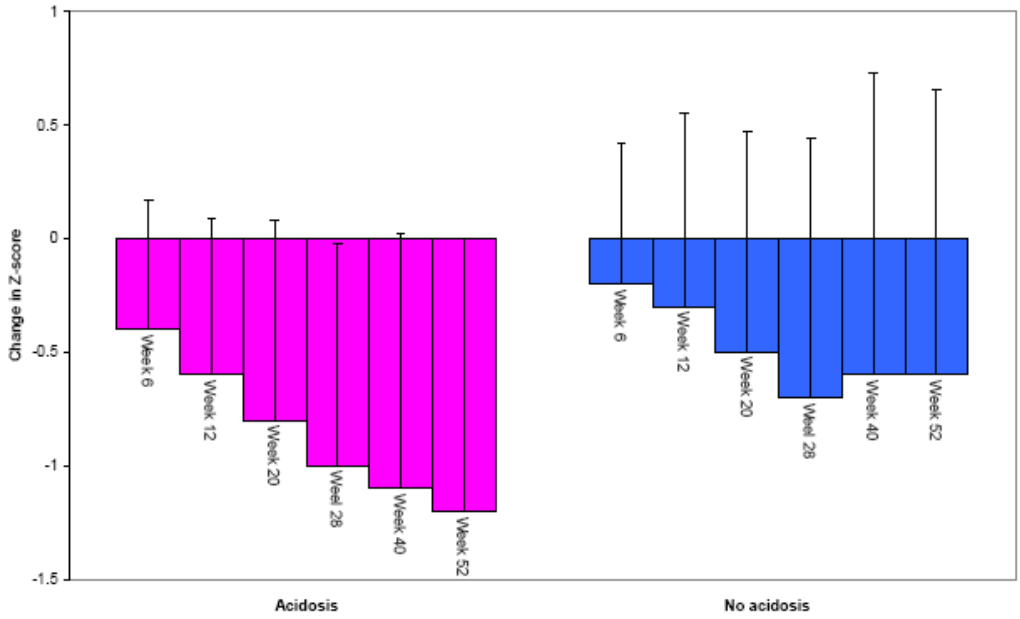
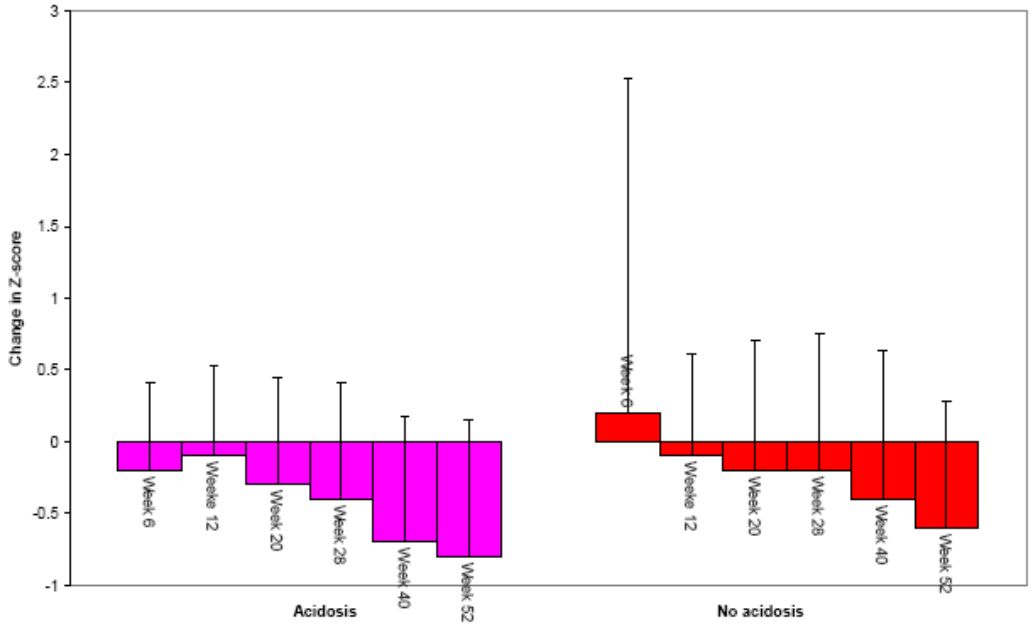


Figure 5: Change from baseline in length Z-score



Consult Conclusions

With the limitations and caveats discussed in the opening section of this consult, the following concluding observations can be made :

- Consistent with observations previously made in adults and older children, topiramate had a suppressive effect on weight in this younger patien population (i.e. infants and children < 2 years of age); within the range of doses studied no distinct dose effect was observed.

- A suppressive effect on length was also observed in the course of these studies. The suppressive effect on weight appeared to precede temporarily that on length; whether this is

indicative of a mechanistic relation between these two phenomena, it remains to be investigated.

- Patients with acidosis had a more pronounced weight Z-score reduction than patients who did not have manifestations of acidosis; a similar, albeit smaller effect was noted on length Z-score.

- The current dataset does not allow a quantification of the individual contribution of weight reductions and acidosis on linear growth.

- (b) (5)

Reviewer Comment

- Although it is not possible to conclude that these reductions in Z scores for weight, length, and head circumference were definitely related to topiramate treatment because these data were not derived from a randomized, double-blinded, placebo-controlled study, I believe that it is difficult to dismiss that they are not possibly related to topiramate treatment, at least to a partial degree. A considerable number of these very young patients had various neurological abnormalities and were likely to have various development impairments. Thus, at least some reductions in Z scores for these parameters relative to the standard (healthy pediatric subjects) would be expected.

- The Endocrine consult (obtained to assess the possibility that topiramate was impairing growth) thought that changes in weight and length were sufficiently impressive to reflect a "suppressive effect" during treatment, possibly related to topiramate and perhaps throught topirmate's effect on weight loss or rate of increase and on the development of metabolic acidosis. Although the data did not permit a mechanistic explanation for these changes, the consult noted that the changes in weight scores appeared to precede the changes in length scores, further suggesting that changes in weight may have contributed to the decrease in length Z scores. The consult further commented that there was no clear, unequivocal dose-response effect of topiramate based primarily upon various modal dose ranges (e.g., < 20, 20-40, > 40 mg/kg/d) analyzed.

- Various subgroup analyses (regarding metabolic acidosis or threshold weight reduction in Z score) were conducted. In general, patients with metabolic acidosis in the long-term, open-label extension study, had greater mean Z score reductions from baseline (for weight and length, but not head circumference than patients without metabolic acidosis suggesting the possibility that metabolic acidosis was at least partially contributing to this change.

  I also believe that there is some evidence for a dose-related effect of long-term topiramate treatment based upon analyses that show that the relative risk (based upon the ratio of the incidence of various threshold Z score reductions from baseline such as $\geq$ 0.5, $\geq$ 1.0, and $\geq$ 2.0 for patients with metabolic acidosis compared to those without metabolic acidosis. This relative risk for the various threshold Z score reductions increased with increasing dose range.

- I recognize that it is difficult to conclude definitively if topiramate's effect on metabolic acidosis and/or weight caused these adverse changes in Z scores observed for weight, length, and head circumference However, topiramate's influence on the development of metabolic acidosis and weight loss and possible secondary effects on bone metabolism suggest that this adverse effect on weight, length, and head circumference is biologically plausible.
- (b) (5)

7.1.16 Overdose Experience

- Not applicable

7.1.17 Postmarketing Experience

EXECUTIVE SUMMARY

This report summarizes all spontaneous, postmarketing cases involvinginfant (24 months of age and younger) topiramate patients that have beenreported to the Benefit Risk Management, a division of Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD), worldwide safety database as of 31 December 2007. The database search method captured all reports from the International Birth Date for topiramate (18 July 1995) through 31 December 2007.

J&JPRD is preparing to submit a supplemental New Drug Application (sNDA) in compliance with a Written Request for studies of topiramate in pediatric (infant) epilepsy. At a pre-sNDA meeting between J&JPRD and the FDA on 01 November 2007, which was convened to discuss the format and content of the sNDA, it was agreed that the pediatric application would contain a safety summary based on the total, cumulative postmarketing experience with topiramate in infant patients 24 months of age and younger. As requested by the FDA, this report includes summary and tabular listings of all reported Adverse Events (AEs), narratives and MedWatch reports for cases involving death, and narratives for cases reporting AEs within 9 special safety topics.

A total of 338 spontaneously-reported, infant topiramate patient cases were retrieved from the worldwide safety database. Fatal outcome was reported in 14 infant topiramate patients (including 1 pair of presumed duplicate cases). Case review did not reveal any pattern in type of death. Medical assessment of death for many cases was limited by the presence of confounding concomitant medications, including other anticonvulsant agents, and/or by the presence of confounding, pre-existing medical conditions (eg, congenital metabolic disorder, multiple birth abnormalities [such as VACTERL syndrome], encephalopathy, chromosomal abnormalities, viral infection). In addition, some of the cases lacked sufficient information for a meaningful evaluation. In two fatal cases, metabolic acidosis was reported, and medical assessment of both cases was limited by confounding, coexisting medical disorders and/or by concomitant medications; therefore, a clear causal relationship to treatment with topiramate could not be established. Among 324 non-fatal, infant topiramate patient cases, 60% were nonserious cases (case level). The majority of reported serious and nonserious AEs were listed events for topiramate. Based on review of the type and System Organ Class-distribution of all AEs reported in these cases, no change in the current safety profile for topiramate was identified.

In addition, a review of the following 9 special safety topics did not indicate a change in the current safety information for topiramate: hyperammonemia/encephalopathy, oligohidrosis/hyperthermia, metabolic acidosis, renal and urinary disorders including renal failure and nephrolithiasis, hepatotoxicity, rash, ocular events, cognitive/neuropsychiatric adverse events, and abnormal weight/growth. A review of 4 cases that involved

neonatal exposure to topiramate via breast milk and associated AEs did not reveal any new safety signals. Based on analysis of spontaneous, postmarketing reports in the BRM worldwide safety database as of 31 December 2007, the overall safety profile for topiramate in infant patients 24 months of age and younger was consistent with that for topiramate as described in the current reference safety document. These reports did not reveal any evidence to indicate that the administration of topiramate to infants 24 months of age and younger.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Clinical data used for assessing safety were good with limitation of short 20 day placebo-controlled phase.

7.2.1.1 Study type and design/patient enumeration

See description of studies.

7.2.1.2 Demographics

This has been outlined previously.

7.2.1.3 Extent of exposure (dose/duration)

Dosage and Duration of Exposure

Study TOPMAT-PEP-1002 Open-Label Treatment (Core) Phase

• Duration of exposure varied by treatment group for the core phase per protocol, with subjects in the lower dosage groups generally receiving study medication for fewer days because the titration time was shorter for lower target dosages. The median numbers of dosing days were 8, 15, 33, and 43 days for subjects in the 3, 5, 15, and 25 mg/kg/d groups, respectively.

• Forty-nine of the 50 subjects who completed the core phase received the full course of study medication. Twelve subjects vomited 38 doses in total, of which most were re-dosed per protocol.

Study TOPMAT-PEP-3001 Double-Blind (Core) Phase

• The mean average, maximum, and final doses in the 3 topiramate groups reflected the planned target doses of 5, 15, and 25 mg/kg/d
• Ninety four percent of subjects who received topiramate and 81% of subjects who received placebo were treated for at least 16 of the planned 20 days. The median treatment duration was 20 days in each treatment group.
• Among subjects who received topiramate, 4% required a dose reduction and 7% required a pause in the uptitration schedule, similar to the proportions of subjects who received placebo (5% and 5%, respectively). The proportions of topiramate-treated subjects who required a pause in the uptitration schedule appeared to be dose related, i.e., the higher the dose, the more likely a subject would require a pause in uptitration.
• The double-blind phase was completed at the target dosage by 95%, 76%, and 84% of subjects in the topiramate 5, 15, and 25 mg/kg/d treatment groups, respectively.

Studies TOPMAT-PEP-1002 and -3001 Integrated Open-Label Extension

• For the core phase and open-label extension phases combined, the overall mean average dose was 21.72 mg/kg/d with a range of 17.90 (for subjects who did not receive double-blind treatment in TOPMAT-PEP-3001, i.e., "PEP-3001 shunt") to 24.48 mg/kg/d (for subjects who received double-blind topiramate in TOPMAT-PEP-3001, i.e., "PEP-3001 TPM").
• Fourteen subjects were exposed to a dosage of topiramate >60 mg/kg/d
• For all analysis categories, the mean treatment duration was 282 days.
• Including both core phase and extension phase exposure, 205 subjects (72%) were exposed to topiramate for at least 6 months (≥181 days), and 146 subjects (51%) were exposed for at least 1 year (>351 days).

Table 3: Extent of Exposure to Topiramate by Analysis Category - Core Phase and Open-Label Extension Phases Combined (TOPMAT-PEP-1002 and TOPMAT-PEP-3001 Integrated OL Extension: Safety Analysis Set)

	PEP-1002 (N=50)	PEP-3001 PBO (N=36)	PEP-3001 TPM (N=108)	PEP-3001 Shunt (N=90)	Total (N=284)
Average dose (mg/kg/d)					
N	50	36	108	90	284
Mean (SD)	22.04 (9.851)	22.59 (12.214)	24.48 (10.320)	17.90 (11.186)	21.72 (11.069)
Median	21.93	21.62	23.21	17.25	21.40
Range	(2.7;40.0)	(4.9;55.2)	(2.7;49.2)	(1.4;44.7)	(1.4;55.2)
Maximum dose (mg/kg/d)					
N	50	36	108	90	284
Mean (SD)	32.41 (16.155)	29.36 (16.216)	34.22 (14.063)	24.60 (14.766)	30.24 (15.432)
Median	30.20	25.30	30.75	24.55	27.20
Range	(3.0;70.6)	(4.9;64.5)	(7.6;78.5)	(2.3;60.0)	(2.3;78.5)
Final dose (mg/kg/d)					
N	50	36	108	90	284
Mean (SD)	24.92 (16.123)	21.59 (14.151)	25.00 (15.074)	16.71 (13.849)	21.93 (15.161)
Median	22.60	20.35	24.45	12.00	20.35
Range	(1.4;65.0)	(4.1;60.2)	(1.1;59.7)	(1.1;60.0)	(1.1;65.0)
Duration of exposure, days					
N	50	36	108	90	284
Category, n (%)					
< 30 days	2 (4)	2 (6)	0	8 (9)	12 (4)
30 to 60 days	2 (4)	1 (3)	3 (3)	7 (8)	13 (5)
61 to 120 days	0	1 (3)	13 (12)	4 (4)	18 (6)
121 to 180 days	1 (2)	5 (14)	26 (24)	4 (4)	36 (13)
181 to 240 days	2 (4)	4 (11)	9 (8)	3 (3)	18 (6)
241 to 270 days	2 (4)	1 (3)	1 (1)	1 (1)	5 (2)
271 to 300 days	3 (6)	2 (6)	2 (2)	1 (1)	8 (3)
301 to 330 days	9 (18)	3 (8)	2 (2)	0	14 (5)
331 to 351 days	6 (12)	0	5 (5)	3 (3)	14 (5)
> 351 days	23 (46)	17 (47)	47 (44)	59 (66)	146 (51)
Mean	321.34	269.22	266.62	282.56	281.63
(SD)	(104.074)	(116.844)	(124.954)	(140.434)	(126.704)
Median	336.00	322.00	306.00	366.00	355.00
Range	(14.0;425.0)	(2.0;395.0)	(35.0;414.0)	(7.0;407.0)	(2.0;425.0)

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Cross-reference: Mod5.3.5.2\TOPMAT-PEP-1002_3001OLE\Table 8

• The WR specified the need to evaluate the safety of topiramate in the target pediatric population in at least 100 subjects over a 1-year treatment exposure at a commonly used dose. A commonly used dose was agreed to be 5 mg/kg/d (14 December 2005 WR, Study Type III; Minutes from 05 September 2007 Meeting, Module 1.6.3). A total of 130 subjects who were in the trial for at least 1 year (>351 days) were exposed to at least 5 mg/kg/d of topiramate for at least 1 year (>351 days) and 142 subjects who were in the trial for at least 1 year (>351 days) were exposed to at least 5 mg/kg/d of topiramate for at least 8 months (>240 days; Table 4).
• The WR also specified a significant portion (defined as 25 subjects; Minutes from 02 March 2006 Type A Meeting, Module 1.6.3) of long-term safety data at doses of >25 mg/kg/d used throughout most of the exposure

(≥8 months) must be collected (14 December 2005 WR, Study Type III; Minutes from 05 September 2007 Meeting, Module 1.6.3). A total of 67 subjects who were in the trial for at least 1 year (>351 days) were exposed to at least 25 mg/kg/d of topiramate for at least 8 months (>240 days).

Table 4: Extent of Exposure to Study Medication at Selected Doses for Subjects Who Had Total Duration of Exposure ≥351 Days by Analysis Category - Core Phase and Open-Label Extension Phases Combined (TOPMAT-PEP-1002 and TOPMAT-PEP-3001 Integrated OL Extension: Safety Analysis Set)

Treatment Duration	PEP-1002 (N=50) n (%)	PEP-3001 PBO (N=36) n (%)	PEP-3001 TPM (N=108) n (%)	PEP-3001 Shunt (N=90) n (%)	Total (N=284) n (%)
Dosage: ≥5 mg/kg/d					
0 Day	28 (56)	19 (53)	61 (56)	33 (37)	141 (50)
≥1 Day	22 (44)	17 (47)	47 (44)	57 (63)	143 (50)
≥30 Days	22 (44)	17 (47)	47 (44)	56 (62)	142 (50)
≥60 Days	22 (44)	17 (47)	47 (44)	56 (62)	142 (50)
≥90 Days	22 (44)	17 (47)	47 (44)	56 (62)	142 (50)
≥120 Days	22 (44)	17 (47)	47 (44)	56 (62)	142 (50)
≥150 Days	22 (44)	17 (47)	47 (44)	56 (62)	142 (50)
≥180 Days	22 (44)	17 (47)	47 (44)	56 (62)	142 (50)
≥210 Days	22 (44)	17 (47)	47 (44)	56 (62)	142 (50)
≥240 Days	22 (44)	17 (47)	47 (44)	56 (62)	142 (50)
≥270 Days	22 (44)	17 (47)	47 (44)	56 (62)	142 (50)
≥300 Days	21 (42)	17 (47)	47 (44)	55 (61)	140 (49)
≥330 Days	21 (42)	16 (44)	46 (43)	54 (60)	137 (48)
≥351 Days	19 (38)	13 (36)	46 (43)	52 (58)	130 (46)
≥365 Days	17 (34)	5 (14)	38 (35)	27 (30)	87 (31)
Dosage: ≥15 mg/kg/d					
0 Day	28 (56)	22 (61)	61 (56)	41 (46)	152 (54)
≥1 Day	22 (44)	14 (39)	47 (44)	49 (54)	132 (46)
≥30 Days	22 (44)	14 (39)	45 (42)	45 (50)	126 (44)
≥60 Days	22 (44)	14 (39)	44 (41)	44 (49)	124 (44)
≥90 Days	22 (44)	14 (39)	43 (40)	43 (48)	122 (43)
≥120 Days	22 (44)	13 (36)	43 (40)	41 (46)	119 (42)
≥150 Days	21 (42)	13 (36)	43 (40)	41 (46)	118 (42)
≥180 Days	20 (40)	13 (36)	42 (39)	39 (43)	114 (40)
≥210 Days	20 (40)	13 (36)	42 (39)	38 (42)	113 (40)
≥240 Days	20 (40)	13 (36)	42 (39)	37 (41)	112 (39)
≥270 Days	19 (38)	13 (36)	42 (39)	36 (40)	110 (39)
≥300 Days	18 (36)	13 (36)	41 (38)	34 (38)	106 (37)
≥330 Days	14 (28)	12 (33)	39 (36)	31 (34)	96 (34)
≥351 Days	12 (24)	7 (19)	27 (25)	22 (24)	68 (24)
≥365 Days	6 (12)	2 (6)	18 (17)	7 (8)	33 (12)

Note: Duration of exposure is defined as the last topiramate dose date minus the first topiramate dose date plus 1. N is the number of subjects in the safety population.

Table 4: Extent of Exposure to Study Medication at Selected Doses for Subjects Who Had Total Duration of Exposure ≥351 Days by Analysis Category - Core Phase and Open-Label Extension Phases Combined (Continued)
(TOPMAT-PEP-1002 and TOPMAT-PEP-3001 Integrated OL Extension: Safety Analysis Set)

Treatment Duration	PEP-1002 (N=50) n (%)	PEP-3001 PBO (N=36) n (%)	PEP-3001 TPM (N=108) n (%)	PEP-3001 Shunt (N=90) n (%)	Total (N=284) n (%)
Dosage: ≥25 mg/kg/d					
0 Day	32 (64)	26 (72)	64 (59)	57 (63)	179 (63)
≥1 Day	18 (36)	10 (28)	44 (41)	33 (37)	105 (37)
≥30 Days	15 (30)	10 (28)	39 (36)	26 (29)	90 (32)
≥60 Days	13 (26)	10 (28)	38 (35)	23 (26)	84 (30)
≥90 Days	13 (26)	10 (28)	36 (33)	21 (23)	80 (28)
≥120 Days	13 (26)	10 (28)	34 (31)	21 (23)	78 (27)
≥150 Days	13 (26)	10 (28)	34 (31)	20 (22)	77 (27)
≥180 Days	13 (26)	10 (28)	32 (30)	18 (20)	73 (26)
≥210 Days	13 (26)	10 (28)	31 (29)	17 (19)	71 (25)
≥240 Days	12 (24)	10 (28)	30 (28)	15 (17)	67 (24)
≥270 Days	11 (22)	10 (28)	30 (28)	13 (14)	64 (23)
≥300 Days	8 (16)	10 (28)	24 (22)	11 (12)	53 (19)
≥330 Days	5 (10)	6 (17)	17 (16)	7 (8)	35 (12)
≥351 Days	2 (4)	1 (3)	8 (7)	3 (3)	14 (5)
≥365 Days	2 (4)	1 (3)	4 (4)	1 (1)	8 (3)

Note: Duration of exposure is defined as the last topiramate dose date minus the first topiramate dose date plus 1. N is the number of subjects in the safety population.
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Cross-reference: Mod5.3.5.2\TOPMAT-PEP-1002_3001OLE\Table 9

Reviewer Comment

Dose-duration exposure was considered quite adequate.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

These were noted when accessed in different sections.

7.2.2.1 Other studies

Not applicable

7.2.2.2 Postmarketing experience

See other post-marketing summary

7.2.2.3 Literature

See other Literature section

7.2.3 Adequacy of Overall Clinical Experience

Overall the clinical experience was adequate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable

7.2.5 Adequacy of Routine Clinical Testing

This was adequate

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Clinical Pharmacology review thought that these were adequate.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

- These have been described in separate safety sections reviewed.

7.2.8 Assessment of Quality and Completeness of Data

Quality of data were good and appeared to be complete.

7.2.9 Additional Submissions, Including Safety Update

Not applicable

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

- These have been described in separate safety sections reviewed.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable

7.4.1.1 Pooled data vs. individual study data

Not applicable

7.4.1.2 Combining data

Not applicable

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

- These are described in separate safety sections reviewed.

7.4.2.2 Explorations for time dependency for adverse findings

- These are described in separate safety sections reviewed.

7.4.2.3 Explorations for drug-demographic interactions

There were no interactions noted.

7.4.2.4 Explorations for drug-disease interactions

These were not assessed.

7.4.2.5 Explorations for drug-drug interactions

Not applicable

7.4.3 Causality Determination

This is noted in safety assessments

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Not applicable be there is no approval

8.2 Drug-Drug Interactions

See Clinincal Pharmacology Review

8.3 Special Populations

Not applicable

8.4 Pediatrics

This is pediatric application as part of a PWR for Exclusivity that has been granted.

8.5 Advisory Committee Meeting

Not applicable

8.6 Literature Review

No significant comments or concerns about what was provided by sponsor

8.7 Postmarketing Risk Management Plan

Not applicable

8.8 Other Relevant Materials

Not applicable

9 OVERALL ASSESSMENT

See Executive Summary at Beginning of this review for these same sections.

9.1 Conclusions

9.2 Recommendation on Regulatory Action

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

9.3.2 Required Phase 4 Commitments

9.3.3 Other Phase 4 Requests

9.4 Labeling Review

- A revised label was prepated as a separate document and is not shown here.
- Issues
  - (b) (4)

9.5 Comments to Applicant

- The main request to the sponsor will be to submit a revised label for topirmate incorporating the DNP recommended revisions regarding the above topics.

10 APPENDICES

10.1 Review of Individual Study Reports

- Not specifically applicable here. Any review of an individual study report was included in the main body of my review.

10.2 Line-by-Line Labeling Review

- Not applicable to this review (not shown here)

REFERENCES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Leonard Kapcala
1/23/2009 08:15:28 PM
MEDICAL OFFICER

HI Norm, Here is my review of topiramate NDA 20844/20505. Please let me know if any questions and sign plese. Thanx. Len

Norman Hershkowitz
1/23/2009 08:43:13 PM
MEDICAL OFFICER