CLINICAL REVIEW

Application Type	NDA
Application Number(s)	20505/20844
Priority or Standard	Standard
Submit Date(s)	5/28/13
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Division / Office	DNP/ODE I
Reviewer Name(s)	Leonard P. Kapcala. M.D.
Review Completion Date	2/21/14
Established Name	topiramate
(Proposed) Trade Name	Topamax
Therapeutic Class	Anticonvulsant (Anti-Epileptic Drug)
Applicant	Janssen Research & Development, LLC
Formulation(s)	Tablets/Capsules
Dosing Regimen	Twice Daily in Divided Doses (50 mg BID)
Indication(s)	Migraine Prophylaxis
Intended Population(s)	Adolescents 12-17 Years

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

In the key pivotal trial (MIG-3006) submitted in this NDA, the 100 mg topiramate dose demonstrated efficacy in adolescents (12-17 years) for the primary analysis of the primary efficacy endpoint, median percentage reduction in monthly migraine rate from baseline over the last 12 weeks of the trial (i.e., maintenance period). Specifically, the median monthly migraine rate over the last 12 weeks of the trial was 1.0 for the 100 mg dose and 2.3 for placebo, showing a 72.2 % reduction for 100 mg and 44.6 % reduction for placebo and a treatment difference of approximately 28 % when the 48 hour rule was applied for counting patient reported migraines in diaries (Table 18). This difference was highly statistically significant (p=0.0164). In addition, the 100 mg topiramate dose demonstrated efficacy in adolescents for a key secondary efficacy endpoint, mean change in monthly migraine rate from baseline over the last 12 weeks of the trial when the 48 hour rule was applied for counting patient reported migraines in diaries. Specifically, the mean monthly migraine rate over the last 12 weeks of the trial was 1.3 for the 100 mg dose and 2..4 for placebo, showing approximately a 3.0 decrease in monthly migraine rate from baseline for 100 mg topiramate and approximately a 1.7 decrease in monthly migraine rate from baseline for placebo (Table 22). The treatment difference of approximately a 1.3 decrease in monthly migraine rate was highly statistically significant (p=0.0087). This efficacy result in adolescents was similar to the efficacy shown in adult migraine prophylaxis trials that used this endpoint as the primary efficacy endpoint.

In addition, the sponsor submitted another randomized, double-blinded, placebo-controlled trial (5 months) of pediatric patients (6-16 yo) in which patients were treated with topiramate (2-3 mg/kg/day) for migraine prophylaxis. This trial was not conducted under the U.S. IND. The efficacy data for a subgroup of adolescents (12-16 yo) in this trial were generally supportive of these same key efficacy endpoints of MIG-3006 but these efficacy results were not statistically significant, possibly because the treatment groups (topiramate, N=49; placebo, N=18) were underpowered for showing statistically significant effects. The treatment difference (topiramate – placebo) was about 16 % (p=0.3326) for median percentage reduction from baseline in monthly migraine rate over the last 12 weeks of the trial and was about – 0.6 (p=0.2952) for mean reduction from baseline in monthly migraine rate over the last 12 weeks of the trial (Table 44).

Although the International Headache Society (IHS) criteria were used for enrolling pediatric patients in MIG-3006 to ensure that patients had bonafide migraine attacks, the IHS algorithm was not applied for counting migraine episodes/attacks in the primary analysis of the primary efficacy endpoint. However, various sensitivity analyses suggested that this was not a problem and that efficacy was clearly demonstrated. Of relevance, when the IHS algorithm (and 48 hour rule) was applied to the ITT population for the mean change from baseline in monthly migraine rate over the last 12 weeks of the trial in MIG-3006, the mean treatment difference for this endpoint was about -1.1 (similar to the analysis result without the IHS algorithm in adolescents

and also in adults) and the unadjusted (i.e., nominal, not adjusted for multiplicity by Hochberg test) p-value was statistically significant (p=0.0278) (Table 43).

Safety was demonstrated from my review of numerous, various analyses of treatment-emergent adverse events (TEAEs), clinical laboratory analytes, and orthostatic vital signs in the placebo-controlled migraine trials in pediatric patients, in pooled analyses of longer-term, open-label pediatric migraine trials, and in pediatric, controlled and open-label epilepsy trials. TEAEs in placebo-controlled, pediatric migraine trials were relatively similar to those in controlled adult migraine trials and various pediatric and adult epilepsy trials (monotherapy and adjunctive therapy). Major safety findings in the pediatric migraine trials include cognitive dysfunction, metabolic acidosis, hyperammonemia, rare kidney stones, and paresthesia. These findings are already included in the Warnings and Precautions section of the Topamax (topiramate) label. In addition, there were some noteworthy outliers (decreased or increased) abnormalities in some clinical laboratory analytes and vital signs that I have recommended be included in the label. Other topics that are currently in the Warnings and Precautions section of the Topamax label but which were not clearly identified as signals in the safety data analyses in the pediatric migraine trials include : acute myopia and secondary angle closure glaucoma, visual field defects, suicidal behavior and ideation, fetal toxicity (including risk of oral clefts from topiramate exposure during pregnancy), withdrawal of antiepileptic drugs (AEDs), sudden unexplained death in epilepsy (SUDEP), and hypothermia with concomitant valproic acid (VPA) use. Overall, I conclude that 100 mg topiramate is reasonably safe for the indication of migraine prophylaxis in adolescents.

It is also noteworthy that this approval would be important because it would be the first Agency approval for migraine prophylaxis in a pediatric population.

I recommend approval of this NDA for topiramate for the indication of migraine prophylaxis in adolescents. My recommendation for approval is based upon the fact that 100 mg topiramate was shown to be effective in adolescents for migraine prophylaxis in MIG-3006 and the safety of this dose is supported by this trial and other migraine prophylaxis trials of pediatric patients as well as monotherapy and adjunctive epilepsy trials in pediatric patients.

1.2 Risk Benefit Assessment

Overall, the risks of 100 mg daily topiramate for migraine prophylaxis in adolescents (12-17 years) does not appear to be greater than the risk for topiramate for migraine prophylaxis for adults and for topiramate treatment of various forms of epilepsy in pediatric and adults patients as monotherapy or adjunctive therapy. In considering the incidence of TEAEs, the topiramate treatment difference in various instances in adolescent migraine trials is less than the incidence of TEAEs for other adults in migraine trials and for adults and pediatric patients in epilepsy trials. The overall safety profile in adolescents in migraine trials is relatively similar to that in adults in migraine trials and generally similar to that in adults and pediatric patients in epilepsy trials.

It is relevant that the 100 mg daily topiramate recommended dose for adolescents for migraine prophylaxis is identical to that for adults. It is also relevant to note that this recommended dose for adolescent migraine is much less than the topiramate dosing for epilepsy in pediatric and adult patients. More specifically, the recommended adjunctive treatment of pediatric epilepsy is 5-9 mg/kg/day, a dose that is much higher than the mg/kg/day dose computed for adolescent migraine patients (mean 1.3, median 1.5, maximum 2.7 mg/kg/day) who were randomized to receive 100 gm daily. The usual adult dose for adjunctive treatment of epilepsy ranges from 200-400 mg daily. In addition, the epilepsy monotherapy dose for patients 10 years and older is 400 mg daily and the daily dosing for epilepsy monotherapy for pediatric patients (2-9 years) ranges from 250 mg – 400 mg daily. If topiramate dosing is similar for adult migraine prophylaxis and much less than dosing for pediatric and adult patients for epilepsy indications and the safety profile is overall considered to be similar to these other populations for these indications, then it appears that the risk benefit assessment is justified for this dose for adolescent migraine prophylaxis. Therefore, I conclude that my risk benefit assessment supports the approval of 100 mg daily topiramate for migraine prophylaxis in adolescents (12-17 years).

Considering that are no Agency approved treatments for migraine prophylaxis in pediatric patients, this acceptable risk benefit assessment is further supported by the fact that this approval would be the first time that adolescents (12-17 years) were offered the opportunity of managing their migraines with a safe and effective drug treatment for prophylaxis.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

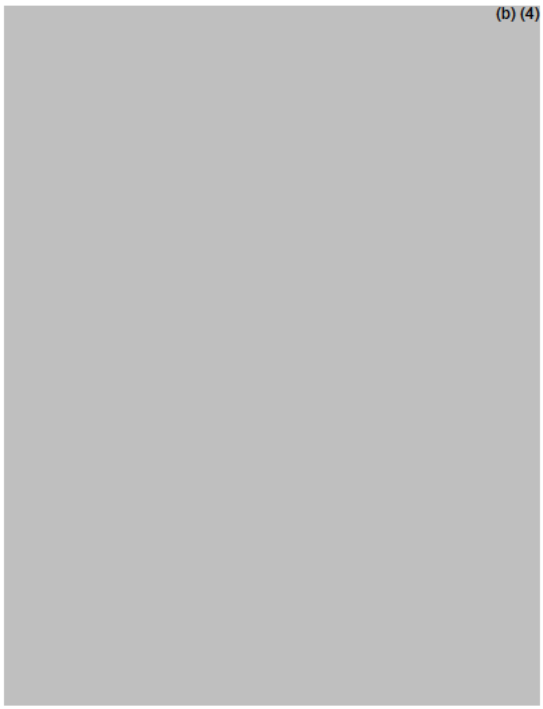
Introduction and Regulatory Background

2.1 Product Information

Topiramate (TOPAMAX®) tablets and sprinkle capsules have been approved by the Food and Drug Administration (FDA) as adjunctive therapy for adults and pediatric patients aged 2 to 16 years with partial-onset seizures (POS), primary generalized tonic-clonic (PGTC) seizures, and seizures associated with Lennox-Gastaut syndrome. Since its global introduction (18 July 1995), topiramate has been approved for antiepileptic adjunctive therapy for adults in more than 100 countries and for children ages 2 to 16 years in more than 70 countries. In the United States (US), topiramate is also approved as monotherapy in adult and pediatric patients (≥ 2 years of age in the US) with newly diagnosed POS or PGTC seizures (as demonstrated in a controlled trial in patients with epilepsy who had no more than 2 seizures in the 3 months prior to enrollment), and as migraine prophylaxis in adults (approved 8/11/04).

The registered formulations of topiramate in the U.S. are coated oral tablets (25-, 50-, 100-, and 200-mg strengths; NDA 20-505) and coated beads in a gelatin capsule that can be swallowed whole or sprinkled on food (sprinkle capsules, containing 15 or 25 mg of topiramate; NDA 20-844).

The structure and chemical name of topiramate that belongs to the pharmacological class, anti-epileptic drug (AED) is shown below here.



2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, there are no drugs approved for migraine prophylaxis for any pediatric patients. The Agency has approved four medications for migraine prophylaxis in adults. They are propranolol (Inderal), timolol (Blocadren), topiramate (Topamax) and divalproex sodium (Depakote).

2.3 Availability of Proposed Active Ingredient in the United States

TOPAMAX® has been available for many years in the U.S. for various indications (see section 2.1) Generic topiramate is also available.

2.4 Important Safety Issues With Consideration to Related Drugs

Topiramate shares many safety issues/toxicities with zonisamide, another antiepileptic drug (AED) that is only approved for adjunctive treatment of partial epilepsy in adults. The most striking toxicities shared by these drugs include various adverse reactions on cognitive function, metabolic acidosis, and oligohydrosis/hyperthermia. The AEDs share several pharmacological actions including inhibition of carbonic anhydrase activity.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In August 2004, Janssen Research & Development, LLC (JRD, the sponsor), formerly known as Johnson & Johnson Pharmaceutical Research & Development, LLC (J&JPRD), received approval of NDA 20-505 (TOPAMAX® [topiramate] Tablet) and NDA 20-844 (TOPAMAX® [topiramate capsule] Sprinkle Capsule) for the use of topiramate in the prophylaxis of migraine headache in adults. In follow-up to that approval, a postmarketing commitment was set forth under the Pediatric Research & Equity Act (PREA) for a study to be conducted in adolescent subjects age 12 to 17 years for the same indication, with a final report to be submitted by 31 August 2007. The sponsor conducted the study and submitted the final study report in August 2007 to fulfill the required pediatric study commitment under PREA. However, an efficacy supplement for migraine prophylaxis in adolescents was not submitted at that time due to concerns by the Food and Drug Administration (FDA) about insufficient long-term safety data in this patient population in support of this indication.

On 13 April 2010, a teleconference between JRD and the FDA was held to discuss the pediatric migraine prophylaxis PREA commitment. At that time, the FDA indicated that the PREA commitment was fulfilled and that they would like JRD to re-consider submitting a supplemental New Drug Application (sNDA) for migraine prophylaxis in adolescents. FDA did acknowledge that previous advice to the Company was that an sNDA was not achievable due to lack of long term safety data, however, after re-evaluating the submission, they believed that a marketing application could be supported by long term safety data from the migraine studies, as well as, epilepsy in both adjunctive and monotherapy settings.

In June 2010, the sponsor communicated to FDA in writing that it would not be pursuing an indication in this patient population (b) (4). Subsequently, in a 13 September 2011 teleconference, the FDA strongly recommended that an efficacy supplement for the indication of adolescent migraine prophylaxis be submitted, as this was also going to be addressed at the Pediatric Advisory Committee (PAC) meeting on 23 September 2011. In follow-up JRD communicated with FDA prior to the PAC on 21 September 2011 indicating their agreement to submit an efficacy supplement for an indication in adolescents for migraine prophylaxis .

During that Pediatric Advisory Committee meeting on 23 September 2011, the Committee discussed the unmet need for approved migraine prophylaxis therapies in the pediatric population and agreed that a pediatric sNDA should be submitted with relevant updates to the labeling. The sponsor, at that time, indicated to the Committee that they were working with FDA to seek an indication for use with topiramate in the adolescent population.
This sNDA submission presents the results of the efficacy and safety analyses and information to support the use of topiramate for prophylaxis of migraine headache in pediatric patients and supports the indication JRD is seeking for use of topiramate in adolescents 12 years of age and older for prophylaxis of migraine headache. The sponsor discussed the content and format of this sNDA at a Type B meeting with FDA in June 2012.

2.6 Other Relevant Background Information

Not applicable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

There were no inspections of any clinical sites. This decision was made in the DNP because there is so much experience with topiramate and if inspections were conducted by the Division of Scientific Investigation, the inspections would have required inspections in some international sites (e.g., Brazil, Argentina, Norway, Finland) because most patients were enrolled in foreign sites and the sites enrolling the most patients were in the countries noted.

Reviewer Comments

I did not have any concerns about the quality or integrity of the data and analyses.

3.2 Compliance with Good Clinical Practices

The sponsor appeared to comply with Good Clinical Practices in conducting its clinical development program.

3.3 Financial Disclosures

The sponsor submitted financial disclosure information as required. There were not Investigators with a financial conflict of interest. For a few investigators, there was not complete financial disclosure information, but the sponsor documented its due diligence for its unsuccessful attempts to contact these few investigators.

Reviewer Comments

I did not have any concerns about the financial disclosure information provided.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Not applicable

4.2 Clinical Microbiology

Not applicable

4.3 Preclinical Pharmacology/Toxicology

Not applicable

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The precise mechanism by which topiramate exerts its anti-seizure or potential antinociceptive effect is unknown; however, electrophysiological and biochemical studies of the effects of topiramate on cultured neurons have revealed four properties that may contribute to topiramate's antiepileptic efficacy.

• First, action potentials elicited repetitively by a sustained depolarization of the neurons are blocked by topiramate in a time-dependent manner, suggestive of a state and voltage dependent sodium channel blocking action.

• Second, topiramate increases the frequency at which γ-aminobutyrate (GABA) activates GABAA receptors, and enhances the ability of GABA to induce a flux of chloride ions into neurons, suggesting that topiramate potentiates the activity of this inhibitory neurotransmitter. This effect was not blocked by flumazenil, a benzodiazepine antagonist, nor did topiramate increase the duration of the channel open time, differentiating topiramate from barbiturates that modulate GABAA receptors.1

• Third, topiramate antagonizes the ability of kainate to activate the kainate/AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; non-NMDA) subtype of excitatory amino acid (glutamate) receptor, but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.2 These effects of topiramate are concentration-dependent within the range of 1 mM to 200 mM. It has a negative modulatory effect on Calcium channels which includes high voltage neurons (at least N or L types).

• Fourth, topiramate also inhibits some isoenzymes of carbonic anhydrase (CA-II and CA-IV). This pharmacologic effect is generally weaker than that of acetazolamide, a known carbonic anhydrase inhibitor

4.4.2 Pharmacodynamics

Topiramate has anticonvulsant activity in rat and mouse maximal electroshock seizure (MES) tests. Topiramate is only weakly effective in blocking clonic seizures induced by the $GABA_A$ receptor antagonist, pentylenetetrazole. Topiramate is also effective in rodent models of epilepsy, which include tonic and absence-like seizures in the spontaneous epileptic rat (SER) and tonic and clonic seizures induced in rats by kindling of the amygdala or by global ischemia.

The following are considered to be major pharmacodynamic effects in humans that are described in the Warning and Precautions section of the label/package insert.

- Acute Myopia and Secondary Angle Closure
- Visual field defect
- Oligohidrosis and Hyperthermia
- Metabolic Acidosis
- Suicidal Behavior and Ideation
- Cognitive/Neuropsychiatric Adverse Reactions
- Fetal Toxicity (risk for oral clefts –cleft lip and/or cleft palate from topiramate exposure during pregnancy, and possible effects on decreased fetal growth, decreased fetal oxygenation, and fetal death, and the fetus' ability to tolerate labor because of metabolic acidosis)
- Sudden Unexplained Death in Epilepsy (SUDEP)
- Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid
- Kidney Stones
- Hypothermia with Concomitant Valproic Acid (VPA) Use
- Paresthesia

4.4.3 Pharmacokinetics

The "sprinkle"/capsule formulation is bioequivalent to the immediate-release tablet formulation and, therefore, may be substituted as a therapeutic equivalent.

Absorption of topiramate is rapid, with peak plasma concentrations occurring at approximately 2 hours following a 400 mg oral dose. The relative bioavailability of topiramate from the tablet formulation is about 80% compared to a solution. The bioavailability of topiramate is not affected by food.

The pharmacokinetics of topiramate are linear with dose proportional increases in plasma concentration over the dose range studied (200 to 800 mg/day). The mean plasma elimination half-life is 21 hours after single or multiple doses. Steady-state is thus reached in about 4 days in patients with normal renal function. Topiramate is 15% to 41% bound to human plasma proteins over the blood concentration range of 0.5 to 250 µg/mL. The fraction bound decreased as blood concentration increased.

Carbamazepine and phenytoin do not alter the binding of topiramate. Sodium valproate, at 500 µg/mL (a concentration 5 to 10 times higher than considered therapeutic for valproate) decreased the protein binding of topiramate from 23% to 13%. Topiramate does not influence the binding of sodium valproate.

Metabolism and Excretion

Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose). Six metabolites have been identified in humans, none of which constitutes more than 5% of an administered dose. The metabolites are formed via hydroxylation, hydrolysis, and glucuronidation. There is evidence of renal tubular reabsorption of topiramate. In rats, given probenecid to inhibit tubular reabsorption, along with topiramate, a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, oral plasma clearance (CL/F) is approximately 20 to 30 mL/min in humans following oral administration.

Special Populations

Renal Impairment

The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30 to 69 mL/min/1.73m^2) and by 54% in severely renally impaired subjects (creatinine clearance <30 mL/min/1.73m^2) compared to normal renal function subjects (creatinine clearance >70 mL/min/1.73m^2). Since topiramate is presumed to undergo significant tubular reabsorption, it is uncertain whether this experience can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. In general, however, use of one-half the usual starting and maintenance dose is recommended in patients with moderate or severe renal impairment

Hemodialysis

Topiramate is cleared by hemodialysis. Using a high-efficiency, counterflow, single pass-dialysate hemodialysis procedure, topiramate dialysis clearance was 120 mL/min with blood flow through the dialyzer at 400 mL/min. This high clearance (compared to 20 to 30 mL/min total oral clearance in healthy adults) will remove a clinically significant amount of topiramate from the patient over the hemodialysis treatment period. Therefore, a supplemental dose may be required.

Hepatic Impairment

In hepatically impaired subjects, the clearance of topiramate may be decreased; the mechanism underlying the decrease is not well understood

Age, Gender, and Race

The pharmacokinetics of topiramate in elderly subjects (65 to 85 years of age, N=16) were evaluated in a controlled clinical study. The elderly subject population had reduced renal function (creatinine clearance [-20%]) compared to young adults. Following a single oral 100 mg dose, maximum plasma concentration for elderly and young adults was achieved at approximately 1 to 2 hours. Reflecting the primary renal elimination of topiramate, topiramate plasma and renal clearance were reduced 21% and 19%, respectively, in elderly subjects, compared to young adults. Similarly, topiramate half-life was longer (13%) in the elderly. Reduced topiramate clearance resulted in slightly higher maximum plasma concentration (23%) and AUC (25%) in elderly subjects than observed in young adults. Topiramate clearance is decreased in the elderly only to the extent that renal function is reduced. As recommended for all patients, dosage adjustment may be indicated in the elderly patient when impaired renal function

(creatinine clearance rate ≤70 mL/min/1.73 m^2) is evident. It may be useful to monitor renal function in the elderly patient

Clearance of topiramate in adults was not affected by gender or race.

Pediatric Pharmacokinetics

Pharmacokinetics of topiramate were evaluated in patients ages aged 2 to 15 years. Patients received either no or a combination of other antiepileptic drugs. A population pharmacokinetic model was developed on the basis of pharmacokinetic data from relevant topiramate clinical studies. This dataset contained data from 1217 subjects including 258 pediatric patients aged 2 to 15 years (with 95 pediatric patients < 10 years of age).

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Pediatric patients on adjunctive treatment exhibited a higher oral clearance (L/h) of topiramate compared to patients on monotherapy. Oral clearance increased with body weight. Clearance was independent of dose. The plasma drug concentration for the same mg/kg dose may be lower in pediatric patients compared to adults and also in younger pediatric patients compared to older pediatric patients .

Drug-Drug Interactions

Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effects of these interactions on mean plasma AUCs are summarized in the table below here. In this table, the second column (AED concentration) describes what happens to the concentration of the AED listed in the first column when topiramate is added. The third column (topiramate concentration) describes how the co-administration of a drug listed in the first column modifies the concentration of topiramate in experimental settings when TOPAMAX® was given alone.

Summary of AED Interactions with TOPAMAX®

AED Co-administered	AED Concentration	Topiramate Concentration
Phenytoin	NC or 25% increase[a]	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide[b]	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE
Lamotrigine	NC at TPM doses up to 400 mg/day	13% decrease

[a] = Plasma concentration increased 25% in some patients, generally those on a twice a day dosing regimen of phenytoin.
[b] = Is not administered but is an active metabolite of carbamazepine.
NC = Less than 10% change in plasma concentration.
AED = Antiepileptic drug.
NE = Not Evaluated.
TPM = Topiramate

In addition to the pharmacokinetic interaction described in the above table, concomitant administration of valproic acid and TOPAMAX® has been associated with hyperammonemia with and without encephalopathy and hypothermia.

CNS Depressants

Concomitant administration of TOPAMAX® □and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse reactions, TOPAMAX® should be used with extreme caution if used in combination with alcohol and other CNS depressants.

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Oral Contraceptives

In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl estradiol (EE), TOPAMAX®, □given in the abs was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. In another study, exposure to EE was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when given as adjunctive therapy in patients taking valproic acid. In both studies, TOPAMAX®□(50 mg/day to 800 mg/day) did not significantly affect exposure to NET. Although there was a dose-dependent decrease in EE exposure for doses between 200 and 800 mg/day, there was no significant dose-dependent change in EE exposure for doses of 50 to 200 mg/day. The clinical significance of the changes observed is not known. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with TOPAMAX®. Patients taking estrogen-containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.

Digoxin

In a single-dose study, serum digoxin AUC was decreased by 12% with concomitant TOPAMAX® □administration. The clinical relevance of this observation has not been established.

Hydrochlorothiazide

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of hydrochlorothiazide (HCTZ) (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that topiramate Cmax increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination.

Metformin

Topiramate treatment can frequently cause metabolic acidosis, a condition for which the use of metformin is contraindicated.

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin (500 mg every 12 hr) and topiramate in plasma when metformin was given alone and when metformin and topiramate (100 mg every 12 hr) were given simultaneously. The results of this study indicated that the mean metformin C_{max} and AUC_{0-12h} increased by 17% and 25%, respectively, when topiramate was added. Topiramate did not affect metformin t_{max}. The clinical significance of the effect of topiramate on metformin pharmacokinetics is not known. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear.

Pioglitazone

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of topiramate and pioglitazone when administered alone and concomitantly. A 15% decrease in the AUCτ,ss of pioglitazone with no alteration in Cmax,ss was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in Cmax,ss and AUCτ,ss respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in Cmax,ss and AUCτ,ss of the active keto-metabolite. The clinical significance of these findings is not known. When TOPAMAX® is added to pioglitazone therapy or pioglitazone is added to TOPAMAX® therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Glyburide

A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glyburide (5 mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 22% decrease in C_{max} and a 25% reduction in AUC24 for glyburide during topiramate administration. Systemic exposure (AUC) of the active metabolites, 4-*trans*-hydroxy-glyburide (M1) and 3-*cis*-hydroxyglyburide (M2), was also reduced by 13% and 15%, and C_{max} was reduced by 18% and 25%, respectively. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration of glyburide.

Lithium

In patients, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic exposure of lithium (27% for C_{max} and 26% for AUC) following topiramate doses up to 600 mg/day. Lithium levels should be monitored when co-administered with high-dose topiramate.

Haloperidol

The pharmacokinetics of a single dose of haloperidol (5 mg) were not affected following multiple dosing of topiramate (100 mg every 12 hr) in 13 healthy adults (6 males, 7 females).

Amitriptyline

There was a 12% increase in AUC and Cmax for amitriptyline (25 mg per day) in 18 normal subjects (9 males, 9 females) receiving 200 mg/day of topiramate. Some subjects may experience a large increase in amitriptyline concentration in the presence of topiramate and any adjustments in amitriptyline dose should be made according to the patient's clinical response and not on the basis of plasma levels.

Sumatriptan

Multiple dosing of topiramate (100 mg every 12 hrs) in 24 healthy volunteers (14 males, 10 females) did not affect the pharmacokinetics of single-dose sumatriptan either orally (100 mg) or subcutaneously (6 mg).

Risperidone

When administered concomitantly with topiramate at escalating doses of 100, 250, and 400 mg/day, there was a reduction in risperidone systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses of topiramate). No alterations of 9-hydroxyrisperidone levels were observed. Co-administration of topiramate 400 mg/day with risperidone resulted in a 14% increase in C_{max} and a 12% increase in AUC_{12} of topiramate. There were no clinically significant changes in the systemic exposure of risperidone plus 9-hydroxyrisperidone or of topiramate; therefore, this interaction is not likely to be of clinical significance.

Propranolol

Multiple dosing of topiramate (200 mg/day) in 34 healthy volunteers (17 males, 17 females) did not affect the pharmacokinetics of propranolol following daily 160 mg doses. Propranolol doses of 160 mg/day in 39 volunteers (27 males, 12 females) had no effect on the exposure to topiramate, at a dose of 200 mg/day of topiramate.

Dihydroergotamine

Multiple dosing of topiramate (200 mg/day) in 24 healthy volunteers (12 males, 12 females) did not affect the pharmacokinetics of a 1 mg subcutaneous dose of dihydroergotamine. Similarly, a 1 mg subcutaneous dose of dihydroergotamine did not affect the pharmacokinetics of a 200 mg/day dose of topiramate in the same study.

Diltiazem

Co-administration of diltiazem (240 mg Cardizem CD®) with topiramate (150 mg/day) resulted in a 10% decrease in C_{max} and a 25% decrease in diltiazem AUC, a 27% decrease in C_{max} and an 18% decrease in des-acetyl diltiazem AUC, and no effect on N-desmethyl diltiazem. Co-administration of topiramate with diltiazem resulted in a 16% increase in C_{max} and a 19% increase in AUC_{12} of topiramate.

Venlafaxine

Multiple dosing of topiramate (150 mg/day) in healthy volunteers did not affect the pharmacokinetics of venlafaxine or O-desmethyl venlafaxine. Multiple dosing of venlafaxine (150 mg Effexor XR®) did not affect the pharmacokinetics of topiramate.

Other Carbonic Anhydrase Inhibitors

Concomitant use of topiramate, a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., zonisamide, acetazolamide, or dichlorphenamide), may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Therefore, if TOPAMAX® is given concomitantly with another carbonic anhydrase inhibitor, the patient should be monitored for the appearance or worsening of metabolic acidosis.

5 Sources of Clinical Data

The NDA was submitted to the following electronic gateway of the Agency :

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5.1 Tables of Studies/Clinical Trials

Table 1 Summary of Migraine Prophylaxis Studies That Included Pediatric Subjects

Study Design/ Start - completion dates/Region	No. Subjects / Age Range	Enrollment Criteria	Study Duration	Study Drug / Dosage	Key Efficacy Endpoints (Protocol-Specified)
Study TOPMAT-MIG-3006					
Multicenter, randomized, DB, PBO-controlled study to evaluate the efficacy and safety of topiramate for the prophylaxis of migraine in pediatric subjects 10 Aug 2005 - 29 Nov 2006 Argentina, Brazil, Finland, France, Israel, Norway, Romania, Spain, United States	103 total, 70 TPM 12 to 17 years[a]	• 12 to 17 years of age • Migraine ± aura, as defined by the proposed revisions to the IHS classification of pediatric migraine • 3 to 12 migraine attacks during the BL period (≤14 migraine or non-migraine headache days)	Pretreatment: ≤9 weeks (screening, 4-week washout period if needed [2-week taper of disallowed prophylactic migraine medications and 2-week observation period]), ≥2-week medication-free, prospective BL period DB: 16 weeks (4 weeks titration, 12 weeks maintenance)	TPM 50 or 100 mg/day, or matching PBO	Primary: Percent reduction from BL to last 12 weeks DB monthly migraine attack rate (48-hour rule) Key Secondary: • Percent reduction from BL to last 12 weeks DB monthly migraine day rate, monthly HA day rate, monthly migraine attack rate (24-hour rule), monthly migraine days with rescue medication. • Percent reduction from BL to last 4 weeks DB monthly migraine attack rate (48-hour rule) • Responder rate(≥50% reduction) in monthly migraine attack rate (48-hour rule)
Study CAPSS-122					
Multicenter, randomized, DB, PBO-controlled, parallel-group comparison study of the efficacy and safety of topiramate vs. PBO in the prophylaxis of migraine in pediatric subjects, plus OLE DB 31 Jul 2001 - 2 Sep 2003 OLE 31 Jul 2001 - 2 Jan 2004 United States	DB: 157 total, 108 TPM, 6 to 16 years OLE: 122	• 6 to 15 years of age, weight >20 kg • Migraine ± aura, as defined by the proposed revisions to the IHS classification of pediatric migraine • 3 to 10 migraine-days per month during the previous 3 months (84 days) prior to screening and during BL (≤15 total headache-days per month)	Pre-randomization phase: up to 56 days, including screening/ washout period and a 28-day prospective BL period DB: 20 weeks (8 weeks titration, 12 weeks maintenance) OLE: 20 weeks (8 weeks titration, 12 weeks maintenance)	TPM titrated to target dosages of 2 to 3 mg/kg/day or until the subject's maximum tolerated dosage was achieved, whichever was lower, or matching PBO	Primary: Number of migraine days per month during DB period vs BL Key Secondary: • Monthly rate of: migraine episodes, non-migraine episodes, total HA (migraine plus non-migraine) days • Percent responders (≥50%, 75%, and 100% reduction) in mean monthly number of migraine days • Severity of migraines (Faces Pain Rating Scale), duration of migraines, frequency and severity of associated migraine symptoms • Frequency and dosage of abortive medications • Child Health Questionnaire • Overall Global Evaluation

Table 1 Summary of Migraine Prophylaxis Studies That Included Pediatric Subjects (Continued)

Study Design/ Start - completion dates/Region	No. Subjects / Age Range	Enrollment Criteria	Study Duration	Study Drug / Dosage	Key Efficacy Endpoints (Protocol-Specified)
Studies TOPMAT-MIGR-001/TOPMAT-MIGR-002/TOPMAT-MIGR-003					
Multicenter, randomized, DB, PBO-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of topiramate in the prophylaxis of migraine (TOPMAT-MIGR-003 included a propranolol arm), plus OLE for 001/002 [b] TOPMAT-MIGR-001: DB: 15 Feb 2001 - 29 Apr 2002 OLE: 15 Feb 2001 - 22 Jan 2003 United States TOPMAT-MIGR-002: DB: 1 Mar 2001 - 4 Apr 2002 OLE: 1 Mar 2001 - 3 Dec 2002 United States, Canada TOPMAT-MIGR-003: 17 Apr 2001 - 11 Apr 2002 Australia, Denmark, Finland, France, Germany, Italy, Korea, the Netherlands, South Africa, Spain, Sweden, Taiwan, United Kingdom	TOPMAT-MIGR-001: DB: 469 total, 354 TPM 13 to 70 years OLE: 288 TPM TOPMAT-MIGR-002: DB: 468 total, 354 TPM 12 to 65 years OLE: 280 TPM TOPMAT-MIGR-003: 568 total, 282 TPM 14 to 66 years	• 12 to 65 years of age • History (≥6 months) consistent with migraine based on IHS criteria • ≤2 previous failures of adequate regimens of migraine prophylaxis • 3 to 12 migraine periods and ≤15 headache days during the prospective BL period	BL: 28 to 42 days, including up to a 14-day washout period DB: 26 weeks (8 weeks titration, 18 weeks maintenance) OLE: up to 6 months or until subject withdrew	TOPMAT-MIGR-001/002: TPM 50, 100, or 200 mg/day, or matching PBO TOPMAT-MIGR-003: TPM 100 or 200 mg/day, or PBO, or propranolol 160 mg/day	Primary: Change in monthly migraine period rate averaged over entire DB phase vs BL Secondary: • Responder rate(≥50% reduction in average monthly migraine period rate) • Onset of action (earliest monthly time point with statistically significant difference for TPM vs PBO in primary efficacy endpoint) • Change in number of monthly migraine attacks • Change in average monthly rate of rescue medication use • Change in number of migraine days per month • HRQOL (subjects ≥18 years of age) • Medical outcomes SF36 • MSQ (role restrictive and role prevention) Other: • Monthly migraine duration • Types of headache • Average migraine severity • Severity of migraine-associated symptoms

[a] Three subjects reached 18 years of age between screening and randomization.
[b] As stated in Table 1 of the minutes of the June 2012 meeting, the 12-month TOPMAT-MIGR-003 blinded extension study is not included in this submission (Mod1.6.3/FDA-Type-B-Meeting-Minutes).
BL=baseline; DB=double-blind; HA=headache; HRQOL=health-related quality of life; IHS=International Headache Society; MSQ=Migraine-Specific Questionnaire; OLE=open-label extension; PBO=placebo; SF36=Medical Outcomes Short Form 36; TPM=topiramate.

Table 2 Description of Migraine Prophylaxis Studies Contributing Data to the Safety Summary

Protocol Number(s)	Study Design
Double-Blind	
TOPMAT-MIG-3006	Randomized, double-blind, placebo-controlled, parallel-group study to evaluate the tolerability, safety, and efficacy of topiramate 50 or 100 mg/day as prophylaxis in pediatric subjects ages 12 to 17 years with episodic migraine headaches with or without aura. The study had 3 phases: a ≤9-week pretreatment phase, a 16-week double-blind treatment phase (including a 4-week titration period and a 12-week maintenance period), and a posttreatment phase (including a 2-week taper of blinded medication, a 4-week study drug-free period, and a follow-up visit).
CAPSS-122	Randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of topiramate in the prophylaxis of migraine with or without aura in pediatric subjects ages 6 to 15 years. The study had 3 phases: prerandomization (screening/washout and 28-day prospective baseline), double-blind (8-week titration and 12-week maintenance), and open-label extension (see below). Study medication was to be titrated to target dosages of 2 to 3 mg/kg/day of topiramate (or matching placebo) or until the subject's maximum tolerated dose was achieved.
TOPMAT-MIGR-001, TOPMAT-MIGR-002[a]	Randomized, double-blind, placebo-controlled, parallel-group studies to evaluate the efficacy and safety of topiramate (50, 100, or 200 mg/day) versus placebo for migraine prophylaxis in subjects between 12 and 65 years of age. Each study had 5 phases: baseline (14-day washout and 28-day prospective baseline period), double-blind (8-week titration period and 18-week maintenance period), blinded transition, then open-label extension and 2-week taper/exit (see below).
TOPMAT-MIGR-003	Randomized, double-blind, parallel-group study that evaluated the efficacy and safety of 2 dosages of topiramate (100 and 200 mg/day) versus placebo and propranolol 160 mg/day for migraine prophylaxis in subjects 12 to 65 years of age. The study included 4 phases: baseline (14-day washout and 28-day prospective baseline period), core double-blind (8-week titration and 18-week maintenance), blinded extension, and taper/exit (up to 7 weeks). During the blinded extension phase, subjects were to continue to receive the same dosage of study medication for up to 12 months after the last subject was randomized or until they were withdrawn.
Open-Label	
CAPSS-122	Twelve-week extension of open-label topiramate (target dosage 2 to 3 mg/kg/day or maximum tolerated dose).
TOPMAT-MIGR-001, TOPMAT-MIGR-002[a]	Six-month extension of open-label topiramate (maximum 1,600 mg/day), followed by 2-week taper/exit.

[a] Studies TOPMAT-MIGR-001 and -002 had identical study designs.
Source: Table 4 in the Integrated Summary of Safety of topiramate application 20-505/S-042 (20-844/S-036), approved July 2011, as well as clinical study reports for each study.

5.2 Review Strategy

Although my review of the NDA was comprehensive, I will focus my review on presenting information and data analyses that I consider most important or relevant to this NDA. My review strategy focused on several principles for presenting information in my review including :

- Emphasizing results (individual trial and pools of trials) of randomized, double-blinded, placebo-controlled trials of pediatric patients for topiramate migraine prophylaxis

- Emphasizing results (efficacy and safety) from MIG-3006 as the key and most important adolescent trial (12-17 yo) in this NDA

- Emphasizing results (efficacy and safety) from CAPSS-122 as a supportive pediatric trial (6-16 yo) for findings in MIG-3006

- Emphasizing pooled results (safety) from MIGR-1-3 as supportive trial for findings in MIG-3006. Efficacy results from these trial are not presented because the pool of these 3 trials consisted of small numbers of adolescent patients (12-17 yo) in each treatment group (placebo, 50 mg, 100 mg, 200 mg) ranging from 11-1 3 patients

- Emphasizing outlier results for clinical laboratory analytes and vital signs (blood pressure and pulse) because central tendency analyses were generally not as informative as outlier analyses

- Emphasizing open-label results of limited data collection in pediatric migraine trials (6-17 years) when safety results indicate some potentially relevant information

- Emphasizing safety results from monotherapy or adjunctive therapy epilepsy trials in pediatric patients (1 month – 16 years) only when there is information specifically pertinent to this NDA for pediatric migraine prophylaxis indication

5.3 Discussion of Individual Studies/Clinical Trials

The sponsor submitted results of randomized, double-blinded, placebo-controlled trials that investigated topiramate for migraine prophylaxis in pediatric patients.

The sponsor submitted MIG-3006, the key placebo-controlled trial supporting the claim that topiramate is safe and effective for migraine prophylaxis in adolescents (12-17 years). Results of this trial will be presented for efficacy (Section 6) and safety (Section 7).

The sponsor also submitted CAPSS-122, a trial that was not conducted under the U.S. IND and that enrolled pediatric patients 6-16 years. This trial's safety results and efficacy results are presented to help support the findings in MIG-3006.

The sponsor submitted pooled results of MIGR-1-3, three trials that were used to support the claim of topiramate for migraine prophylaxis in adults. These trials included small numbers of adolescents (12-17 years). Safety results of these trials were submitted primarily to help support findings in MIG-3006.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The sponsor is seeking an indication of prophylaxis of migraine in adolescent patients (12-17 years old).

6.1.1 Methods

Study TOPMAT-MIG-3006
Study TOPMAT-MIG-3006 evaluated the efficacy, safety, and tolerability of topiramate (dosages of 50 and 100 mg/day) compared with placebo as prophylaxis in pediatric subjects, 12 to 17 years of age with episodic migraine headaches with or without aura as defined by the proposed IHS classification of pediatric migraine. As shown in the study design figure in Figure 1, the study included 3 phases: a pretreatment phase, a double-blind treatment phase (4-week titration period followed by a 12-week maintenance period), and a posttreatment phase (including a 2-week taper of blinded medication). During the double-blind phase of the study, topiramate was started at a dosage of 25 mg/day and titrated up until the final target dosage (50 or 100 mg/day) or the maximum dosage tolerated had been achieved. During the titration period, either a pause, a halt, or a dosage reduction was allowed for intolerability; during the maintenance phase, a single dosage reduction of study drug was allowed for safety and/or tolerability concerns. Subjects were considered to have completed the study if all assessments at Week 16 of the double-blind phase were completed.

Figure 1 Study Design for TOPMAT-MIG-3006

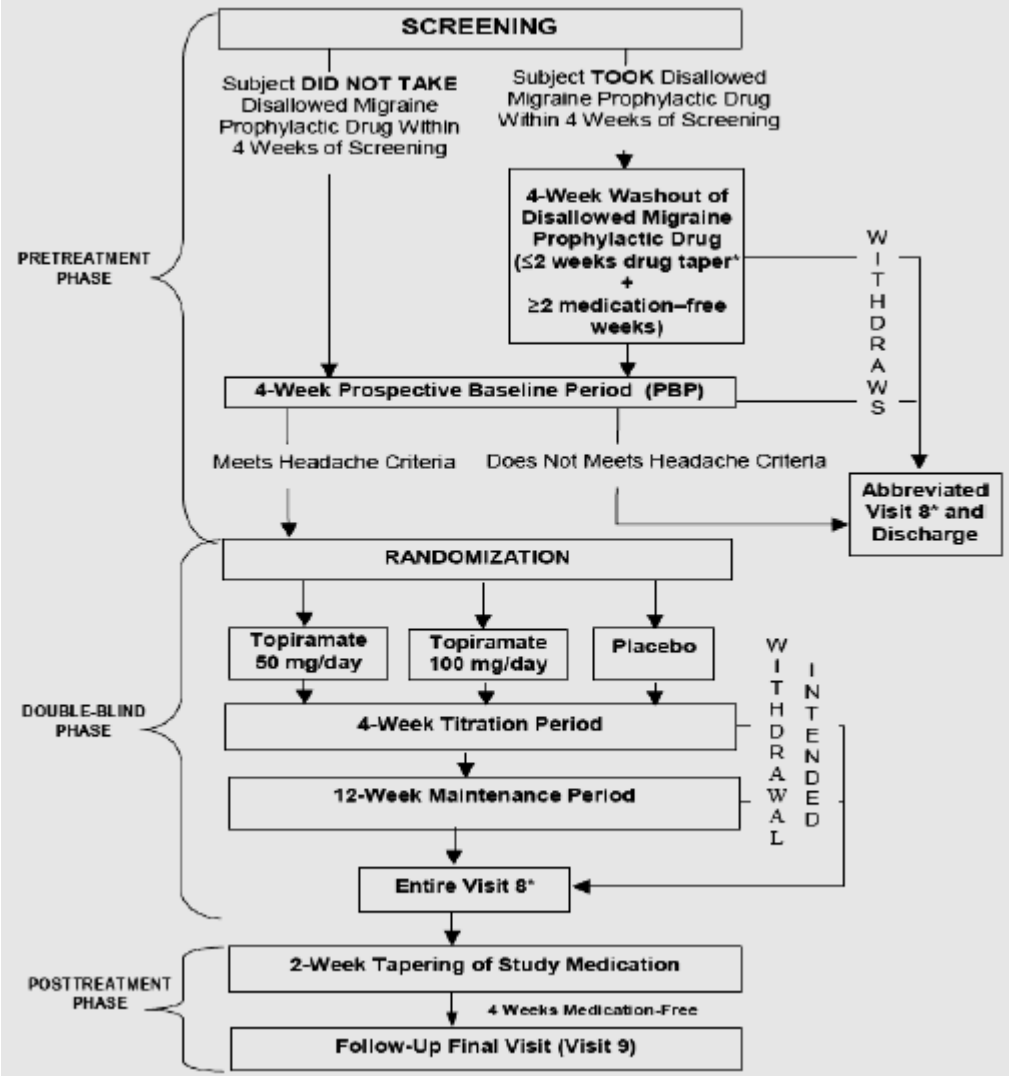


Table 3 shows the time of key study procedures for MIG-3006.

Table 3 Schedule of Time of Key Study Procedures for MIG-3006

	Pretreatment Phase			Double-Blind Treatment Phase						Posttreatment Phase
	Screening	Washout Period[a]	Prospective Baseline Period	Titration Period			Maintenance Period			
Visit	1		2	3	4	5	6	7	8	9
Day	−36 to −29	−57 to −29	-28	1	14	28	56	84	112	154
Screening and Administrative										
Informed consent and assent	X									
Medical history and current therapy	X									
Retrospective, 3-month headache history	X									
Inclusion/exclusion criteria	X		X	X						
Randomization (End of Visit 3; Day 1)				X						
12-lead ECG	X									
Safety, Efficacy, and Study Medication										
Physical and neurologic examinations	X			X	X	X	X	X	X[b]	X
Monitor for visual/ocular and renal/urinary disturbances, depression/suicidality, rash, oligohidrosis, heat intolerance	X		X	X	X	X	X	X	X[b]	X
Height and weight	X			X					X[b]	
Vital Signs	X			X	X	X	X	X	X[b]	X
Dispense and review headache and medication records			X	X	X	X	X	X	X[b]	X
Neuropsychological Test (CANTAB)			X	X					X	
Profile of Mood States (POMS)	X			X		X	X	X	X[b]	X
Quality of life and disability (PedsQL 4.0/PedMIDAS)	X			X		X	X	X	X[b]	X
Clinical laboratory evaluations[c]	X			X		X	X	X	X[b]	
Pregnancy test (serum at Visit 1, otherwise urine)	X			X	X	X	X	X	X[b]	
Topiramate plasma sample for safety assessment									X	
Record adverse events and concomitant medications	X	X	X	X	X	X	X	X	X[b]	X
Dispense study medication				X	X	X	X	X	X	

[a] Subjects who had used prophylactic migraine therapy for any reason within 4 weeks of screening, had to complete a 4-week washout period.
[b] Subjects who discontinued prior to the double-blind treatment phase had to complete only these Visit 8 procedures.
[c] Hematology, chemistry, and urinalysis.

Study CAPSS-122

Study CAPSS-122 evaluated the efficacy and safety of topiramate (flexible dosing; target of 2.0 to 3.0 mg/kg/day) compared with placebo in pediatric subjects 6 to 15 years of age for the prophylaxis of migraine with or without aura as defined by the proposed IHS classification of pediatric migraine As shown in the study design figure in Figure 2, the study had 3 phases, pre-randomization (screening/washout and prospective baseline), double-blind, and an openlabel extension. The double-blind phase consisted of 2 periods: titration and maintenance. The titration period immediately followed the 28-day prospective baseline period and extended for approximately 56 days. All subjects received a starting dosage of 15 mg/day of topiramate (or matching placebo) for the first week, followed by an increase to 30 mg/day of topiramate (or matching placebo) for the second week. Starting at Week 3, subjects were to receive 50 mg/day of topiramate (or matching placebo). Study medication was titrated to target dosages of 2.0 to 3.0 mg/kg/day of topiramate (or matching placebo) or until the subject's maximum tolerated dosage was achieved, whichever was lower. During the maintenance period, the dosage of study medication was to remain constant. Subjects were considered to have completed the double-blind phase of the study if they completed the maintenance period through Day 141.

Figure 2 Study Design for CAPSS-122

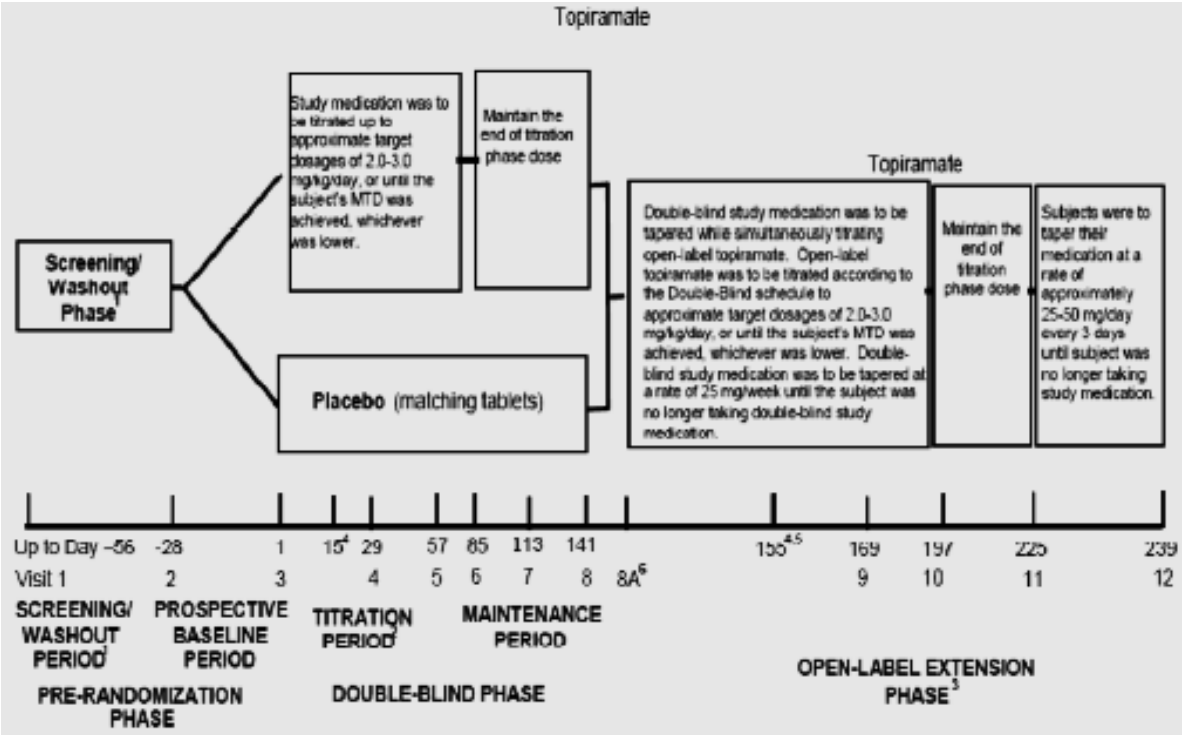


Table 4 shows the time and events schedule for CAPSS-122.

Table 4 **Time and Events Schedule for CAPSS-122**

	Pre-randomization Phase		Double-Blind Phase							
	Screening/ Washout Period[a]	Prospective Baseline Period[b]	Titration Period			Maintenance Period				
	Visit 1 (Up to Day –56)	Visit 2 (Day –28)	Visit 3 (Day 1)	Day 15	Visit 4 (Day 29)	Visit 5 (Day 57)	Visit 6 (Day 85)	Visit 7 (Day 113)	Visit 8 (Day 141)	Visit 8A[f] (Day 155)
Informed Consent	X									
Medical History	X									
Headache History	X									
Update Headache History		X								
Physical Examination	X								X	
Neurological Examination	X									
Clinical Laboratory Tests	X				X[c]	X[c]	X[c]		X	
Urine Pregnancy Test			X		X	X	X	X	X	X
Drug Screen	X									
Vital Signs[d]	X	X	X		X	X	X	X	X	X
Collect Headache Record			X		X	X	X	X	X	X
Review Headache Record			X	X	X	X	X	X	X	X
Phone contact [e]				X						
Child Health Questionnaire			X			X			X	
Overall Global Evaluation									X	
Review Adverse Events				X	X	X	X	X	X	X
Dispense Headache Record		X	X		X	X	X	X	X	
Dispense Study Medication			X		X	X	X	X	X	
Collect and Count Unused Study Medication					X	X	X	X	X	X

[a] Period equal to a minimum of 2 weeks for all medications used for migraine prophylaxis, as described in Attachment 3.
[b] Subjects must have had 3-10 migraine-days during the prospective baseline period.
[c] Liver function tests (aspartate aminotransferase, alanine aminotransferase, total bilirubin and alkaline phosphatase) were to be performed.
[d] Height was to be recorded at Visit 1 only.
[e] The subject's parent or guardian was to be contacted to discuss the tolerability and efficacy of the study medication and compliance with the completion of the headache record.
[f] Visit 8A was to be conducted for those subjects who tapered study medication but did not enter the open-label extension phase.

Studies TOPMAT-MIGR-001, TOPMAT-MIGR-002, and TOPMAT-MIGR-003

Studies TOPMAT-MIGR-001 and TOPMAT-MIGR-002 were identical in design; each evaluated the efficacy and safety of topiramate (dosages of 50, 100, and 200 mg/day) compared with placebo in subjects between 12 and 65 years of age for the prophylaxis of migraine with or without aura conforming to IHS criteria. As shown in the study design figure in Figure 3, each study had 5 phases: a baseline phase of up to 42 days (washout and prospective baseline period), a double-blind phase (8 weeks of titration and 18 weeks of maintenance), a blinded transition phase of up to 7 weeks, a 6-month open-label extension phase, and a 2-week taper/exit phase. During the double-blind phase, study medication began at a daily dosage of 25 mg/day and was titrated upwards in weekly increments of 25 mg/day until either the assigned dosage or maximum tolerated dosage was achieved. During maintenance, the dosage of study medication was to remain constant; however, a total of 2 dosage reductions were allowed during the doubleblind phase. Subjects were considered to have completed the double-blind phase if they completed all 26 weeks of double-blind treatment.

Study TOPMAT-MIGR-003 was similar in design and entry criteria to Studies TOPMATMIGR-001 and TOPMAT-MIGR-002, except that it evaluated the efficacy and safety of 2 dosages of topiramate (100 and 200 mg/day) instead of 3 dosages and compared topiramate with both placebo and propranolol (160 mg/day) for migraine prophylaxis. As shown in the study design figure in Figure 4, the study included 4 phases: a baseline phase of up to 42 days, a core double-blind phase, a blinded extension phase of up to 12 months, and a taper/exit phase of up to 7 weeks. The core double-blind phase was divided into 2 periods:

titration (8 weeks) and maintenance (18 weeks). For subjects assigned to receive topiramate, the initial daily dosage was topiramate 25 mg/day, while for subjects assigned to receive propranolol, the initial daily dosage was propranolol 20 mg/day. The dosage of study medication was titrated upwards in weekly increments of 25 mg/day for topiramate and 20 mg/day for propranolol until either the assigned dosage or maximum tolerated dosage was achieved. During maintenance, the dosage of study medication was to remain constant; however, a total of 2 dosage reductions were allowed during the core double-blind phase. Subjects were considered to have completed the core double-blind phase if they completed all 26 weeks of core double-blind treatment (i.e., 8 weeks of titration and 18 weeks of maintenance).

Figure 3 Study Design for MIGR-001/002

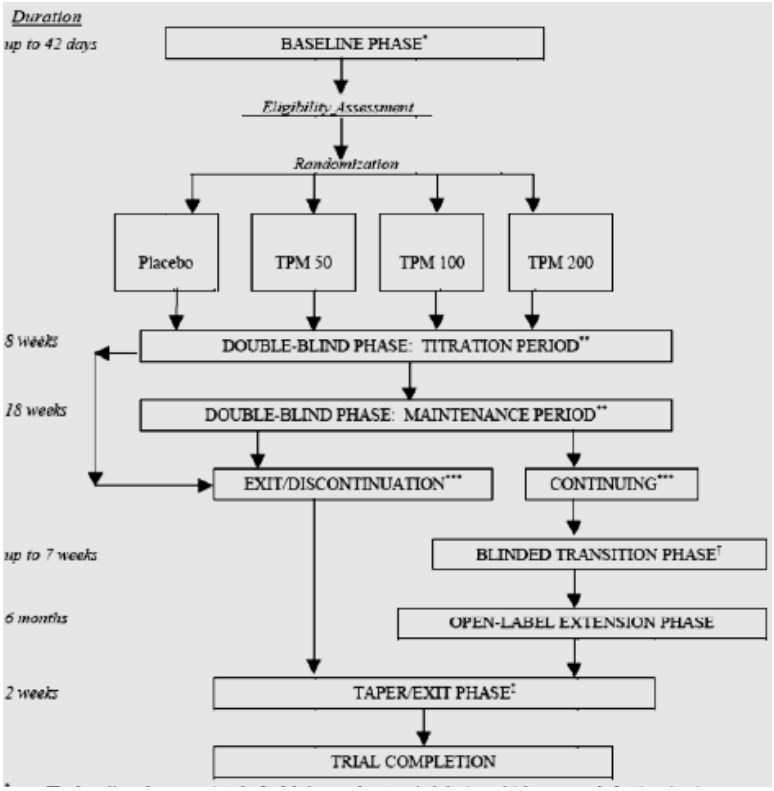
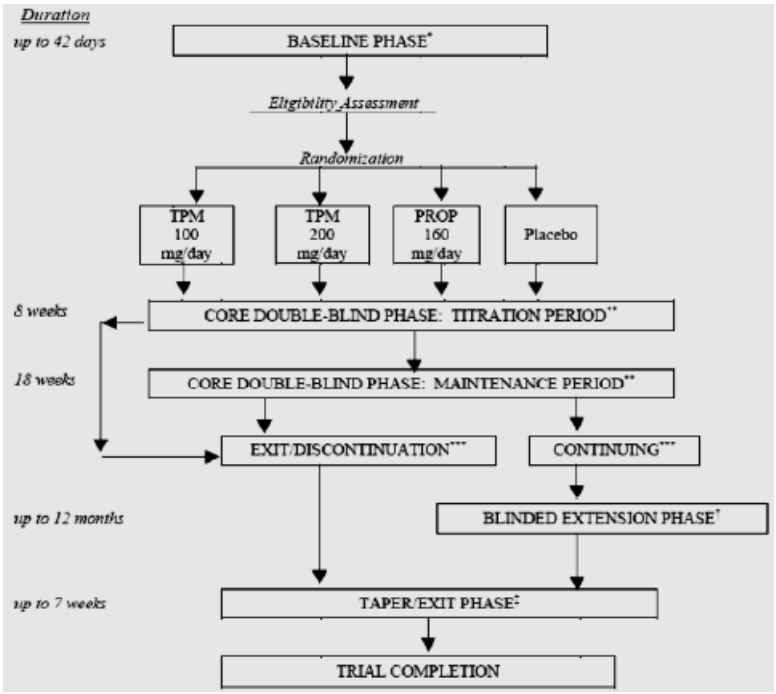


Figure 4 Study Design for MIGR-003



Time and events schedules for each of the trials pooled trials (MIGR-1-3) for safety analyses are not presented. In general, the events scheduled for MIG-3006 and CAPSS-122 were conducted for MIGR-1-3 and at relatively similar times.

Study Entry Criteria for Migraine Headaches
Each study required subjects to meet IHS criteria for migraine headaches1 for study entry; however, the criteria differed somewhat in the pediatric studies compared with the adult studies. In the pediatric Studies TOPMAT-MIG-3006 and CAPSS-122, to ensure diagnostic consistency subjects were required to have headache symptoms meeting the proposed revisions to the IHS Classification of Pediatric Migraine with or without aura. These proposed revisions were modifications of the 1988 IHS pediatric migraine criteria to increase the sensitivity for diagnosis of migraine in the pediatric population, and addressed the duration, characteristics, and location of pain, and the characteristics of either photophobia or phonophobia. The proposed revisions for pediatric migraine (IHS-R criteria) included changes in duration (change from 2 to 48 hours to 1 to 48 hours), location (change from unilateral to bilateral [frontal/temporal] or unilateral), and associated symptoms (to allow for photophobia and/or phonophobia as concomitant symptoms).4,5 For the adult and pediatric Studies TOPMAT-MIGR-001, TOPMAT-MIGR-002, TOPMAT-MIGR-003, the IHS criteria used were those developed for the adult population, with a caveat for headache duration in children <15 years of age compared with adults (in children below 15 years of age, 2 to 48 hours; in adults, 4 to 72 hours). A comparison of the IHS and IHS-R migraine criteria used in the pediatric and adult studies is shown in Table 5.

In addition to having migraine symptoms meeting the IHS criteria, subjects also had to meet entry criteria regarding the frequency of migraine headaches prior to screening and during the baseline period in order to enter the double-blind treatment phase of the studies. The criteria and terminology used to describe and count migraine frequency differed across the studies; migraine frequency was referred to as "migraine attack" in TOPMAT-MIG-3006, "migraine episode" in CAPSS-122 and "migraine period" in TOPMAT-MIGR-001/002/003. A comparison of the entry criteria for migraine headache frequency across these studies and definitions of the terms is shown in Table 6.

Table 5 International Headache Society (IHS) Diagnostic Criteria for Migraine

	TOPMAT-MIG-3006 / CAPSS-122 [a]	TOPMAT-MIGR-001/002/003
Migraine Without Aura	At least 5 attacks fulfilling the following criteria: • Headache lasting 1 to 72 hours (TOPMAT-MIG-3006) or 1 to 48 hours (CAPSS-122) • Headache has at least 2 of the following 4 features: o Either bilateral or unilateral (frontal/temporal) location o Pulsating quality o Moderate to severe intensity o Aggravation by routine physical activities • At least 1 of the following accompanies headache: o Nausea and/or vomiting o Photophobia and phonophobia (may be inferred from subject's behavior)	At least 5 attacks fulfilling the following criteria: • Headache lasts 4 to 72 hours (untreated or unsuccessfully treated). In children below 15 years of age, attacks may last 2 to 48 hours. If the subject falls asleep and wakes up without migraine, duration of attack is until time of awakening. • Headache has at least 2 of the following characteristics: o Unilateral location o Pulsating quality o Moderate or severe intensity (inhibits or prohibits daily activities) o Aggravation by walking stairs or similar routine physical activity • During headache, at least 1 of the following occurs: o Nausea and/or vomiting o Photophobia and phonophobia • At least 1 of the following is present: o History, physical, and neurologic examinations do not suggest an organic disorder. o History, physical, and neurologic examinations do suggest an organic disorder but it is ruled out by appropriate investigations. o An organic disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.
Migraine With Aura	At least 2 attacks fulfilling the following criteria: • At least 3 of the following characteristics are present: o One or more fully reversible aura symptoms occur, indicating focal cortical and/or brain-stem dysfunction o At least 1 aura symptom develops gradually over more than 4 minutes, or 2 or more symptoms occur in succession o No single aura symptom lasts more than 60 minutes. o Headache follows less than 60 minutes.	At least 2 attacks fulfilling the following criteria: • At least 3 of the following characteristics present: o One or more fully reversible aura symptoms occur, indicating brain dysfunction o At least one aura symptom develops gradually over more than 4 minutes, or 2 or more symptoms occur in succession. o No single aura symptom lasts more than 60 minutes. o Headache follows aura with a free interval of less than 60 minutes (it may also begin before or simultaneously w/ the aura). • History, physical examination, and, where appropriate, diagnostic tests exclude a secondary cause.

[a] Studies TOPMAT-MIG-3006 and CAPSS-122 used the proposed revisions to the IHS Classification of Pediatric Migraine with or without aura (IHS-R criteria).

Table 6 Comparison of Inclusion Criteria for Migraine Headaches Across Studies

	TOPMAT-MIG-3006	CAPSS-122	TOPMAT-MIGR-001/002/003
Prior to Screening	Average of 3 to 12 (inclusive) migraine attacks and no more than 14 headache days (migraine and non-migraine) per month during the 3 months prior to screening, as determined by a retrospective history given by the subject, his or her parent or guardian, or both	Average of 3 to 10 migraine-days (inclusive) per month for the previous 3 months prior to screening.	Established history consistent with migraine, with or without aura, conforming to IHS criteria for at least 6 months prior to screening
Baseline	3 to 12 migraine attacks (inclusive) and ≤14 headache days (migraine and non-migraine) during the 4-week prospective baseline period, as recorded on the headache and medication record	3 to 10 migraine-days (inclusive) during the 4-week prospective baseline period	3 to 12 migraine periods (inclusive) and ≤15 headache days (migraine and non-migraine) per month during the prospective baseline period (28 days) based on headache/medication record
Definitions	**Migraine attack**: all recurrences of migraine symptoms within 48 hours of onset (48-hour rule of individual attacks) **Headache day**: a calendar day during which the subject experienced headache pain for ≥1 hour, if untreated, or ≥30 minutes, if interrupted with rescue medication	**Migraine episode**: a headache with symptoms fulfilling the criteria for pediatric migraine according to the proposed IHS Classification of Pediatric Migraine. Duration of migraine episode was from onset of painful migraine symptoms to resolution of pain or 24 hours after onset of painful symptoms, whichever was shorter. Migraine episodes persisting or recurring within 24 hours were considered the same episode. Aura symptoms that resolved without pain after abortive medication was taken ≤60 minutes from aura onset were considered a migraine episode. Aura symptoms occurring and resolving without abortive medication were not considered a migraine episode. **Migraine day**: a calendar day (12:00 AM to 11:59 PM) in which the subject experienced a migraine episode according to the below definition	**Migraine period:** length of time between the onset and cessation of painful migraine symptoms. Duration of a migraine period could be ≤24 hours; if symptoms ended and recurred within 24 hours of the onset, they were considered part of the initial migraine period. Any symptoms lasting beyond 24 hours of the initial onset were considered to be part of a new, distinct migraine period. **Headache day**: a calendar day during which a subject experienced headache pain for ≥30 minutes

Overview of Efficacy Assessments

Information on headaches was recorded similarly in the 5 studies, with subjects reporting information on the headache records. In the pediatric studies, the subjects' parents or guardians assisted their children in filling out the headache and medication records and in checking these documents for accuracy. Headache and medication records were reviewed and verified by the investigators, who confirmed whether the headache was a migraine or not based on clinical judgment and/or an algorithm to define migraine with or without aura (the algorithm was used in TOPMAT-MIG-3006 and TOPMAT-MIGR-001/002/003), and entered the information onto the corresponding case report form (CRF) pages at each of the protocol-specified study visits. For the purposes of this submission, the key efficacy analyses use the headache classifications based on the clinical judgment of the investigator.

A summary of the headache information recorded in each of the studies is provided in Table 7. Full details for all protocol-specified efficacy assessments are available in the individual reports for each study.

Table 7 Information Collected on Headache Records by Subjects in Each Study

TOPMAT-MIG-3006	CAPSS-122	TOPMAT-MIGR-001/002/003
Headache Type		
• Headache type: migraine or non-migraine; presence or absence of aura with or without migraine	• Number, description, and duration of migraine and non-migraine episodes	• Headache type: aura only, migraine with aura, migraine without aura, non-migraine headache
Headache Severity		
• Headache severity measured on a 10-point scale (range?) • Laterality • Whether or not the headache was pulsating • Aggravated by physical activity	• Headache severity using the Wong-Baker Faces Pain Rating Scale • Presence of unilateral or bilateral pain • Throbbing pain • Increased pain due to physical activity	• Worst pain during the headache classified as mild, moderate, or severe • Whether the pain was one-sided • Throbbing pain • Increased pain with physical activity
Associated Symptoms		
• Associated migraine symptoms: photophobia, phonophobia, nausea, vomiting, abdominal pain	• Severity of associated migraine symptoms: photophobia, phonophobia, nausea/vomiting, abdominal pain	• If present, severity of nausea, sensitivity to light (photophobia), and sensitivity to sound (phonophobia), classified as none, mild, moderate, or severe • Presence or absence of vomiting
Medication Use		
• Medication(s) used, if any, for abortive treatment of headache, including dosage and time of administration	• Acute, abortive migraine medications used for migraine and non-migraine headache episodes	• Any medications used to treat each headache (or treatment taken when aura occurred)
Other Measures		
• Subject-reported outcome questionnaires exploring the impact of migraine on home, school, and social functioning (PedMIDAS) and on physical, emotional, school, and social functioning (PedsQL)	• Functional disability	• Effect of migraine on the ability to work and perform usual activities outside of work

PedMIDAS=Pediatric Migraine Disability Assessment Scale. PedsQL=Pediatric Quality of Life Inventory, version 4.0.

Classification of Headache Records

The key efficacy evaluations in this ISE are based on the headache types collected on the headache records by the subjects and verified by the investigators, who confirmed whether the headache was a migraine or not based on clinical judgment. This approach is consistent with the approach used in the analyses for the pivotal Study efficacy endpoints using the subject-recorded headache symptoms, which were confirmed by the investigator based on clinical judgment see

below). A sensitivity analysis based on an algorithm using the IHS criteria for counting migraine attacks was also performed; algorithms for the determination of migraine headache based on the IHS criteria were found in the SAP.

A blinded review of the database for TOPMAT-MIG-3006 before database lock determined that the IHS criteria were not consistently applied by investigators during the prospective baseline to determine eligibility for randomization, as the protocol inclusion criteria requiring 3 to 12 migraine attacks in the 28-day prospective baseline did not specify the use of the IHS criteria for headache classification. As such, investigators used the subject's determination of headache type to determine eligibility for randomization, consistent with the protocol.

Therefore, for consistency with the randomization procedure and also with the approach used in the 3 topiramate migraine prophylaxis clinical studies for adults, which included subjects 12 to 65 years old, the analysis plan was revised to assess the primary and secondary efficacy endpoints using the subject-recorded headache symptoms, which were confirmed by the investigator based on clinical judgment. The algorithm was used for analysis purposes, and not for classification.

In Study TOPMAT-MIG-3006, a headache record could be classified into 1 of 5 categories, based on the subject-recorded headache symptoms and confirmed by the investigator:

- Migraine with aura
- Migraine without aura
- Aura only with rescue medication
- An "aura, no pain" record accompanied by ingestion of rescue medication within 30 minutes
  of aura onset was classified as a "migraine - aura only" record.
- Any other type of headache (excluding aura only without rescue medication) was considered a non-migraine headache.

In Studies CAPSS-122 and TOPMAT-MIGR-001/002/003, a headache record was classified into 1 of 4 categories :

- Migraine with aura
- Migraine without aura
- An aura only headache was treated as a migraine.
- Any other type of headache was considered a non-migraine headache.

Derived Headache Records

Migraine Attacks

In the individual studies, the terms used to describe the occurrence of migraine symptoms included migraine attack (TOPMAT-MIG-3006), migraine episode (CAPSS-122), and migraine period (TOPMAT-MIGR-001/002/003). In order to standardize the terminology in this ISE, the term migraine attack is used.

Two rules are used to define a single migraine attack, the 48-hour rule and the 24-hour rule, and the 48-hour rule is the primary rule in the efficacy analysis. Using the 48-hour rule, a single migraine attack is defined as all recurrences of migraine symptoms within 48 hours of onset. The steps to derive a migraine attack record based on the 48-hour rule are as follows:
1. Any missing date or time were imputed according to the rules described in Table 4 of the SAP.
2. Overlapping records are combined by setting the headache start date/time as the earliest start date/time of overlapping records, and the headache end date/time as the latest date/time of the records; the severity of combined records will be set as the worst severity.
3. For any migraine headache record that covers 2 study phases, that migraine record will be separated into 2 according to the following:

- Records with onset before baseline phase start date and stopping after baseline phase start date will be split into 2, with the splitting point 00:00 on baseline phase start date.
- Records with onset before double-blind phase start date and stopping after double-blind Phase start date will be split into 2, with splitting point 00:00 on Study Day 1.
- Records with onset before double-blind phase end date and stopping after double-blind phase end date will be split into 2, with splitting point 23:59 on double-blind phase end date.

4. Migraine onset time: in the case of migraine, onset time coincides with the onset time of migraine symptoms. In the case of aura only, onset time coincides with onset time of aura symptoms.
5. The onset time of the current migraine event will be compared with the onset time of the previous migraine. If the difference is greater than 48 hours, the current migraine will be considered a new, distinct migraine. If the difference is less than or equal to 48 hours, the onset time will coincide with the onset time of the previous migraine, while the stop time will coincide with stop time of the current migraine. In a similar fashion, the previous migraine will be compared with the next current migraine and so on. The severity of the combined migraine record will be set as the worst severity of the records to be combined.
The procedures to derive migraine attack records using the 24-hour rule are similar, except that 48 hours is replaced with 24 hours for the above determination of migraine attacks.

Baseline Characteristics
The following baseline migraine characteristics are also summarized:

- Migraine Day: A migraine day is defined as a calendar day (12:00 AM to 11:59 PM) in which the subject experiences a migraine attack.
- Non-Migraine Headache Attack: A headache record that was classified as a non-migraine headache or did not fulfil the criteria for pediatric migraine according to the IHS criteria is a non-migraine headache record. Derivation of a non-migraine headache attack record followed Steps 1 to 3 listed above for deriving a migraine attack.
- Headache Day: A headache day is defined as a calendar day (12:00 AM to 11:59 PM) during which the subject experienced a headache attack (excluding "aura only" headaches), either migraine or non-migraine.
- Migraine Day with Rescue Medication: A migraine day with rescue medication is defined as a migraine day during which the subject also took rescue medication.

Migraine Characteristics

Baseline migraine characteristics, including monthly migraine attack rate (using the 24- or 48-hour rule), monthly migraine day rate, monthly headache day rate, monthly migraine day with rescue medication rate, and monthly rate for specific types of headache records (migraine with and without aura, aura only with rescue medication, non-migraine headache, aura only) are summarized by treatment group. Descriptive statistics (n, mean, standard deviation, median, and range) of these parameters are provided.

A subject's monthly migraine day rate for a particular period is calculated as the total number of migraine days during that period, divided by the number of days in that period, times 28.
A subject's monthly headache day rate for a particular period is calculated as the total number of headache days during that period, divided by the number of days in that period, times 28.
A subject's monthly migraine day with rescue medication rate for a particular period is defined as the total number of migraine days with rescue medication during that period, divided by the number of days in that period, times 28.

A subject's monthly rate for specific types of headache records for a particular period is defined as the total number of headache records of a specific type in a particular period, divided by the number of days in that period, times 28.

Statistical Analyses

Table 8 shows the statistical analysis methods for key efficacy endpoints.

Table 8 Analysis Methods for the ITT and the Completer population for All Controlled Migraine Trials

%Change from baseline migraine rate	
Primary analysis	**Sensitivity analysis**
ANCOVA model on ranks with age group[1], treatment group, and analysis center as factors and monthly migraine attack rate at baseline phase as a covariate	Same as the primary analysis
Change from baseline migraine rate	
Primary analysis	**Sensitivity analysis**
ANCOVA model with age group, treatment group, and analysis center as factors and monthly migraine attack rate at baseline phase as a covariate	Same as the primary analysis
Responder Rate (both 50% and 100%)	
Primary analysis	**Sensitivity analysis**
Cochran-Mantel-Haenszel test[2] stratified by analysis center and age group.	Same as the primary analysis

1 Two age groups: 12-14 and 15-17 years old.
2 Exact test was performed instead if the count in any cell of the contingency table was less than 5.

Study CAPSS-122 was analyzed using the same methods as the MIG-3006, except without the age group factor.

6.1.2 Demographics

A summary of demographic and baseline characteristics for the ITT analysis dataset is presented for Study TOPMAT-MIG-3006 in Table 9, Study CAPSS-122 in

Table **10**,and Studies TOPMAT-MIGR- 001/002/003 in Table 11.

- Within each of the study groups, treatment groups were generally well matched.
- Studies TOPMAT-MIG-3006 and TOPMAT-MIGR-001/002/003 included a higher percentage of female than male subjects, while in Study CAPSS-122 there were slightly more male than female subjects. Mean age of subjects in Studies TOPMAT-MIG-3006 and TOPMAT-MIGR-001/002/003 was approximately 14 years. In Study CAPSS-122, the mean age was approximately 11 years, as this study enrolled subjects down to 6 years of age and had a higher percentage of subjects between 6 and 11 years of age compared with subjects 12 to 17 years of age.

Table 9 Demographics and Baseline Characteristics: Study TOPMAT-MIG-3006 (Intent-to-Treat Analysis Set)

	Placebo (N=33)	TPM 50 mg/day (N=35)	TPM 100 mg/day (N=35)	Any TPM (N=70)	Total (N=103)
SEX, n (%)					
N	33	35	35	70	103
MALE	12 (36)	10 (29)	18 (51)	28 (40)	40 (39)
FEMALE	21 (64)	25 (71)	17 (49)	42 (60)	63 (61)
RACE, n (%)					
N	33	35	35	70	103
WHITE	29 (88)	31 (89)	28 (80)	59 (84)	88 (85)
BLACK	4 (12)	2 (6)	5 (14)	7 (10)	11 (11)
ASIAN	0	0	0	0	0
OTHER	0	2 (6)	2 (6)	4 (6)	4 (4)
AGE (Years)					
N	33	35	35	70	103
Category, n (%)					
6-11 YEARS	0	0	0	0	0
12-17 YEARS	33 (100)	35 (100)	35 (100)	70 (100)	103 (100)
Mean	14.4	14.2	14.2	14.2	14.2
SD	1.71	1.60	1.54	1.56	1.60
Median	14.0	14.0	14.0	14.0	14.0
Minimum	12	12	12	12	12
Maximum	18	17	18	18	18
DB BASELINE WEIGHT (kg)					
N	33	35	35	70	103
Mean	57.53	55.67	57.82	56.74	57.00
SD	11.792	12.536	14.282	13.383	12.842
Median	57.30	53.80	55.00	55.00	55.60
Minimum	35.5	30.6	32.8	30.6	30.6
Maximum	80.0	79.7	95.3	95.3	95.3
DB BASELINE HEIGHT (cm)					
N	33	35	35	70	103
Mean	162.7	160.5	161.7	161.1	161.6
SD	8.441	8.768	8.310	8.500	8.472
Median	162.0	159.5	162.0	160.3	161.2
Minimum	145	135	145	135	135
Maximum	184	180	180	180	184
DB BASELINE BMI (kg/m2)					
N	33	35	35	70	103
Mean	21.65	21.53	21.94	21.73	21.71
SD	3.808	4.352	4.312	4.306	4.134
Median	21.10	20.30	21.50	20.75	21.00
Minimum	16.7	14.9	15.0	14.9	14.9
Maximum	30.8	32.3	30.4	32.3	32.3

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Table 10 Demographics and Baseline Characteristics: Study CAPSS-122 (Intent-to-Treat Analysis Set)

	Placebo (N=49)	TPM 2-3 mg/kg/day (N=108)	Total (N=157)
SEX, n (%)			
N	49	108	157
MALE	26 (53)	55 (51)	81 (52)
FEMALE	23 (47)	53 (49)	76 (48)
RACE, n (%)			
N	49	108	157
WHITE	43 (88)	78 (72)	121 (77)
BLACK	5 (10)	28 (26)	33 (21)
ASIAN	1 (2)	0	1 (1)
OTHER	0	2 (2)	2 (1)
AGE (Years)			
N	49	108	157
Category, n (%)			
6-11 YEARS	31 (63)	59 (55)	90 (57)
12-17 YEARS	18 (37)	49 (45)	67 (43)
Mean	10.7	11.3	11.1
SD	2.58	2.45	2.49
Median	11.0	11.0	11.0
Minimum	6	6	6
Maximum	15	16	16
DB BASELINE WEIGHT (kg)			
N	49	108	157
Mean	46.00	50.62	49.17
SD	15.057	24.858	22.320
Median	44.09	47.11	45.91
Minimum	20.4	21.5	20.4
Maximum	86.2	150	150
DB BASELINE HEIGHT (cm)			
N	49	107	156
Mean	144.1	147.9	146.7
SD	14.000	14.169	14.185
Median	142.2	148.9	146.9
Minimum	116	118	116
Maximum	174	176	176
DB BASELINE BMI (kg/m2)			
N	49	107	156
Mean	21.78	22.25	22.10
SD	5.320	7.861	7.147
Median	20.20	20.70	20.50
Minimum	14.9	13.1	13.1
Maximum	37.2	53.3	53.3

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Table 11 Demographics and Baseline Characteristics: Pooled Studies TOPMAT-MIGR-001/002/003 (Intent-to-Treat Analysis Set)

	Placebo (N=12)	TPM 50 mg/day (N=11)	TPM 100 mg/day (N=13)	TPM 200 mg/day (N=13)	Any TPM (N=37)	Total (N=49)
SEX, n (%)						
N	12	11	13	13	37	49
MALE	3 (25)	2 (18)	3 (23)	6 (46)	11 (30)	14 (29)
FEMALE	9 (75)	9 (82)	10 (77)	7 (54)	26 (70)	35 (71)
RACE, n (%)						
N	12	11	13	13	37	49
WHITE	9 (75)	9 (82)	12 (92)	13 (100)	34 (92)	43 (88)
BLACK	2 (17)	1 (9)	1 (8)	0	2 (5)	4 (8)
ASIAN	0	0	0	0	0	0
OTHER	1 (8)	1 (9)	0	0	1 (3)	2 (4)
AGE (Years)						
N	12	11	13	13	37	49
Category, n (%)						
6-11 YEARS	0	0	0	0	0	0
12-17 YEARS	12 (100)	11 (100)	13 (100)	13 (100)	37 (100)	49 (100)
Mean	14.8	14.3	14.2	14.2	14.2	14.4
SD	1.91	1.95	1.54	1.42	1.59	1.67
Median	15.0	14.0	14.0	14.0	14.0	14.0
Minimum	12	12	12	12	12	12
Maximum	17	17	17	16	17	17
DB BASELINE WEIGHT (kg)						
N	12	11	13	13	37	49
Mean	59.48	67.42	68.28	62.68	66.06	64.45
SD	13.958	18.923	19.432	12.080	16.746	16.221
Median	57.10	66.40	63.20	67.30	66.40	62.70
Minimum	39.5	39.9	40.7	40.0	39.9	39.5
Maximum	89.1	106	102	76.9	106	106
DB BASELINE HEIGHT (cm)						
N	12	11	13	13	37	49
Mean	159.2	160.2	160.8	163.0	161.4	160.9
SD	8.291	7.895	5.101	6.510	6.447	6.913
Median	162.5	162.5	161.0	161.3	161.3	162.5
Minimum	137	145	152	152	145	137
Maximum	168	168	169	172	172	172
DB BASELINE BMI (kg/m2)						
N	12	11	13	13	37	49
Mean	23.71	26.04	26.18	23.56	25.22	24.85
SD	6.585	5.852	6.413	4.316	5.564	5.795
Median	20.95	26.70	23.30	23.50	23.60	23.50
Minimum	16.7	15.1	17.4	16.0	15.1	15.1
Maximum	37.0	37.6	35.7	30.1	37.6	37.6

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Baseline Disease Characteristics

ITT Dataset

A summary of baseline migraine characteristics for the ITT analysis dataset is presented for Study TOPMAT-MIG-3006 in Table 12, Study CAPSS-122 in Table 13, and Studies TOPMAT-MIGR-001/002/003 in Table 14.

- Treatment groups were generally well matched for baseline migraine characteristics in Study TOPMAT-MIG-3006 and in Study CAPSS-122. In these 2 studies, the mean monthly migraine attack rate (48-hour rule) ranged from 4.1 to 4.2 across topiramate groups and 4.1 to 4.3 in the placebo groups.

- In Studies TOPMAT-MIGR-001/002/003, baseline migraine characteristics were more variable across treatment groups. In this study, the mean monthly migraine attack rate (48-hour rule) was higher in the 100 mg/day and 200 mg/day groups (4.9 and 4.2, respectively) than in the 50 mg/day and placebo groups (3.3 in each group).

Table 12 Baseline Migraine Characteristics: Study TOPMAT-MIG-3006 (Intent-to-Treat Analysis Set)

	Placebo (N=33)	TPM 50 mg/day (N=35)	TPM 100 mg/day (N=35)	Any TPM (N=70)	Total (N=103)
Monthly migraine attack rate (using 48-hour rule)					
N	33	35	35	70	103
Mean (SD)	4.1 (1.47)	4.1 (1.74)	4.2 (1.59)	4.2 (1.66)	4.1 (1.59)
Median	3.6	4.0	4.0	4.0	4.0
Range	(2;7)	(1;7)	(2;9)	(1;9)	(1;9)
Monthly migraine day rate					
N	33	35	35	70	103
Mean (SD)	6.1 (3.02)	6.4 (2.86)	6.9 (3.02)	6.6 (2.93)	6.5 (2.95)
Median	5.2	6.7	6.0	6.4	6.0
Range	(2;14)	(2;12)	(3;14)	(2;14)	(2;14)
Monthly headache day rate					
N	33	35	35	70	103
Mean (SD)	6.8 (3.05)	7.6 (3.23)	7.2 (3.07)	7.4 (3.13)	7.2 (3.10)
Median	6.0	8.0	7.0	7.4	7.0
Range	(3;14)	(2;14)	(3;14)	(2;14)	(2;14)
Monthly migraine attack rate (using 24-hour rule)					
N	33	35	35	70	103
Mean (SD)	4.9 (2.03)	4.7 (2.17)	4.7 (1.73)	4.7 (1.95)	4.7 (1.97)
Median	4.3	4.0	4.8	4.7	4.7
Range	(2;9)	(1;9)	(2;9)	(1;9)	(1;9)
Monthly migraine day with rescue medication rate					
N	33	35	35	70	103
Mean (SD)	3.5 (2.76)	3.8 (3.16)	4.1 (2.92)	4.0 (3.02)	3.8 (2.93)
Median	2.9	3.1	4.0	3.8	3.0
Range	(0;13)	(0;12)	(0;12)	(0;12)	(0;13)
Monthly Rate - Migraine with aura					
N	33	35	35	70	103
Mean (SD)	1.4 (2.16)	0.7 (1.20)	1.0 (1.86)	0.8 (1.56)	1.0 (1.79)
Median	0.0	0.0	0.0	0.0	0.0
Range	(0;8)	(0;4)	(0;8)	(0;8)	(0;8)
Monthly Rate - Migraine without aura					
N	33	35	35	70	103
Mean (SD)	3.9 (3.37)	4.3 (2.83)	4.3 (2.41)	4.3 (2.61)	4.2 (2.86)
Median	3.4	4.0	4.7	4.0	4.0
Range	(0;15)	(0;12)	(0;13)	(0;13)	(0;15)
Monthly Rate - Migraine Aura only					
N	33	35	35	70	103
Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)
Median	0.0	0.0	0.0	0.0	0.0
Range	(0;0)	(0;0)	(0;0)	(0;0)	(0;0)
Monthly Rate - Non-migraine headache					
N	33	35	35	70	103
Mean (SD)	0.7 (1.98)	1.0 (1.44)	0.4 (0.79)	0.7 (1.19)	0.7 (1.48)
Median	0.0	0.0	0.0	0.0	0.0
Range	(0;9)	(0;7)	(0;3)	(0;7)	(0;9)
Monthly Rate - Aura only					
N	33	35	35	70	103
Mean (SD)	0.0 (0.17)	0.1 (0.23)	0.1 (0.35)	0.1 (0.30)	0.1 (0.27)
Median	0.0	0.0	0.0	0.0	0.0
Range	(0;1)	(0;1)	(0;1)	(0;1)	(0;1)

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Table 13 Baseline Migraine Characteristics: Study CAPSS-122 (Intent-to-Treat Analysis Set)

	Placebo (N=49)	TPM 2-3 mg/kg/day (N=108)	Total (N=157)
Monthly migraine attack rate (using 48-hour rule)			
N	49	108	157
Mean (SD)	4.3 (1.40)	4.1 (1.32)	4.2 (1.34)
Median	4.0	4.0	4.0
Range	(3;8)	(1;8)	(1;8)
Monthly migraine day rate			
N	49	108	157
Mean (SD)	5.4 (1.87)	5.3 (1.74)	5.4 (1.78)
Median	5.0	5.0	5.0
Range	(3;10)	(2;9)	(2;10)
Monthly headache day rate			
N	49	108	157
Mean (SD)	6.1 (2.23)	5.7 (1.93)	5.8 (2.03)
Median	6.0	6.0	6.0
Range	(3;13)	(2;11)	(2;13)
Monthly migraine attack rate (using 24-hour rule)			
N	49	108	157
Mean (SD)	4.9 (1.59)	4.7 (1.60)	4.8 (1.60)
Median	5.0	4.1	5.0
Range	(3;9)	(1;9)	(1;9)
Monthly migraine day with rescue medication rate			
N	49	108	157
Mean (SD)	4.6 (2.18)	4.1 (2.09)	4.2 (2.13)
Median	5.0	4.0	4.0
Range	(1;9)	(0;9)	(0;9)
Monthly Rate - Migraine with aura			
N	49	108	157
Mean (SD)	0.6 (1.46)	0.6 (1.43)	0.6 (1.44)
Median	0.0	0.0	0.0
Range	(0;8)	(0;7)	(0;8)
Monthly Rate - Migraine without aura			
N	49	108	157
Mean (SD)	4.7 (1.78)	4.7 (2.01)	4.7 (1.94)
Median	4.1	5.0	5.0
Range	(1;9)	(0;9)	(0;9)
Monthly Rate - Migraine Aura only			
N	49	108	157
Mean (SD)	0.0 (0.20)	0.0 (0.14)	0.0 (0.16)
Median	0.0	0.0	0.0
Range	(0;1)	(0;1)	(0;1)
Monthly Rate - Non-migraine headache			
N	49	108	157
Mean (SD)	0.7 (1.25)	0.4 (0.94)	0.5 (1.05)
Median	0.0	0.0	0.0
Range	(0;6)	(0;4)	(0;6)
Monthly Rate - Aura only			
N	49	108	157
Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)
Median	0.0	0.0	0.0
Range	(0;0)	(0;0)	(0;0)

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Table 14 Baseline Migraine Characteristics: Pooled Studies TOPMAT-MIGR-001/002/003 (Intent-to-Treat Analysis Set)

	Placebo (N=12)	TPM 50 mg/day (N=11)	TPM 100 mg/day (N=13)	TPM 200 mg/day (N=13)	Any TPM (N=37)	Total (N=49)
Monthly migraine attack rate (using 48-hour rule)						
N	12	11	13	13	37	49
Mean (SD)	3.3 (1.36)	3.3 (1.18)	4.9 (1.96)	4.2 (1.20)	4.2 (1.60)	4.0 (1.58)
Median	3.0	3.5	5.0	4.0	3.7	3.7
Range	(1;6)	(2;5)	(3;8)	(2;6)	(2;8)	(1;8)
Monthly migraine day rate						
N	12	11	13	13	37	49
Mean (SD)	5.5 (2.50)	6.3 (2.79)	8.2 (4.12)	6.3 (2.14)	7.0 (3.20)	6.6 (3.09)
Median	4.4	5.8	9.0	5.9	6.0	5.9
Range	(2;10)	(2;11)	(3;15)	(3;12)	(2;15)	(2;15)
Monthly headache day rate						
N	12	11	13	13	37	49
Mean (SD)	6.4 (2.50)	7.0 (2.45)	8.7 (3.87)	7.6 (2.58)	7.8 (3.06)	7.5 (2.97)
Median	6.3	6.8	9.0	7.0	7.0	7.0
Range	(3;11)	(2;11)	(4;15)	(4;13)	(2;15)	(2;15)
Monthly migraine attack rate (using 24-hour rule)						
N	12	11	13	13	37	49
Mean (SD)	3.8 (1.56)	3.8 (1.61)	5.4 (2.50)	4.7 (1.49)	4.7 (1.99)	4.5 (1.92)
Median	3.7	4.4	5.8	4.7	4.7	4.5
Range	(1;7)	(2;7)	(3;10)	(2;8)	(2;10)	(1;10)
Monthly migraine day with rescue medication rate						
N	12	11	13	13	37	49
Mean (SD)	3.7 (2.17)	3.3 (1.81)	4.8 (3.25)	4.5 (2.09)	4.3 (2.51)	4.1 (2.42)
Median	2.7	2.9	4.0	4.2	3.9	3.9
Range	(1;8)	(0;6)	(0;11)	(2;10)	(0;11)	(0;11)
Monthly Rate - Migraine with aura						
N	12	11	13	13	37	49
Mean (SD)	0.2 (0.39)	0.5 (0.97)	0.7 (1.63)	0.7 (1.06)	0.6 (1.24)	0.5 (1.10)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	(0;1)	(0;3)	(0;6)	(0;3)	(0;6)	(0;6)
Monthly Rate - Migraine without aura						
N	12	11	13	13	37	49
Mean (SD)	4.2 (2.50)	3.7 (1.59)	5.3 (2.78)	4.2 (2.05)	4.4 (2.26)	4.4 (2.30)
Median	3.7	3.9	4.7	4.6	4.0	3.9
Range	(1;8)	(0;6)	(2;12)	(1;8)	(0;12)	(0;12)
Monthly Rate - Migraine Aura only						
N	12	11	13	13	37	49
Mean (SD)	0.0 (0.00)	0.1 (0.24)	0.0 (0.00)	0.1 (0.33)	0.1 (0.24)	0.1 (0.21)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	(0;0)	(0;1)	(0;0)	(0;1)	(0;1)	(0;1)
Monthly Rate - Non-migraine headache						
N	12	11	13	13	37	49
Mean (SD)	1.0 (1.00)	0.8 (0.84)	0.5 (0.70)	1.5 (2.41)	0.9 (1.58)	0.9 (1.45)
Median	0.9	0.9	0.0	0.0	0.0	0.7
Range	(0;3)	(0;3)	(0;2)	(0;6)	(0;6)	(0;6)
Monthly Rate - Aura only						
N	12	11	13	13	37	49
Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	(0;0)	(0;0)	(0;0)	(0;0)	(0;0)	(0;0)

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Reviewer Comments

All treatment groups were reasonably well matched for demographic and disease characteristics in all trials.

6.1.3 Subject Disposition

Patient disposition in the different migraine trials with pediatric patients is presented according to treatment in the tables that follow.

Table 15 Disposition of Patients in Study MIG-3006

Analysis Set: Intent-To-Treat

Subject Completed Treatment/Trial Reason For Withdrawal/Termination	Placebo (N=33) n (%)	TPM 50 mg/day (N=35) n (%)	TPM 100 mg/day (N=35) n (%)	Total (N=103) n (%)
Total no. subjects with disposition	33 (100)	35 (100)	35 (100)	103 (100)
COMPLETED	26 (79)	29 (83)	30 (86)	85 (83)
WITHDRAWN	7 (21)	6 (17)	5 (14)	18 (17)
ADVERSE EVENT	1 (3)	3 (9)	3 (9)	7 (7)
LOST TO FOLLOW-UP	0	1 (3)	0	1 (1)
SUBJECT CHOICE	1 (3)	0	1 (3)	2 (2)
PREGNANCY	1 (3)	0	0	1 (1)
LACK OF EFFICACY	2 (6)	0	0	2 (2)
OTHER	2 (6)	2 (6)	1 (3)	5 (5)

Table 16 Disposition of Patients in Study CAPSS-122

Analysis Set: Intent-To-Treat

Subject Completed Treatment/Trial Reason For Withdrawal/Termination	Placebo (N=49) n (%)	TPM 2-3 mg/kg/day (N=108) n (%)	Total (N=157) n (%)
Total no. subjects with disposition	49 (100)	108 (100)	157 (100)
COMPLETED	42 (86)	89 (82)	131 (83)
WITHDRAWN	7 (14)	19 (18)	26 (17)
LOST TO FOLLOW-UP	1 (2)	3 (3)	4 (3)
LIMITING ADVERSE EVENT	2 (4)	7 (6)	9 (6)
SUBJECT CHOICE	1 (2)	4 (4)	5 (3)
SIGNIFICANT PROTOCOL VIOLATION	0	1 (1)	1 (1)
LACK OF EFFICACY	2 (4)	2 (2)	4 (3)
OTHER	1 (2)	2 (2)	3 (2)

Table 17 Disposition of Patients in Study MIGR-001,-002,-003

Analysis Set: Intent-To-Treat

Subject Completed Treatment/Trial Reason For Withdrawal/Termination	Placebo (N=12) n (%)	TPM 50 mg/day (N=11) n (%)	TPM 100 mg/day (N=13) n (%)	TPM 200 mg/day (N=13) n (%)	Total (N=49) n (%)
Total no. subjects with disposition	12 (100)	11 (100)	13 (100)	13 (100)	49 (100)
COMPLETED	5 (42)	7 (64)	9 (69)	11 (85)	32 (65)
WITHDRAWN	7 (58)	4 (36)	4 (31)	3 (23)	18 (37)
ADVERSE EVENT	2 (17)	0	0	0	2 (4)
LOST TO FOLLOW-UP	2 (17)	1 (9)	1 (8)	1 (8)	5 (10)
SUBJECT CHOICE	0	0	1 (8)	1 (8)	2 (4)
OTHER	3 (25)	3 (27)	2 (15)	1 (8)	9 (18)

Reviewer Comments

The mean completion rate for all treatment groups in both trials that enrolled solely pediatric patients was 83 % and the completion rate across treatment groups was relatively similar (Table 15, Table 16). The most common reason for discontinuing prematurely was adverse event in all topiramate treatment groups. In placebo groups in each trial, there were 2 most common reasons for discontinuing prematurely. In MIG-3006 placebo, the most common reasons for discontinuing prematurely were lack of efficacy and other. In CAPSS-122 placebo, the most common reasons for discontinuing prematurely were lack of efficacy and adverse event.

The mean completion rate in MIGR-1-3 for all treatment groups was considerably lower at 65 % (Table 17). Perhaps somewhat surprisingly, the lowest completion rate was 42 % in placebo patients who in theory would have had the lowest risk for adverse events and was highest (85 %) in the highest topiramate dose group (200 mg) who in theory would have had the highest risk for adverse events. In 50 mg and 100 mg topiramate, the most common reason for discontinuing prematurely was other. In the 200 mg topiramate group, the reason for discontinuing prematurely was other, subject choice, and lost to follow-up in 3 patients. In placebo, the most common reason for discontinuing prematurely was other.

6.1.4 Analysis of Primary Endpoint(s)

MIG-3006

The percent reduction from baseline to the last 12 weeks of the double-blind phase in average monthly migraine attack rate for the ITT analysis set of the key efficacy trial, Study TOPMAT-MIG-3006, is shown in Table 18.

The sponsor noted the following observations :

- Baseline median values for monthly migraine attack rate were similar in the topiramate groups and slightly lower in the placebo-treated subjects.

- The median monthly migraine attack rate over the last 12 weeks of double-blind phase was lower in the 100 mg/day group (1.00) compared with the 50 mg/day group and placebo groups (2.33 in each group).
- Median percent reduction was greatest in the 100 mg/day group (72.2%) compared with the 50 mg/day group (44.6%) and placebo (44.4%).
- The 100 mg/day group was statistically superior to the placebo group after multiple comparison adjustment (p=0.0164). The 50 mg/day group was not statistically different from placebo.

Table 18 Percent Reduction from Baseline to the Last 12 Weeks of Double-Blind Phase in Average Monthly Attack Rate (Using 48-Hour Rule): Study TOPMAT-MIG-3006 (Intent-to-Treat Analysis Set)

Category	Placebo (N=33)	TPM 50 mg/day (N=35)	TPM 100 mg/day (N=35)	Any TPM (N=70)
Baseline				
N	33	35	35	70
Median (Range)	3.61 (1.9;7.5)	4.00 (1.0;7.2)	4.00 (1.9;9.0)	4.00 (1.0;9.0)
Last 12 Weeks of Double-Blind Phase				
N	33	35	35	70
Median (Range)	2.33 (0.0;7.3)	2.33 (0.0;7.0)	1.00 (0.0;4.5)	1.51 (0.0;7.0)
Percent Reduction (%)				
N	33	35	35	70
Median (Range)	44.44 (-36.4;100.0)	44.64 (-125.0;100.0)	72.22 (0.0;100.0)	63.69 (-125.0;100.0)
P-value VS. Placebo		0.7975	0.0164*	0.1871

Percent reduction is the difference between values at baseline and last 12 weeks of Double-Blind Phase, divided by value at baseline, times 100.
P-values for comparisons relative to placebo are generated by applying an ANCOVA model on ranks that includes subject's stratified age at baseline, treatment group, and analysis center as factors and monthly migraine attack rate during baseline period as a covariate.
P-values for the dose groups are the adjusted p-value according to the Hochberg multiple comparison procedure.
The p-values for the 'Any TPM' group are unadjusted.
* indicates p-value is less than 0.05 (two-sided).
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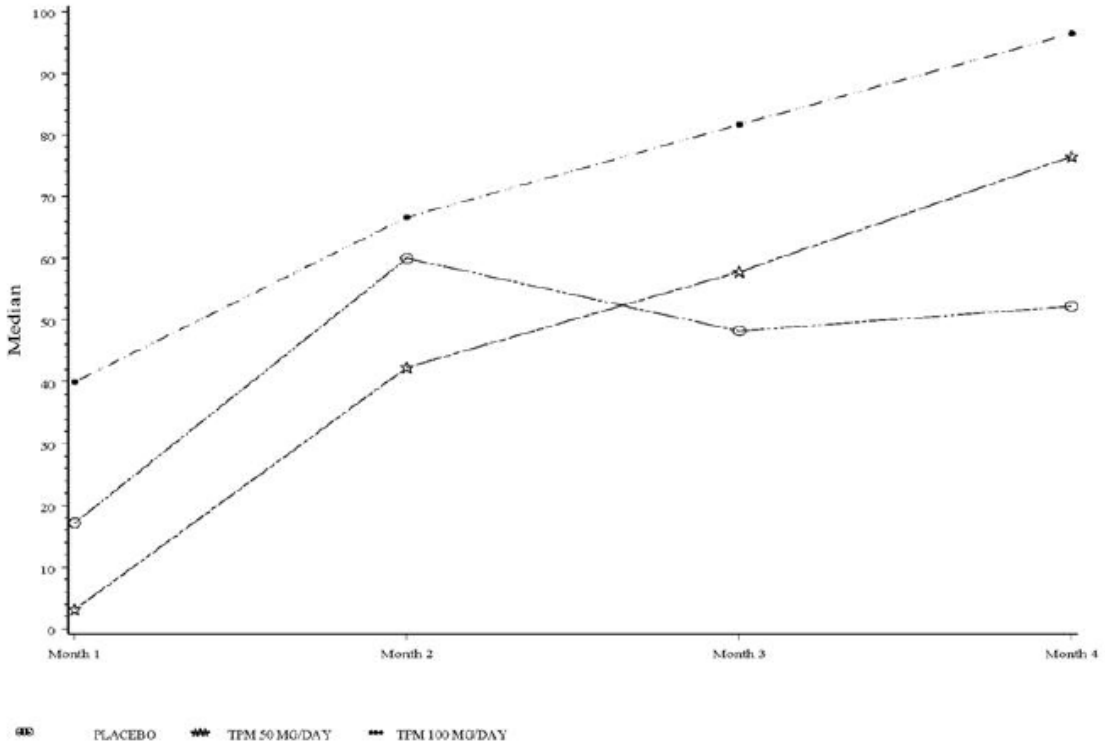
Monthly Percent Reduction Over Time

The monthly percent reduction over time in average monthly migraine attack rate for the ITT analysis set of Study TOPMAT-MIG-3006 is shown in Figure 5.

The sponsor noted the following observations :

- Both topiramate groups showed a general trend towards an increasingly higher percent reduction in average monthly migraine attack rate with longer treatment duration, while the reduction in the placebo group seen in Months 1 and 2 plateaued in Months 3 and 4.
- The 100 mg/day group had a statistically significant difference from placebo after multiple comparison adjustment starting at Month 3, which was maintained at Month 4 (p= 0.0260 and 0.0103, respectively).

Figure 5 Monthly Percent Reduction Over Time in Average Monthly Migraine Attack Rate (Using 48-Hour Rule): Study TOPMAT-MIG-3006 (Intent-to-Treat Analysis Set)



A statistically significant difference was seen in favor of TPM 100 mg/day vs. placebo at Month 3 and Month 4 ($p<0.05$).

During the review of this NDA by the primary statistical reviewer, Dr. Tristan Massie, he noted some discrepancies between the derived efficacy data in MIG-3006. Table 19 outlines differences/discrepancies for computed efficacy data between the sponsor and Dr. Massie.

Table 19 Differences between Statistical Reviewer and Sponsor in Derived Efficacy Data for MIG-3006

SUBJECT ID	TRT GRP	Length of DB Phase	Reviewer Baseline Rate	Sponsor Baseline Rate	Reviewer Double Blind Period Rate	Sponsor Double Blind Period Rate	Reviewer Percent Reduction	Sponsor Percent Reduction
TOPMAT-MIG-3006-001006-101114	TPM 100 mg/day	127	3.0	4.0[a]	1.67	1.67	44.44	58.33
TOPMAT-MIG-3006-001010-101027	Placebo	106	7.3	7.3	3.33	3.00[b]	54.08	58.67
TOPMAT-MIG-3006-047002-147017	Placebo	118	5.8	5.8	6.67	6.33[c]	-15.08	-9.33
TOPMAT-MIG-3006-047002-147018	TPM 100 mg/day	132	6.0	6.0	3.33	3.00[d]	44.44	50.00

[a]Sponsor has one more migraine than me during BASELINE; last baseline migraine was 60 min short of 48 hours so not counted by me
[b]Sponsor has one less migraine than me during Double Blind Phase; had one on dbday 24 (patient had 106 total db days)would be during titration and was first day of last 12 weeks
[c]Sponsor has one less migraine than me during Double Blind Phase;
[d]Sponsor has one less migraine than me during Double Blind Phase; patient has one migraine 48 hours from previous one not sure if sponsor counted this one

Reviewer Comments

- *Topiramate (100 mg dose) produced a statistically significant reduction (p=0.0164; p value adjusted for multiple comparisons) percentage change from baseline in the monthly migrate rate compared to placebo (Table 18) for the last 12 weeks of treatment in MIG-3006, the key pivotal trial upon which this NDA is based. These results for the ITT population had been computed using patient diaries for migraines (applying the 48 hour rule). The treatment difference for this percentage reduction relative to placebo was 28%. This result shows that 100 mg daily topiramate is effective for adolescents for migraine prophylaxis.*

- *There is no treatment difference for the 50 mg topiramate group vs placebo indicating no efficacy of this dose, Of interest, the monthly percentage reduction for 50 mg is essentially identical to that of placebo. This observation raises the question of whether there might be a threshold effect for topiramate based upon a minimal plasma exposure for topiramate to produce a therapeutic benefit. This observation may be somewhat unique in that lower doses of drugs that produce efficacy at higher doses often show some numerical treatment difference (in the direction of therapeutic benefit) from placebo (without statistically significant difference), especially when the difference in daily dosing is not markedly lower than the dose showing statistically significant efficacy.*

- *Figure 5 shows the monthly percentage reduction from baseline over the whole trial (MIG-3006). The reduction (from baseline) in monthly migraine rate for the 100 mg topiramate dose shows a progressive increase over time (4 months) with the maximal reduction (~ 95 %) occurring at month 4. Of interest, the reduction (from baseline) in monthly migraine rate for the placebo group is between that of the low and high dose topiramate dose groups for months 1 and 2. However, at months 3 and 4 the point estimate for the 50 mg topiramate group shows numerically greater reductions than reductions for placebo. Over the whole period, the 50 mg dose group parallels reductions of the 100 mg dose group at each month. This pattern for the 50 mg dose group, especially at months 3 and 4 suggests some effect of the 50 mg dose group and contradicts the suggestion I noted for a complete lack of effect of this dose in the preceding comments. I believe that the fact that the results are averaged over the whole 4 months negates the seeming effect of this low dose group in the latter half of the trial because the effect of placebo (vs 50 mg) is greater in the first half of the trial but lower in the second half.*

- *Table 19 shows differences/discrepancies for efficacy data (derived percent reductions over the last 12 weeks based on the 48 hour rule and subject classification of migraines) in MIG-3006 between the computations by the sponsor and the primary reviewer. This table was abstracted from Dr. Massie's review of this NDA. Dr. Massie noted in his review that : "It turns out that these discrepancies did not affect the significance of TPM 100 mg compared to placebo in terms of the percent reduction over the last 12 weeks. There were similar discrepancies for the same subjects when the IHS algorithm was applied using the 48 hour rule." Based upon Dr. Massie's conclusion about these discrepancies, I have no concerns regarding the efficacy findings showing that efficacy of the 100 mg topiramate dose was demonstrated in this trial.*

- *The primary statistical reviewer, Dr. Tristan Massie, reviewed the issue about patients who enrolled MIG-3006 but who did not have any migraines at baseline according to the IHS classification algorithm. In his review, Dr. Massie noted :*

  "Four out of 33 placebo subjects, 4 of 35 TPM 50 mg subjects, and 2 of 35 TPM 100 mg subjects had no IHS migraines during baseline which leads to an undefined percent change from baseline. The average rate during the last 12 weeks of DB for these subjects

were 1 (1.67, 2.33, 0, and 0), 0.42 (1.33, 0.333, 0, and 0), and 0 (0 and 0) for placebo, TPM 50 mg, and TPM 100 mg, respectively. The subjective 48 hour rule rates for these subjects were 4.0, 4.3, 4.0, and 3.2 for placebo; 3.3, 2.3, 0.6 and 7.0 for TPM 50 mg; and 0.0 and 0.0 for TPM 100 mg."

Dr. Massie presented some sensitivity analyses related to this issue and ultimately concluded that efficacy results for the 100 mg topiramate dose in MIG-3006 were robust. Based upon his sensitivity analyses and those submitted by the sponsor, Dr. Massie did not have serious concerns about not conducting the primary analysis of the primary efficacy endpoint based upon migraines classified according to the IHS algorithm at baseline and during treatment. Refer to Dr. Massie's review for his perspective on this issue. Additional discussion of this issue is also presented in my Reviewer Comments at the end of the various sensitivity analyses presented in Section 6.1.10.

- *The primary statistical reviewer, Dr. Tristan Massie, found the 100 mg topiramate dose group to be effective (vs placebo) based upon the primary analysis of the primary efficacy endpoint for trial MIG-3006. Dr. Massie did not have any serious concerns with the efficacy data in this key, pivotal trial. The following is his conclusion abstracted from his review :*
  "The clinical trial efficacy data from study 3006 provided in this application seems to support the efficacy of Topiramate 100 mg in migraine prophylaxis for adolescents."

CAPSS-122

The primary efficacy outcome was the change in the mean monthly (28-day) rate of migraine days. This variable was computed for the prospective baseline period and the double-blind phase for the ITT population and the Evaluable-for-Efficacy population and is presented in Table 20 respectively. Decreases in the mean monthly (28-day) rate of migraine-days per month in the ITT population were 2.6 days in the topiramate group and 2.0 days in the placebo group. The between-group difference approached statistical significance (p=0.061). This primary efficacy endpoint was different than that designated as the primary efficacy endpoint in MIGRF-3006 (i.e., percentage reduction change from baseline in the average monthly migraine attack rate for the last 12 weeks).

Table 20 Summary and Analysis of Monthly (28-Day) Rate of Migraine Days
(Intent-to-Treat Population in Protocol CAPSS-122)

Monthly Rate of Migraine Days[a]	Topiramate (N=108)	Placebo (N=49)	p-value[c]
Prospective Baseline[b]			
n	108	49	
Mean	5.4	5.5	
Median	5.0	5.0	
SD	1.72	1.95	
(Min,Max)	(2.0, 9.0)	(3.0, 11.0)	
Double-Blind			
n	108	49	
Mean	2.8	3.5	0.061
Median	2.3	2.8	
SD	2.39	3.11	
(Min,Max)	(0.0, 15.3)	(0.2, 19.6)	
Change from Baseline			
n	108	49	
Mean	-2.6	-2.0	
Median	-2.6	-2.2	
SD	2.64	3.07	
(Min,Max)	(-8.8, 8.3)	(-6.2, 12.6)	

[a] 28-Day Rate of Migraine Days = ((total number of migraine days during the double-blind phase / total duration (days) of double-blind phase) * 28).
[b] Prospective baseline = total number of migraine days in the last 28 days prior to randomization.
[c] p-value for the comparison of placebo versus topiramate is based on Cochran-Mantel-Haenszel Test, with scores=modridit, stratified by baseline headache rate.

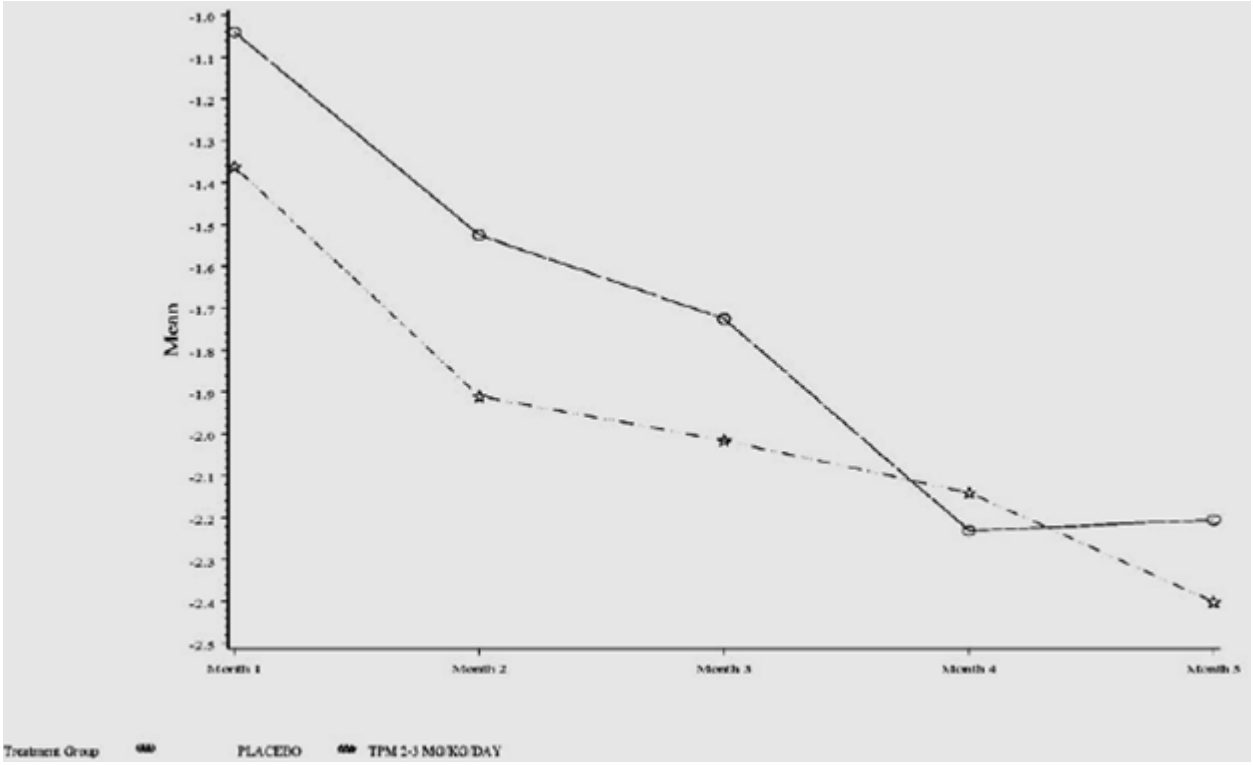
Table 21 provides a tabular analysis of results over time for the primary efficacy endpoint. Figure 6 shows these results over time as a figure.

Table 21 Summary and Analysis of Monthly (28-Day) Rate of Migraine Days[a] By Visit (Intent-to-Treat Population in Protocol CAPSS-122)

	Statistic	Prospective Baseline[b]	Visit 4 (Day 29)	Visit 5 (Day 57)	Visit 6 (Day 85)	Visit 7 (Day 113)	Visit 8 (Day 141)	p-value[c]
Topiramate (N=108)	n	108	108	102	95	93	89	
	Mean	5.4	3.6	2.7	2.7	2.6	2.2	0.126
	Median	5.0	3.0	2.3	2.0	1.0	1.5	
	SD	1.72	2.67	2.29	3.01	2.89	2.48	
	(Min,Max)	(2.0, 9.0)	(0.0, 15.3)	(0.0, 12.0)	(0.0, 19.0)	(0.0, 16.0)	(0.0, 9.7)	
Placebo (N=49)	n	49	49	49	45	44	42	
	Mean	5.5	4.3	3.8	3.2	2.8	2.8	
	Median	5.0	4.0	3.0	3.0	2.0	2.7	
	SD	1.95	3.60	3.97	2.98	2.74	2.26	
	(Min,Max)	(3.0, 11.0)	(0.0, 23.0)	(0.0, 24.0)	(0.0, 14.0)	(0.0, 9.3)	(0.0, 7.7)	

[a] 28-Day Rate of Migraine Days = ((total number of migraine days at each 28-day window/total duration (days) in window) * 28).
[b] Prospective baseline = total number of migraine days in the last 28 days prior to randomization.
[c] p-value for the comparison of placebo versus topiramate from the negative binomial general estimating equation (GEE) with treatment group, visit and analysis center as qualitative factors, and baseline migraine days as a covariate with the log of the number of days in the visit window as the offset value.

Figure 6 Monthly Change Over Time in Average Monthly Migraine Attack Rate Using 48 Hour Rule: Study CAPSS-122 (Intent-to-Treat Analysis Set)



Reviewer Comments

- *In CAPSS-122, the primary analysis of the primary efficacy endpoint (change from baseline in the monthly-28 day rate for migraine days) showed that the topiramate group (2-3 mg/day) was not statistically significant (p = 0.061) over the whole trial period (20 weeks for completers) compared to placebo results for the ITT population of pediatric patients ranging from 6 to 16 years (Table 20). Although the treatment difference (topiramate – placebo) in the mean change from baseline in monthly migraine rate was relatively small (- 0.6), the p value for this treatment difference seems to be trending toward statistical significance (p < 0.05).*

- *I note that this primary efficacy endpoint assesses the change in the monthly rate of migraine days, not migraine days according to the 48 hour rule for counting separate migraine episodes/attacks as was assessed in MIG-3006. Nevertheless, efficacy in CAPSS-122 will subsequently be presented and discussed in various sensitivity analyses in which a 48 hour and 24 hour rule is applied for counting separate migraine episodes/attacks.*

- *The primary analysis of the primary efficacy endpoint for CAPSS-122 includes the titration period in which lower doses of topiramate were administered and in which the doses may have been too low to exert a therapeutic benefit. Consequently, I thought that it would be important to examine the effect over time to see if there was a suggestion of topiramate efficacy over time, particularly in the maintenance phase and especially toward the end of the trial. Table 21 shows the results for CAPSS-122 for the monthly migraine rate in migraine days for the topiramate and placebo groups over the whole trial period by study visit. Baseline monthly migraine rates following a 28 day baseline period were similar in both groups. The monthly migraine rates decrease for both treatment groups starting at the first visit (day 29) midway through the titration period. However, the mean treatment difference between the mean migraine rates for topiramate and placebo is relatively constant for most visits throughout the whole trial (ranging between -0.5 to -0.7 in favor of topiramate). Only at day 113 (second last trial visit), is the treatment difference (– 0.2) much small than that at all other post-baseline visits. Figure 6 illustrates that there is a small treatment difference for the change (i.e., reduction) from baseline for topiramate vs placebo at months 1, 2, 3, and 5, with the reduction being greater for topiramate at these visits but these small differences were not statistically significant. These results do not suggest that topiramate may been shown to be effective if treatment continued for a longer period.*

MIGR-001,-002,-003

The primary efficacy endpoint in each of these three trial was the change from baseline in the monthly migraine attack rate over the whole study period. **However, results of this primary efficacy endpoint (nor other efficacy endpoints) will not be presented here because these three trials were pooled for review in this NDA primarily for safety results and safety**

comparisons. In addition, the total number of adolescent patients in these three trials was very small (N=11 for placebo and N=37; divided amongst up to 4 treatment groups in 3 trials) and made analyses of these patients underpowered for demonstrating efficacy.

Nevertheless, pooled results of these patients will be presented for efficacy in sections 6.6 (Other Endpoints) and 6.10 (Additional Efficacy Issues/Analyses).

6.1.5 Analysis of Secondary Endpoints(s)

Analyses of secondary efficacy endpoints are presented here for Trials MIG-3006 and CAPSS-122.

Migraine Attack Rate

The change from baseline to the last 12 weeks of the double-blind phase in average monthly migraine attack rate for the ITT analysis set of Study TOPMAT-MIG-3006 is shown in Table 22.

The sponsor noted the following observations :

- Baseline mean values for monthly migraine attack rate were similar in the topiramate and placebo groups.
- The mean monthly migraine attack rate over the last 12 weeks of the double-blind phase was lower in the 100 mg/day group (1.30) compared with the 50 mg/day group and placebo group (2.37 in each group).
- Mean change (reduction) from baseline was greatest in the 100 mg/day group (-2.95) compared with the 50 mg/day group (-1.71) and placebo (-1.72).
- The 100 mg/day group was statistically superior to the placebo group after multiple comparison adjustment (p=0.0087). The 50 mg/day group was not statistically different from placebo.

Table 22 Change from Baseline to the Last 12 Weeks of Double-Blind Phase in Average Monthly Attack Rate Using 48-Hour Rule: Study TOPMAT-MIG-3006 (Intent-to-Treat Analysis Set)

Category	Placebo (N=33)	TPM 50 mg/day (N=35)	TPM 100 mg/day (N=35)	Any TPM (N=70)
Baseline				
N	33	35	35	70
Mean (SD)	4.09 (1.475)	4.08 (1.744)	4.25 (1.588)	4.17 (1.658)
Last 12 Weeks of Double-Blind Phase				
N	33	35	35	70
Mean (SD)	2.37 (1.929)	2.37 (1.837)	1.30 (1.226)	1.83 (1.642)
Change from Baseline				
N	33	35	35	70
Mean (SD)	-1.72 (1.759)	-1.71 (2.008)	-2.95 (1.455)	-2.33 (1.849)
P-value VS. Placebo		0.9845	0.0087*	0.1166

Change from Baseline is the difference between values at baseline and the last 12 weeks of Double-Blind Phase.
P-values for comparisons relative to placebo are generated by applying a linear model that includes subject's stratified age at baseline, treatment group, and analysis center as factors and monthly migraine attack rate during baseline period as a covariate.
P-values for the dose groups are the adjusted p-value according to the Hochberg multiple comparison procedure.
The p-values for the 'Any TPM' group are unadjusted.
* indicates p-value is less than 0.05 (two-sided).
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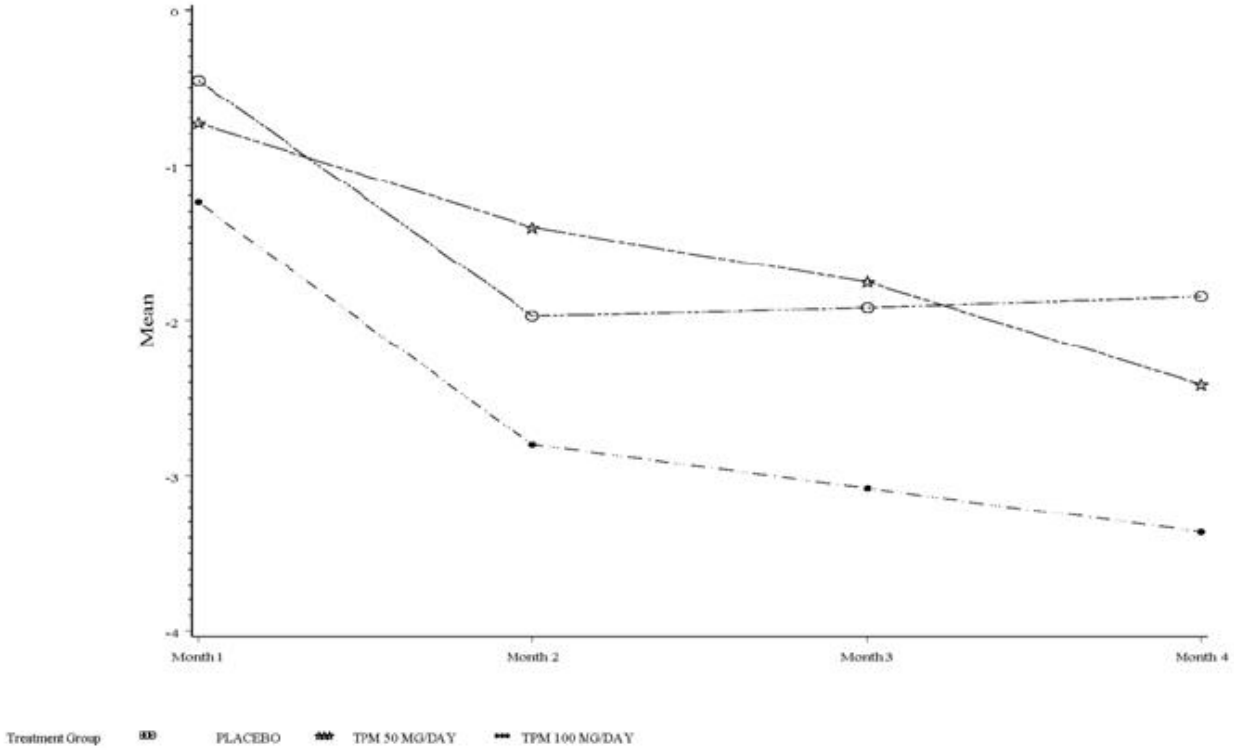
Monthly Change Over Time

The monthly change over time in average monthly migraine attack rate for the ITT analysis set of Study TOPMAT-MIG-3006 is shown in Figure 7.

The sponsor noted the following observations :

- Both topiramate groups showed a general trend towards a larger mean reduction in average monthly migraine attack rate with increasing treatment duration, while the reduction in the placebo group seen in Months 1 and 2 plateaued in Months 3 and 4.
- In the 100 mg/day group, there was a separation from placebo at Month 1, with a trend towards a statistically significant difference from placebo after multiple comparison adjustment at Month 3 (p= 0.0575), which reached significance at Month 4 (p= 0.0152).

Figure 7 **Monthly Change Over Time in Average Monthly Migraine Attack Rate (Using 48-Hour Rule): Study TOPMAT-MIG-3006 (Intent-to-Treat Analysis Set)**



A statistically significant difference was seen in favor of TPM 100 mg/day vs. placebo at Month 4 ($p<0.05$).

Reviewer Comments

- *Table 22 shows results for a key secondary efficacy endpoint, the change in monthly migraine rate (according to patient diaries and the 48 hour rule) from baseline over the last 12 weeks of the MIG-3006 trial for the ITT population. Baseline monthly migraine rates were similar amongst all treatment groups. Whereas the mean change for the 50 mg topiramate group was the same as that for placebo, the mean change for the 100 mg group was -2.95, a change that was highly statistically significant from that of placebo (p=0.0087) and indicated a treatment difference of -1.2 vs placebo. This is very similar in magnitude to the results of the two positive migraine prophylaxis trials that supported the approval of topiramate (100 mg daily) for that indication in adults. In those trials, the mean treatment difference for the mean change from baseline in monthly migraine rate (as per 48 hour rule in ITT population) over the whole 6 month treatment period was -1.0 and -1.3.* ***Thus, these results suggest similar efficacy of 100 mg topiramate for migraine prophylaxis in adults and adolescents.*** *It is also noteworthy that migraines were classified in the baseline and treatment periods according to the IHS algorithm in the adult trials and according to patient migraine diaries in the adolescent trials. This issue will subsequently be addressed in section 6.1.10 Additional Efficacy Issues/Analyses in the presentation of various sensitivity analyses.*

- *Figure 7 present results of the mean change from baseline in monthly migraine rate over time for the whole trial (MIG-3006). At 1 month, the difference for monthly migraine rate reduction between 100 mg topiramate and placebo is slightly less than 1 migraine per month for the 100 mg topiramate group and this difference is approximately maintained over the trial. This result indicates that if an adolescent takes 100 mg of topiramate daily, he/she will experience on the average 1 less migraine attack per month. I consider this positive result for this efficacy endpoint to be extremely important because it mimics the positive result observed in the adult trials that facilitated the initial approval of topiramate for migraine prophylaxis in adults.*

- *Although there appears to be no suggestion of any benefit of the 50 mg topiramate group vs placebo over the first 3 months, there is a suggestion that the reduction in monthly migraine rate is somewhat greater than that of placebo based upon the mean numerical difference at month 4. However, it is difficult to say whether this relatively difference noted on only one occasion is anything more than random variation of both groups over time and a therefore merely a chance event. It is also difficult to dismiss the observation that the 50 mg topiramate group exhibited the best results relative to placebo for two efficacy endpoints (i.e., percentage reduction and mean absolute change in monthly migraine rate) at the final trial visit.*

Between-Treatment Comparison in Responder Rate (Last 12 Weeks of Double-Blind Phase)

A between-treatment comparison of the $\geq$ 50% and 100% responder rates for the ITT analysis set of Study TOPMAT-MIG-3006 is shown in Table 23.

- At the $\geq$ 50% response threshold, the percentage of responders was higher in the 100 mg/day group (83%) compared with the 50 mg/day (46%) and placebo (45%) groups. The responder rate for the 100 mg/day group was statistically significantly higher relative to placebo after multiple comparison adjustment (p=0.0048).
- At the 100% response threshold, the percentage of responders was slightly higher in the 100 mg/day group (20%) compared with the 50 mg/day (14%) and placebo (12%) groups, but neither topiramate dosage was statistically significantly different from placebo.

Table 23 Between-Treatment Comparison in Responder Rate (Using 48-Hour Rule): Study TOPMATMIG- 3006 (Intent-to-Treat Analysis Set)

Parameter of Efficacy Analysis	Category	Placebo (N=33)	TPM 50 mg/day (N=35)	TPM 100 mg/day (N=35)	Any TPM (N=70)
≥50% Responder Rate	N	33	35	35	70
	Number of Responders	15	16	29	45
	Responder Rate	45%	46%	83%	64%
	Difference		0%	37%	19%
	95% CI		(-23%, 24%)	(16%, 58%)	(-2%, 39%)
	P-Value VS. Placebo		1.0000	0.0048*	0.0874
100% Responder Rate	N	33	35	35	70
	Number of Responders	4	5	7	12
	Responder Rate	12%	14%	20%	17%
	Difference		2%	8%	5%
	95% CI		(-14%, 18%)	(-9%, 25%)	(-9%, 19%)
	P-Value VS. Placebo		1.0000	1.0000	0.7455

≥50% Responder rate is the percentage of subjects who had at least a 50% reduction in the average monthly migraine attack rate from baseline.
100% Responder rate is the percentage of subjects who had a 100% reduction in the average monthly migraine attack rate from baseline.
The difference is the treatment responder rate of TPM minus placebo.
Confidence interval is for the pairwise difference of TPM minus placebo.
P-values for comparisons relative to placebo are generated by applying the Cochran-Mantel-Haenszel pair wise test between Topiramate and placebo controlling for analysis center and age group, P-values for the dose groups are the adjusted p-value according to the Hochberg multiple comparison procedure.
The p-values for the 'Any TPM' group are unadjusted.
Exact test was performed instead if the count in any cell of the contingency table was less than 5.
* indicates p-value is less than 0.05 (two-sided).
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Reviewer Comments

Table 23 shows that there was a statistically significant difference in the percentage of patients who were at least 50 % responders for 100 mg topiramate vs placebo. Although the proportion of patients who were 100 % responders was greater for 100 mg topiramate vs placebo, this treatment difference (8 %) was not statistically significant.

CAPSS-122

Proportion of Migraine Responders

The proportions of migraine responders are shown in Table 24 for the ITT population. The proportion of 50% responders in the ITT population (subjects with a 50% or more reduction in the mean monthly rate of migraine episodes from the prospective baseline period to the double-blind phase) was greater in the topiramate group (54.6%) compared to the placebo group (46.9%). These proportions were not statistically significant (p=0.396). Six subjects in the topiramate group and no subjects in the placebo group were considered 100% responders, meaning they did not experience any migraines in the double-blind phase. This difference approached statistical significance (p=0.085).

Table 24 Between-Treatment Comparison in Responder Rate (Using 48-Hour Rule): StudyCAPSS-122 (Intent-to-Treat Analysis Set)

Parameter of Efficacy Analysis	Category	Placebo (N=49)	TPM 2-3 mg/kg/day (N=108)
≥50% Responder Rate	N	49	108
	Number of Responders	24	60
	Responder Rate	49%	56%
	Difference		7%
	95% CI		(-10%, 23%)
	P-Value VS. Placebo		0.5650
100% Responder Rate	N	49	108
	Number of Responders	3	8
	Responder Rate	6%	7%
	Difference		1%
	95% CI		(-7%, 10%)
	P-Value VS. Placebo		1.0000

≥50% Responder rate is the percentage of subjects who had at least a 50% reduction in the average monthly migraine attack rate from baseline.
100% Responder rate is the percentage of subjects who had a 100% reduction in the average monthly migraine attack rate from baseline.
The difference is the treatment responder rate of TPM minus placebo.
Confidence interval is for the pairwise difference of TPM minus placebo.
P-values are based on the Cochran-Mantel-Haenszel pair wise test between Topiramate and placebo controlling for analysis center.
Exact test was performed instead if the count in any cell of the contingency table was less than 5.
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Reviewer Comments

There was a small treatment difference (7 %) in the topiramate group (vs placebo) for responders with at least a 50 % reduction in monthly migraine rate but this difference was not statistically significant. There was no noteworthy treatment difference for the proportion of 100 % responders.

6.1.6 Other Endpoints

CAPSS-122

Although this trial did not analyze results for the percentage reduction from baseline to the last 12 weeks of the double-blind phase in the final study report, the sponsor analyzed this trial for this primary efficacy endpoint for MIG-3006

The percent reduction from baseline to the last 12 weeks of the double-blind phase in average monthly migraine attack rate for the ITT analysis set of Study CAPSS-*122* is shown in Table 25.

- Baseline median values for monthly migraine attack rate were similar between the topiramate and placebo groups.
- The median monthly migraine attack rate over the last 12 weeks of the double-blind phase was lower in the topiramate group (1.67) compared with the placebo group (2.33).
- Median percent reduction was higher in the topiramate group (58.3%) compared with the

placebo group (47.6%), but there was no statistically significant difference between the groups.

Table 25 Percent Reduction from Baseline to the Last 12 Weeks of Double-Blind Phase in Average Monthly Attack Rate (Using 48-Hour Rule): Study CAPSS-122 (Intent-to-Treat Analysis Set)

Category	Placebo (N=49)	TPM 2-3 mg/kg/day (N=108)
Baseline		
N	49	108
Median (Range)	4.00 (3.0;8.0)	4.00 (1.0;8.0)
Last 12 Weeks of Double-Blind Phase		
N	49	108
Median (Range)	2.33 (0.0;9.3)	1.67 (0.0;10.2)
Percent Reduction (%)		
N	49	108
Median (Range)	47.62 (-133.3;100.0)	58.33 (-273.3;100.0)
P-value VS. Placebo		0.2491

Percent reduction is the difference between values at baseline and last 12 weeks of Double-Blind Phase, divided by value at baseline, times 100.
P-values for comparisons relative to placebo are generated by applying an ANCOVA model on ranks that includes treatment group and analysis center as factors, and monthly migraine attack rate during baseline period as a covariate.
* indicates p-value is less than 0.05 (two-sided).
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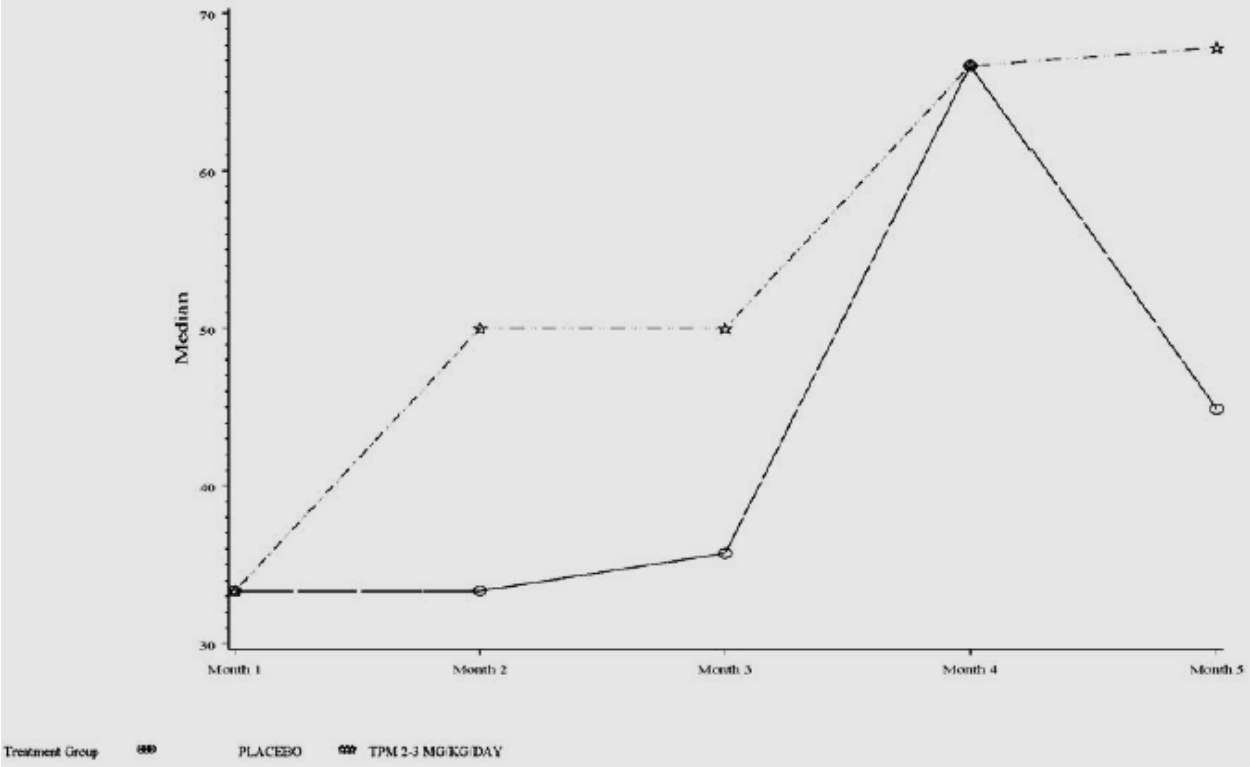
Monthly Percent Reduction Over Time

The monthly percent reduction over time in average monthly migraine attack rate for the ITT analysis set of Study CAPSS-122 is shown in Figure 8.

- The topiramate group showed a general trend towards an increasingly higher percent reduction in average monthly migraine attack rate with longer treatment duration, while the percent reduction in the placebo group was smaller than in the topiramate groups and remained relatively constant over time (except for a spike at Month 4).

- There were no statistically significant differences between topiramate and placebo at any monthly time point.

Figure 8 Monthly Percent Reduction Over Time in Average Monthly Migraine Attack Rate Using 48 Hour Rule: Study CAPSS-122 (Intent-to-Treat Analysis Set)



Reviewer Comments

The median % reduction in monthly migraine rate was only slightly greater for topiramate (58 %) than that for placebo (48 %) (Table 25) in CAPSS-122. This small difference was not statistically significant.

Figure 8 illustrates the pattern of the percentage reduction from baseline in monthly migraine rate over time (5 months). Although the topiramate group shows a generally progressively increasing percentages over time, the placebo groups shows relatively stable percentage reductions between months 1-3 and then a large increase at month 4 and a relatively large decrease at the final month (month 5). Over the whole trial, there appear to be noteworthy numerical differences (suggesting benefit of topiramate) at months 2,3, and 5.

6.1.7 Subpopulations

The following tables are the sponsor's summary tables for MIG-3006 and CAPSS-122 for the primary efficacy endpoints for each trial for subgroups/subpopulations according to age and gender.

Table 26 **Summary of Percent Reduction from Baseline to the Last 12 Weeks of the Double-Blind Phase in Average Monthly Migraine Attack Rate Using 48-Hour Rule, by Age Group: Studies TOPMAT-MIG-3006, and CAPSS-122, (Intent-to-Treat Analysis Set)**

		TOPMAT-MIG-3006			CAPSS-122		
		6-11 yr	12-17 yr	All	6-11 yr	12-17 yr	All
Placebo	N		33	33	31	18	49
	Median		44.44	44.44	46.43	50.85	47.62
	Range		(-36.4;100.0)	(-36.4;100.0)	(-37.5;100.0)	(-133.3;100.0)	(-133.3;100.0)
TPM 2-3 mg/kg/day	N				59	49	108
	Median				52.38	66.67	58.33
	Range				(-103.6;100.0)	(-273.3;100.0)	(-273.3;100.0)
TPM 50 mg/day	N		35	35			
	Median		44.64	44.64			
	Range		(-125.0;100.0)	(-125.0;100.0)			
TPM 100 mg/day	N		35	35			
	Median		72.22	72.22			
	Range		(0.0;100.0)	(0.0;100.0)			
TPM 200 mg/day	N						
	Median						
	Range						
Any TPM	N		70	70	59	49	108
	Median		63.69	63.69	52.38	66.67	58.33
	Range		(-125.0;100.0)	(-125.0;100.0)	(-103.6;100.0)	(-273.3;100.0)	(-273.3;100.0)

Table 27 **Summary of Change from Baseline to the Last 12 Weeks of the Double-Blind Phase in Average Monthly Migraine Attack Rate Using 48-Hour Rule, by Age Group: Studies TOPMAT-MIG-3006, and CAPSS-122 (Intent-to-Treat Analysis Set)**

		TOPMAT-MIG-3006			CAPSS-122		
		6-11 yr	12-17 yr	All	6-11 yr	12-17 yr	All
Placebo	N		33	33	31	18	49
	Mean(SD)		-1.72(1.759)	-1.72(1.759)	-2.01(1.555)	-1.66(2.375)	-1.88(1.881)
TPM 2-3 mg/kg/day	N				59	49	108
	Mean(SD)				-1.90(1.878)	-2.21(2.088)	-2.04(1.972)
TPM 50 mg/day	N		35	35			
	Mean(SD)		-1.71(2.008)	-1.71(2.008)			
TPM 100 mg/day	N		35	35			
	Mean(SD)		-2.95(1.455)	-2.95(1.455)			
TPM 200 mg/day	N						
	Mean(SD)						
Any TPM	N		70	70	59	49	108
	Mean(SD)		-2.33(1.849)	-2.33(1.849)	-1.90(1.878)	-2.21(2.088)	-2.04(1.972)

Table 28 **Summary of Percent Reduction from Baseline to the Last 12 Weeks of the Double-Blind Phase in Average Monthly Migraine Attack Rate Using 48-Hour Rule, by Sex: Studies TOPMAT-MIG-3006, and CAPSS-122 (Intent-to-Treat Analysis Set)**

		TOPMAT-MIG-3006			CAPSS-122		
		Male	Female	All	Male	Female	All
Placebo	N	12	21	33	26	23	49
	Median	61.71	39.58	44.44	56.94	33.33	47.62
	Range	(-33.3;100.0)	(-36.4;100.0)	(-36.4;100.0)	(-37.5;100.0)	(-133.3;100.0)	(-133.3;100.0)
TPM 2-3 mg/kg/day	N				55	53	108
	Median				46.67	67.86	58.33
	Range				(-273.3;100.0)	(-64.7;100.0)	(-273.3;100.0)
TPM 50 mg/day	N	10	25	35			
	Median	61.11	44.64	44.64			
	Range	(-125.0;100.0)	(-69.7;100.0)	(-125.0;100.0)			
TPM 100 mg/day	N	18	17	35			
	Median	66.67	73.33	72.22			
	Range	(0.0;100.0)	(28.2;100.0)	(0.0;100.0)			
TPM 200 mg/day	N						
	Median						
	Range						
Any TPM	N	28	42	70	55	53	108
	Median	66.67	58.80	63.69	46.67	67.86	58.33
	Range	(-125.0;100.0)	(-69.7;100.0)	(-125.0;100.0)	(-273.3;100.0)	(-64.7;100.0)	(-273.3;100.0)

Table 29 **Summary of Change from Baseline to the Last 12 Weeks of the Double-Blind Phase in Average Monthly Migraine Attack Rate Using 48-Hour Rule, by Sex: Studies TOPMAT-MIG-3006, and CAPSS-122 (Intent-to-Treat Analysis Set)**

		TOPMAT-MIG-3006			CAPSS-122		
		Male	Female	All	Male	Female	All
Placebo	N	12	21	33	26	23	49
	Mean(SD)	-2.47(1.918)	-1.29(1.548)	-1.72(1.759)	-2.19(1.677)	-1.53(2.070)	-1.88(1.881)
TPM 2-3 mg/kg/day	N				55	53	108
	Mean(SD)				-1.69(2.046)	-2.41(1.841)	-2.04(1.972)
TPM 50 mg/day	N	10	25	35			
	Mean(SD)	-1.84(2.479)	-1.66(1.844)	-1.71(2.008)			
TPM 100 mg/day	N	18	17	35			
	Mean(SD)	-2.48(1.209)	-3.45(1.559)	-2.95(1.455)			
TPM 200 mg/day	N						
	Mean(SD)						
Any TPM	N	28	42	70	55	53	108
	Mean(SD)	-2.25(1.751)	-2.39(1.930)	-2.33(1.849)	-1.69(2.046)	-2.41(1.841)	-2.04(1.972)

Reviewer Comments

- *The sponsor age subgroup tables for Study MIG-3006 showed results for adolescents 12-17 years old, the same age range for all patients enrolled in this trial.*

  However, Dr. Massie (Agency Statistical Reviewer) conducted age subgroup analyses according to the 3 ages subgroups. There were 45 patients in the 12-< 15 yo subgroup, 44 patients in the 15-17 yo subgroup, and 3 patients in the > 17 yo subgroup. The treatment difference for mean and median percent reduction for the 100 mg topiramate dose vs placebo suggested relatively similar efficacy of that dose for the 2 youngest subgroups. There was no suggestion of efficacy in the oldest subgroup that consisted of only 3 patients in 2 treatment groups. A test for a differential treatment effect by Age group did not reveal a significant effect comparing the 2 youngest age subgroups.

- *Table 26 and Table 27 show age subgroup results for CAPSS-122 patient according to 6-11 and 12-17 yo age subgroups for both efficacy endpoints. Table 26 shows a treatment difference (topiramate % – placebo %) for median percentage reduction of monthly migraine rate of 16 % for the older subgroup and 6 % for the younger subgroup. Table 27 shows that the treatment difference for topiramate for the mean change from baseline in monthly migraine rate is almost – 0.5 in the 12-17 yo subgroup and non-existent in the younger subgroup. It is difficult to explain these observations that suggest topiramate efficacy in females but not in males*

- *Table 28 and Table 29 show gender subgroup results for both efficacy endpoints for CAPSS-122 patients. There were similar numbers of male and female patients. Although there was no suggestion of treatment benefit for topiramate for either endpoint in males, there was a suggestion of noteworthy numerical efficacy in females. The treatment difference for topiramate (vs placebo) in females was 34 % for median % reduction from baseline in monthly migraine rate and – 0.9 for mean change from baseline for monthly migraine rate. It is difficult to explain these observations that suggest topiramate efficacy in females but not in males.*

The primary statistical reviewer (Dr. Massie) also conducted subgroup/subpopulation analyses for the primary efficacy endpoint for the *key pivotal trial, MIG-3006, according to race (Table 29) and geographic region (Table 30). Results of these analyses are presented here.*

Eighty five percent (85%) of randomized subjects were white, 11% were black, and 4% were 'other'. A test for a differential treatment effect by Race was not significant, p=.5980. A second categorization pooling the two small groups resulting in a white vs other comparison also did not reveal a significant difference in any treatment groups by race, p=.4677.

Table 30 **Percent Reduction in Monthly Migraine Rate Over Last 12 Weeks According to Race for Study MIG-3006**

	Race												All
	BLACK				OTHER				WHITE				
	% Reduction in Monthly Migraine Attack Rate				% Reduction in Monthly Migraine Attack Rate				% Reduction in Monthly Migraine Attack Rate				
	N	Mean	Median	StdErr	N	Mean	Median	StdErr	N	Mean	Median	StdErr	N
Treatment Group													
Placebo	4	48.3	46.7	11.4	0	.	.	.	29	41.4	44.4	8.4	33
TPM 100 mg/day	5	90.8	88.9	2.4	2	83.3	83.3	16.7	28	65.5	66.7	4.8	35
TPM 50 mg/day	2	50.0	50.0	50.0	2	-7.5	-7.5	59.2	31	35.7	44.6	9.7	35
All	11	68.0	86.7	10.2	4	37.9	59.2	36.3	88	47.1	56.2	4.8	103

Table 31 **Percent Reduction in Monthly Migraine Rate Over Last 12 Weeks According to Geographic Region for Study MIG-3006**

	Pooled Center												All
	ARGENTINA+BRAZIL				EUROPE+ISRAEL				UNITED STATES OF AMERICA				
	% Reduction in Monthly Migraine Attack Rate				% Reduction in Monthly Migraine Attack Rate				% Reduction in Monthly Migraine Attack Rate				
	N	Mean	Median	StdErr	N	Mean	Median	StdErr	N	Mean	Median	StdErr	N
Treatment Group													
Placebo	10	49.1	52.2	12.4	15	33.1	33.3	12.1	8	51.1	51.6	15.1	33
TPM 100 mg/day	11	80.0	86.7	5.4	11	67.6	66.7	6.5	13	64.0	66.7	8.7	35
TPM 50 mg/day	9	38.8	63.1	25.1	16	37.8	33.3	10.8	10	23.8	48.1	18.0	35
All	30	57.3	67.3	9.1	42	43.9	46.4	6.4	31	47.7	58.7	8.2	103

Reviewer Comments

- *It is difficult to make much of the subgroup analysis for race because the vast majority of patients (85 %) were Caucasian, and only 11 % were Black and 4 % were "other" racial groups. As expected the result for the 100 mg group for Caucasians essentially reflected the overall result of all patients for that dose (Table 30). The mean and median percent reduction in monthly migraine rate in Black and "other" racial patients in the 100 mg topiramate group was numerically greater than mean and median percent reduction in that dose for Caucasian patients tending to support the view that topiramate is effective in all these races. The statistical test for differential treatment effect did not suggest any difference.*

  Dr. Massie also noted that a second categorization pooling the two small groups (Black and other) resulting in a white vs other comparison also did not reveal a significant difference in any treatment groups by race, p=.4677.

- *The distribution of patients was relatively evenly divided amongst 3 geographic regions (U.S., Brazil and Argentina, and Europe plus Israel). The treatment difference for mean and median percent reduction for the 100 mg topiramate dose vs placebo suggested relatively similar efficacy of that dose for all 3 regions (Table 31). The statistical test for differential treatment effect did not suggest any difference.*

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The following is the sponsor's analysis of clinical information relevant to dosing recommendations.

This section provides a summary of the data that pertain to the dose-response relationships for effectiveness, based on the results of the analyses of the key efficacy endpoints across study groups, the subgroup analyses for age and sex, and the sensitivity analyses. Taken together, the findings presented provide support for the dosage selection for prophylaxis of migraine in children $\geq$ 12 years of age, i.e., 100 mg/day.

The recommended total daily maintenance dosage is 100 mg/day, administered in 2 divided doses. The recommended titration rate for topiramate to 100 mg/day is shown in the Titration Schedule below (Table 32). The starting dosage is 25 mg/day, dosed in the evening. Dosage and titration rate should be guided by clinical outcome. If required, a longer interval between dosage adjustments can be used.

Table 32 Titration Schedule for Topiramate Maintenance Dosage (100 mg/day)

	Target Dosage: 100 mg/day		
Week	Dosage (mg/day)	Morning Dose (mg)	Evening Dose (mg)
1	25	0/0	25/0
2	50	25/0	25/0
3	75	25/0	25/25
4	100	25/25	25/25

Source: Table 2 of TOPMAT-MIG-3006 Clinical Study Report (Mod5.3.5.1/TOPMAT-MIG-3006).

In addition, this section includes a brief summary of the conclusions on dosing recommendations derived from a comparison of the blood-level data available from adolescent subjects in Studies TOPMAT-MIG-3006 and TOPMAT-MIGR-001/002/003 with blood level data from adults.

Key Efficacy Endpoints

In Study TOPMAT-MIG-3006, the pivotal study supporting the proposed indication of prophylaxis of migraine in children ≥ 12 years of age, the 100 mg/day dosage group (ITT population) demonstrated a consistent, statistically significant effect (compared with placebo) for the key efficacy endpoints of percent reduction in the average monthly migraine attack rate (baseline to the last 12 weeks of the double-blind phase), change in the average monthly migraine attack rate (baseline to the last 12 weeks of the double-blind phase), and ≥ 50% responder rate. There was clear separation between the 100 mg/day group and the 50 mg/day and placebo groups in the magnitude of the effects of each dosage on each of these 3 endpoints :

- Percent reduction (median) in the average monthly migraine attack rate: 72%, 45%, and 44% in the 100 mg/day, 50 mg/day, and placebo groups, respectively
- Change (mean) in the average monthly migraine attack rate: -2.95, -1.71, and -1.72 in the 100 mg/day, 50 mg/day, and placebo groups, respectively
- ≥ 50% responder rate: 83%, 46%, and 45% in the 100 mg/day, 50 mg/day, and placebo groups, respectively

In general, there was a separation from placebo for the 100 mg/day dosage at Month 1, with a statistically significant difference from placebo by Month 4 for mean change in average monthly migraine attack rate, and by Month 3 for the other 2 parameters.

In addition, an analysis of the percent reduction of average monthly migraine attack rate from baseline to the last 28 days of the double-blind phase showed clear separation between the 100 mg/day group and the 50 mg/day and placebo groups, and a statistically significant difference from placebo for the 100 mg/day group (100%, 66%, and 61% in the 100 mg/day, 50 mg/day, and placebo groups, respectively).

While there was a quantitative difference in the 100% responder rate between the 3 dosage groups (20%, 14%, and 12% in the 100 mg/day, 50 mg/day, and placebo groups, respectively), the differences did not reach statistical significance.

For all of the parameters described above, the results for the completer population were generally comparable, both qualitatively and quantitatively.

Additional support for the effectiveness of the 100 mg/day dosage comes from the results of Study CAPSS-122 and the pooled data from adolescent subjects from Studies TOPMAT-MIGR-001/002/003. In Study CAPSS-122, which used a flexible, weight-dependent dosage regimen targeted at 2-3 mg/kg/day, subjects received actual average daily dosages (mean and median) similar to those in the 100 mg/day groups of Study TOPMAT-MIG-3006 and TOPMAT-MIGR-001/002/003. While the topiramate group in Study CAPSS-122 did not show a statistically significant effect compared with placebo, topiramate-treated subjects did demonstrate a quantitatively greater median percent reduction in the average monthly migraine attack rate from baseline to the last 12 weeks of the double-blind phase (58% vs. 48%) and greater mean change (reduction) in the average monthly migraine attack rate from baseline to the last 12 weeks of the double-blind phase (-2.04 vs. -1.88), and a higher > 50 % responder rate (56% vs. 49%).

In the pooled dataset of adolescent subjects from Studies TOPMAT-MIGR-001/002/003, there was no clear dose-response among the 3 topiramate dosages tested, and none demonstrated a statistically significant effect vs. placebo. However, the assessment of dose-response was limited by the smaller number of subjects in each dosage group compared with the other study groups. All 3 dosages did demonstrate quantitatively different effects from placebo on the key endpoints. In particular, consistent with the other study groups, the 100 mg/day group showed a greater effect than did placebo for median percent reduction in the average monthly migraine attack rate from baseline to the last 12 weeks of the double-blind phase (75% vs. 37%), greater mean change in the average monthly migraine attack rate from baseline to the last 12 weeks of the double-blind phase (-3.22 vs. -0.77), and higher $\geq$ 50% responder rate (69% vs. 33%). These results were generally comparable for the ITT and completer datasets.

Age
Across the 3 study groups, subjects 12 to 17 years of age in the topiramate 100 mg/day group (and the 2-3 mg/kg/day group in Study CAPSS-122) demonstrated comparable results for the key endpoints. In Study CAPSS-122, which enrolled subjects down to 6 years of age, the older age group (12 to 17 years of age) had a greater median percent reduction in the average monthly migraine attack rate (baseline to the last 12 weeks of the double-blind phase), greater mean change (reduction) in the average monthly migraine attack rate (baseline to the last 12 weeks of the double-blind phase), and a higher $\geq$ 50% responder rate, compared with the younger age group (6 to 11 years of age). The 100% responder rate was higher in the younger age group than in the older age group. These results were generally comparable for the ITT and completer datasets.

Sex
In Study TOPMAT-MIG-3006, both sexes demonstrated a dose-response for the median percent reduction in the average monthly migraine attack rate (baseline to the last 12 weeks of the double-blind phase), mean change in the average monthly migraine attack rate (baseline to the last 12 weeks of the double-blind phase), and $\geq$ 50% responder rate. The separation between dosages was more pronounced in female subjects for median percent reduction and mean change from baseline. At the 100 mg/day dosage, the results for these endpoints were generally

comparable between the sexes. Overall, results were generally comparable for the ITT and completer datasets.

There was no consistent pattern favoring one sex over the other for the topiramate treatment groups in CAPSS-122 or TOPMAT-MIGR-001/002/003. Consistently across the 3 study groups, male subjects had a greater median percent reduction from baseline to the last 12 weeks of the double-blind phase in average monthly migraine attack rate (48-hour rule), a greater change from baseline to the last 12 weeks of the double-blind phase in average monthly migraine attack rate (48-hour rule), and a higher $\geq$ 50% responder rate than female subjects in the placebo group.

Sensitivity Analysis
The results of the sensitivity analysis demonstrated that the 100 mg/day dosage in Study TOPMAT-MIG-3006 was effective under other selected analysis conditions for median percent reduction in the average monthly migraine attack rate (baseline to the last 12 weeks of the double-blind phase), mean change in the average monthly migraine attack rate (baseline to the last 12 weeks of the double-blind phase), and $\geq$ 50% responder rate. In particular, a statistically significant effect after multiple comparison adjustment was noted for each of these endpoints with 3 combinations of analysis conditions :

- 48-hour rule, last 12 weeks of the double-blind phase, baseline migraine attacks/month $\geq$ 3
- 24-hour rule, last 12 weeks of the double-blind phase, baseline migraine attacks/month $\geq$ 1
- 24-hour rule, last 12 weeks of the double-blind phase, baseline migraine attacks/month $\geq$ 3

These results were generally comparable for the ITT and completer datasets.

Topiramate Plasma Concentration Data
There were no new studies performed to evaluate level-response relationships in the pediatric population. Existing data from the 3 adult migraine studies (TOPMAT-MIGR-001, TOPMATMIGR- 002, and TOPMAT-MIGR-003) submitted in the NDA for migraine prophylaxis in adults (NDAs 20-505/S-022 and 20-844/S-019/Item 8/ISE: Topiramate Prophylaxis for Migraine Headache) showed no consistent relationship between the efficacy of topiramate in reducing the average monthly migraine period rate and the average final plasma concentration of topiramate. A pooled analysis of plasma concentration data from pediatric subjects in migraine prophylaxis clinical Studies TOPMAT-MIGR-001, TOPMAT-MIGR-002, TOPMAT-MIGR-003, and TOPMAT-MIG-3006 is shown in Table 33. Topiramate plasma levels were not obtained in Study CAPSS 122. In general, the plasma levels in pediatric subjects were similar across age groups at dosages of 100 and 200 mg/day, and comparable to maximum plasma concentration (Cmax) values in healthy adults administered these dosages. Because there were no differences in mean topiramate plasma concentrations among age groups ranging from 12 years to adults (18 years and older), dosage adjustment based on age may not be necessary.

Table 33 **Mean (%CV) Plasma Topiramate Concentrations (µg/mL) by Treatment Group: Studies TOPMAT-MIGR-001, TOPMAT-MIGR-002, TOPMAT-MIGR-003, TOPMAT-MIG-3006**

Age Group	50 mg/day (25 mg every 12 hours)	100 mg/day (50 mg every 12 hours)	200 mg/day (100 mg every 12 hours)
12 to 14 years	n=21	n=28	n=14
	BQL	2.78	5.17
		(69.4)	(40.4)
15 to 17 years	n=12	n=19	n=9
	BQL	2.29	5.80
		(103.9)	(28.8)
18 years and older	n=133	n=529	n=488
	2.46	3.68	5.00
	(18.0)	(28.4)	(42.2)

BQL: Below the Quantification Limit (0.01, 2.00, or 2.01 µg/mL)

Table 34 Summary of Daily Treatment Dosage in Milligrams for the Pooled Double-Blind Migraine Prophylaxis Studies (Average includes Titration Period)

	2-3 mg/kg/d	50 mg/d	100 mg/d	200 mg/d	Any TPM
Average Daily Dosage, mg					
All subjects					
N	108	46	48	13	215
Mean	79.12	42.28	75.64	137.08	73.97
Standard deviation	32.778	9.192	18.465	39.200	34.465
Median	72.63	45.35	80.47	149.31	70.83
Minimum	11.3	1.6	14.0	56.7	1.6
Maximum	160.1	48.8	94.2	172.8	172.8
Age 6-11 years					
N	59	-	-	-	59
Mean	66.47	-	-	-	66.47
Standard deviation	29.321	-	-	-	29.321
Median	62.77	-	-	-	62.77
Minimum	11.3	-	-	-	11.3
Maximum	141.2	-	-	-	141.2
Age 12-17 years					
N	49	46	48	13	156
Mean	94.34	42.28	75.64	137.08	76.80
Standard deviation	30.384	9.192	18.465	39.200	35.900
Median	95.32	45.35	80.47	149.31	75.91
Minimum	21.3	1.6	14.0	56.7	1.6
Maximum	160.1	48.8	94.2	172.8	172.8
Maximum Daily Dosage, mg					
All subjects					
N	- [b]	46	48	13	107
Mean	- [b]	50.54	96.88	182.69	87.38
Standard deviation	- [b]	8.315	16.000	38.709	45.346
Median	- [b]	50.00	100.00	200.00	100.00
Minimum	- [b]	25.0	25.0	75.0	25.0
Maximum	- [b]	75.0	125.0	200.0	200.0
Age 6-11 years					
N	- [b]	-	-	-	-
Age 12-17 years					
N	- [b]	46	48	13	107
Mean	- [b]	50.54	96.88	182.69	87.38
Standard deviation	- [b]	8.315	16.000	38.709	45.346
Median	- [b]	50.00	100.00	200.00	100.00
Minimum	- [b]	25.0	25.0	75.0	25.0
Maximum	- [b]	75.0	125.0	200.0	200.0
Minimum Daily Dosage, mg					
All subjects					
N	- [b]	46	48	13	107
Mean	- [b]	13.04	14.58	11.54	13.55
Standard deviation	- [b]	12.626	12.456	12.972	12.514
Median	- [b]	25.00	25.00	0.00	25.00
Minimum	- [b]	0.0	0.0	0.0	0.0
Maximum	- [b]	25.0	25.0	25.0	25.0
Age 6-11 years					
N	- [b]	-	-	-	-
Age 12-17 years					
N	- [b]	46	48	13	107
Mean	- [b]	13.04	14.58	11.54	13.55
Standard deviation	- [b]	12.626	12.456	12.972	12.514
Median	- [b]	25.00	25.00	0.00	25.00
Minimum	- [b]	0.0	0.0	0.0	0.0
Maximum	- [b]	25.0	25.0	25.0	25.0

[a] Included Study CAPSS-122, Study TOPMAT-MIG-3006, and adolescents (aged 12-17 years) from Studies TOPMAT-MIGR-001, -002, and -003.

[b] Maximum and minimum daily dosages were not available in Study CAPSS-122, the only migraine prophylaxis study with subjects aged 6-11 years.

Table 35 Summary of Treatment Dosage in Milligrams for the Pooled Open-Label Migraine Prophylaxis Studies

	---------- Any Topiramate ----------		
	All Subjects	Age 6-11 Years	Age 12-17 Years
Average Daily Dosage, mg			
N	158	66	92
Mean	95.25	71.18	112.52
Standard deviation	47.658	31.383	49.934
Median	87.71	68.33	106.40
Minimum	0.0	1.2	0.0
Maximum	204.7	177.0	204.7
Maximum Daily Dosage,[b] mg			
N	36	-	36
Mean	152.78	-	152.78
Standard deviation	72.648	-	72.648
Median	187.50	-	187.50
Minimum	0.0	-	0.0
Maximum	300.0	-	300.0
Minimum Daily Dosage,[b] mg			
N	36	-	36
Mean	20.83	-	20.83
Standard deviation	33.004	-	33.004
Median	0.00	-	0.00
Minimum	0.0	-	0.0
Maximum	100.0	-	100.0

[a] Included Study CAPSS-122 and adolescents (aged 12-17 years) from Studies TOPMAT-MIGR-001 and -002.
[b] Maximum and minimum daily dosages were not available in Study CAPSS-122, which was the only migraine prophylaxis study with subjects aged 6-11 years and the only study with mg/kg dosing.

Trial CAPSS-122 did not collect data for the minimal and maximal daily doses of topiramate used. However, baseline weight data were provided for all patients and those who were 6-11 yo and 12-17 yo. Based upon baseline weight data for CAPSS-122 and the fact that the target for maintenance dosing was 2-3 mg/kg, Table 36 show the projected range of dosing in the maintenance period for all patient.

Table 36 Projected Daily Topiramate Dosing in Maintenance Period of CAPSS-122 for Pediatric Patient Weight and Targeted Dosing 2-3 Mg/Kg/Day

Patients	Weight	Mg of Daily Topiramate Dosing (2-3 mg/kg)
All Patients (N=108)		
Mean	51	102-153
Median	47	94-141
Minimum	22	44-66
Maximum	150	300-450
6-11 Years (N=59)		
Mean	39	78-117
Median	35	70-105
Minimum	22	44-66
Maximum	91	182-273
12-17 Years (N=49)		
Mean	65	130-195
Median	55	110-165
Minimum	31	62-93
Maximum	150	300-450

Table 37 shows that the mean and median daily dose of topiramate in CAPSS-122 for all pediatric patients was approximately 100 mg and that the maximal daily dose was 200 mg.

Table 37 Summary of Computed and Reported Daily Topiramate Dosage Maintenance Period for Topiramate-Treated Patients in CAPSS-122

	Computed	Reported[c]
n[d]	93	102
Mean	99.6	109.1
Median	95.4	100.0
SD	40.88	47.43
Min, Max	(31.7, 199.4)	(15.0, 200.0)

Reviewer Comments

- *In the first part of this section, the sponsor outlined its views supporting dosing recommendations (100 mg topiramate daily; 50 mg BID) in adolescent patients (12-17 yo) for migraine prophylaxis. In the latter part of this section, I have provided several tables regarding dose in the topiramate trials of pediatric patients for migraine prophylaxis. Initially, I will discuss the tables that I have inserted.*

- *Table 34 shows various descriptive statistics for the daily treatment dosage of different topiramate doses for the pooled placebo-controlled migraine prophylaxis trials (MIG-3006, CAPSS-122, MIG-1-3). For the maximal daily dose of the 100 mg dose group for all patients and for adolescents (12-17 yo), the mean is 97 mg and the median dose is 100 mg. For the average daily dose of the 100 mg dose group for all patients and for adolescents (12-17 yo), the mean dose is 76 mg and the median dose is 80 mg. In considering the average daily dose, it is important to recall that this computation includes the titration period (that occurred over several weeks in all the trials) making it impossible for the average dose to be 100 mg because of the lower daily topiramate dose in the first several weeks of each trial.*

- *Table 35 shows descriptive statistics for the treatment dosage of topiramate in the pooled open-label trials for all patients (6-17 yo) and patients in each age subgroup (6-11 yo and 12-17 yo). In considering the daily topiramate dosage for longer-term safety data, the average daily dose for all patients was 95 mg and the median daily dose was 88 mg. In all patients and in adolescents, the mean maximal daily dose was 153 mg and the median daily dose was 188 mg. In adolescents (12-17 yo), the average daily dose was 113 mg and the median daily dose was 106 mg. These data support the observation that topiramate dosing in the open-label trials was essentially at and above the daily recommended dose (100 mg daily) for adolescents for migraine prophylaxis . Consequently safety data collected in these trials are relevant for helping support the safety of the recommended daily dose based upon longer term treatment than the relatively shorter treatment periods in the placebo-controlled trials.*

- *Table 36 shows the projected topiramate dosing in the maintenance period of CAPSS-122 for pediatric patients (including by age subgroups) when the targeted topiramate dose was 2-3 mg/kg/day. For all patients, the mean ranged from 102-153 mg, the median ranged from 94-141 mg, and the maximum ranged from 300-450 mg. For adolescent patients (12-17 yo), the mean ranged from 130-195 mg, the median ranged from 110-165 mg, and the maximum ranged from 300-450 mg. The exposures that were for the most part at or above the daily recommended dose of 100 mg supports the safety data collected in CAPSS-122 as being relevant to the safety of the recommended daily dose of topiramate. Considering that most adolescent patients in this trial received a daily dose of 100 mg or greater in the maintenance period but did not show statistically significant efficacy, this observation argues against the likelihood that greater efficacy might have been demonstrated if patients in MIG-3006 had also been treated with a higher dose than*

100 mg daily. This is not surprising in view of the fact that the adult migraine prophylaxis trials did not show greater efficacy for the primary efficacy endpoint with a 200 mg daily dose compared to a 100 mg daily dose. In fact, the efficacy of 100 mg and 200 and dose groups were similar but there was increased toxicity in patients treated with 200 mg compared to that in patients treated with 100 mg.

- *Table 37 summarizes results for computed and reported daily topiramate dosage in the maintenance period for topiramate-treated patients in CAPSS-122. The mean and median computed dose was near 100 mg and relatively close to the mean and median reported dose.*

- *I agree with the sponsor's conclusion that 100 mg is an appropriate recommended dose for adolescent for migraine prophylaxis. I base my conclusion on the fact that 100 mg was the only effective dose for prophylaxis of migraine in MIG-3006 for the primary efficacy endpoint and the key secondary efficacy endpoint and all the sponsor's arguments and presentation in the first part of this section.*

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No analyses were performed for persistence of efficacy or tolerance due to lack of sufficient long-term efficacy data in adolescent subjects.

6.1.10 Additional Efficacy Issues/Analyses

The following outlines my initial request for multiple sensitivity analyses to assess the influence of multiple variables on the treatments and particularly the treatment difference/effect (topiramate – placebo) for several efficacy endpoints in the pediatric migraine controlled trials. Following the description of the sensitivity analyses conducted is the sponsor's summary interpretation of these analyses.

DNP Requests for Sensitivity Analyses

On 28 May 2013, Janssen Research & Development (JRD) submitted to the Food and Drug Administration (FDA) a supplemental New Drug Applications (sNDA) seeking a new indication for TOPAMAX (topiramate) tablets (NDA 20-505) and sprinkle capsules (NDA 20-844) for use in adolescents 12 years of age and older for the prophylaxis of migraine headache. In follow-up to the sNDA submission, the FDA requested additional efficacy analyses and this response document addresses those requests.

Request 1
During the period from 3 June to 11 June 2013, FDA requested and JRD agreed to provide a more comprehensive presentation for the existing sensitivity analyses (which covered the entire double-blind [DB] phase and the last 12 weeks of the DB phase) in the Integrated Summary of

Efficacy (ISE) dated 9 May 2013. This request is summarized as follows:

- New tables with inclusion of data for placebo, each randomized topiramate target dose group, and the "any" topiramate dose group were requested.
- The tables would be produced for the following 5 individual study datasets:
    - TOPMAT-MIG-3006
    - CAPSS-122 - all subjects
    - CAPSS-122 - subjects age 6 to 11 years old
    - CAPSS-122 - subjects age 12 to 17 years old
    - TOPMAT-MIGR-001/002/003

    Analyses for both the intent-to-treat (ITT) and completer datasets were to be provided (ITT observed case dataset was not required).

Request 2

During the period from 4 June to 11 June 2013, FDA requested and JRD agreed to provide additional sensitivity analyses on the efficacy data for treatment during the last 28 days of the study. This request is summarized as follows:

- Sensitivity analyses that would include the period from baseline to the last 28 days of treatment in the DB phase (as done for other sensitivity analyses previously conducted for the entire DB phase and for the last 12 weeks of the DB phase) were to be submitted for the following 4 efficacy endpoints:
    - Percent reduction in average monthly migraine attack rate
    - Change from baseline in average monthly migraine attack
    - 50% responder rate (>50% reduction in average monthly migraine attack rate)
    - 100% responder rate (100% reduction in average monthly migraine attack rate)

    The analyses for the 4 efficacy endpoints were to be conducted according to the following combination of parameters (as previously done for the other sensitivity analyses):
    - 48-hour rule, last 28 days, with International Headache Society (IHS) criteria, baseline migraine frequency ≥1
    - 48-hour rule, last 28 days, with IHS criteria, baseline migraine frequency ≥3
    - 48-hour rule, last 28 days, without IHS criteria, baseline migraine frequency ≥1
    - 48-hour rule, last 28 days, without IHS criteria, baseline migraine frequency ≥3
    - 24-hour rule, last 28 days, with IHS criteria, baseline migraine frequency ≥1
    - 24-hour rule, last 28 days, with IHS criteria, baseline migraine frequency ≥3
    - 24-hour rule, last 28 days, without IHS criteria, baseline migraine frequency ≥1
    - 24-hour rule, last 28 days, without IHS criteria, baseline migraine frequency ≥3

    The analyses were to be conducted for the following 5 individual study datasets:
    - TOPMAT-MIG-3006
    - CAPSS-122 - all subjects
    - CAPSS-122 - subjects age 6 to 11 years old
    - CAPSS-122 - subjects age 12 to 17 years old
    - TOPMAT-MIGR-001/002/003

Analyses for both the ITT and completer datasets were to be provided (ITT observed case dataset was not required).
The analyses were to show all treatments for each respective analysis (ie, placebo, each randomized topiramate target dose, and any topiramate dose group) on the same page, presenting baseline results, results for the last 28 days of treatment, change from baseline (for percent migraine frequency reduction change from baseline and migraine frequency rate change from baseline) for each treatment, treatment difference from placebo for each topiramate dose and any topiramate dose, and respective p-values for all treatment comparisons.

A summary interpretation of these analyses/results was to be prepared for the last 28 days of treatment for comparison with the results of the sensitivity analyses for the entire DB phase and for the last 12 weeks of the DB phase for each of the 5 study datasets. Interpretation of results for each tabular analysis was not considered to be necessary; but instead, the sponsor's interpretation of whether these additional sensitivity analyses provided new information not suggested by the sensitivity analyses already submitted and what the results suggest/support.

Sponsor Summary Interpretation Of Sensitivity Analyses/Results
The results of the sensitivity analyses for each of the 4 efficacy endpoints are described for the ITT analysis set because the results for the completer analysis set were not substantively different from the results for the ITT set. Where provided in the summary text, data are presented in ranges bracketed by the lowest and highest values obtained from analysis of each combination of 24- or 48-hour rule, with or without IHS algorithm, and baseline migraine frequency of ≥3 or ≥1 for the particular endpoint. The results (ranges) for the entire DB phase, which included both the titration and maintenance periods for each study, were generally lower than the results noted for either the last 28 days of treatment or the last 12 weeks of the DB phase, as would be expected if the largest proportion of the change observed for each of the 4 efficacy endpoints had occurred during the period when subjects were on stable doses of topiramate, and thus these results are not discussed further in the summary.

Percent Reduction in Average Monthly Migraine Attack Rate From Baseline to the Last 28 Days of Treatment of the DB Phase (ITT)

Study TOPMAT-MIG-3006

- The percent reduction in average monthly migraine attacks with topiramate was higher in the last 28 days of treatment than in the last 12 weeks of the DB phase at both the 50 mg dose (64.1%-86.2% vs 4.6%-66.7%, respectively) and the 100 mg dose (90.0%-100.0% vs 65.1%-77.3%, respectively).

- Statistically significant differences between topiramate and placebo at the 100 mg dose were observed for 3 of the 8 analysis combinations in the last 28 days of the study and 5 of 8 of the analysis combinations in the last 12 weeks of the DB phase. All of the analysis combinations that were statistically significantly different from placebo in the last 28 days of treatment were also statistically significant different from placebo in the last 12

weeks of the DB phase. The percent reductions were considerably higher in the last 28 days of treatment indicating that the monthly attack rates were continuing to improve at the end of the treatment period.

- Statistically significant differences between topiramate and placebo were found only for the 100 mg dose in both the last 28 days of treatment and the last 12 weeks of the DB phase.
- The analysis combinations that were statistically significantly different from placebo at the 100 mg dose in the last 28 days of treatment and the last 12 weeks of the DB phase were as follows:
- 48-hour rule, baseline migraine frequency ≥1 headache/month (100.0%, p=0.0298 in the last 28 days of treatment and 72.2%, p=0.0164 in the last 12 weeks of the DB phase)
- 48-hour rule, baseline migraine frequency ≥3 headaches/month (91.7%, p=0.0298 in the last 28 days of treatment and 72.8%, p=0.0077 in the last 12 weeks of the DB phase)
- 24-hour rule, baseline migraine frequency ≥1 headache/month (93.7%, p=0.0376 in the last 28 days of treatment and 73.3%, p=0.0216 in the last 12 weeks of the DB phase)

Study CAPSS-122 (All Subjects and Subjects 6 to 11 Years Old and 12 to 17 Years Old)

- The percent reductions in average monthly migraine attack rates from baseline to the last 28 days of treatment with topiramate (2-3 mg/kg/day) followed a pattern similar to the reductions observed in the last 12 weeks of the DB phase in all subjects and in the subgroups of subjects 12 to 17 years old and 6 to 11 years old.
- For all subjects, the percent reduction in average monthly migraine attack rates from baseline to the last 28 days of treatment was similar to the percent reduction over the last 12 weeks of the DB phase (60.0%-66.7% vs 58.3%-61.9%, respectively), indicating that the improvements in monthly migraine attack rates noted in the last 12 weeks of the DB phase had not declined and were sustained during the last 28 days of treatment.
- Statistically significant differences in the percent reduction in average monthly migraine attack rates from baseline to the last 28 days of treatment between topiramate and placebo were found for all subjects in this study; none of the differences were statistically significant for the subgroups of subjects 12 to 17 years old and 6 to 11 years old.
- For all subjects, the statistically significant differences between topiramate and placebo in percent reductions in average monthly migraine attack rates from baseline to the last 28 days of treatment were found for the following analysis combinations:
- 48-hour rule, IHS algorithm, baseline migraine frequency ≥3 headaches/month (63.3% vs 33.3%, p=0.0483)
- 24-hour rule, IHS algorithm, baseline migraine frequency ≥1 headache/month (66.7% vs 43.9%, p=0.0422)
- 24-hour rule, IHS algorithm, baseline migraine frequency ≥3 headaches/month (66.7% vs 40.0%, p=0.0304)
- Among subjects 12 to 17 years old, no recognizable trend was found in the percent reduction in average monthly migraine attack rates between the last 12 weeks of the DB phase (range, 66.7%-73.6%) and the last 28 days of treatment (range, 66.7%-75.0%) for any of the analysis combinations, suggesting that the reductions in migraine attack rates

observed with topiramate in the last 12 weeks of the DB phase had been maintained through the last 28 days of treatment in this age group.

- Among subjects 6 to 11 years old, the percent reductions in average monthly migraine attack rates observed with topiramate were notably higher in the last 28 days of treatment (range, 60.0%-62.5%) than in the last 12 weeks of the DB phase (range, 51.2%-55.6%) suggesting that migraine attack rates were continuing to improve in the last 28 days of treatment with topiramate in this age group.

Change from Baseline in Average Monthly Migraine Attack From Baseline to the Last 28 days of Treatment of the DB phase

Study TOPMAT-MIG-3006

- The changes in monthly migraine attack rates at the 50 mg dose (range, -2.2 to -3.0) were similar to the changes at the 100 mg dose (range, -2.7 to -3.5) in the last 28 days of treatment, but lower (range, -1.7 to -2.6) than the 100 mg dose (range, -2.7 to -3.4) in the last 12 weeks of the DB phase.
- The difference in the changes in monthly migraine attack rates between topiramate and placebo in both the last 28 days of treatment and the last 12 weeks of the DB phase were statistically significant at the 100 mg dose for the analysis combination of 48-hour rule and baseline migraine frequency ≥1 headache/month. The changes were almost identical between the 2 time periods: -3.1, p=0.0465 for the 28-day treatment period compared with -3.0, p=0.0087 for the last 12 weeks of the DB phase).

Study CAPSS-122 (All Subjects and Subgroups of Subjects 6 to 11 Years Old and 12 to 17 Years Old)

- The changes in average monthly migraine attack rates from baseline to the last 28 days of treatment and in the last 12 weeks of the DB phase were similar for all subjects and the subgroup of subjects 12 to 17 years old and 6 to 11 years old. During the period from baseline to the last 28 days of treatment, these changes ranged from -2.03 to -2.76 for all subjects, -2.4 to -3.2 for subjects 12 to 17 years old , and -1.8 to -2.4 for subjects 6 to 11 years old. In the last 12 weeks of the DB phase these changes were -1.86 to -2.50, -2.0 to -2.7, and -1.7 to -2.4, respectively.
- The differences in changes in average monthly migraine attack rates between topiramate and placebo were not statistically significant for any of the analysis combinations in all subjects and in both age subgroups in either the last 28 days of treatment or the last 12 weeks of the DB phase.

The 50% Responder Rate (>50% Reduction in Average Monthly Migraine Attack Rate From Baseline to the Last 28 days of Treatment of the DB Phase)

Study TOPMAT-MIG-3006

- The 50% responder rates observed with topiramate were statistically significantly different from those observed with placebo only at the 100 mg dose in the last 28 days of

treatment with the 24-hour rule and baseline frequency ≥1 headache/month analysis combination (difference 32%, p=0.0170).

- None of the differences in 50% responder rates between placebo and the 50 mg dose of topiramate were statistically significant in the last 28 days of treatment).
- The 50% responder rates were higher than placebo at both the 50 and 100 mg doses of topiramate in the last 28 days of treatment.
- The differences from placebo in 50% responder rates in the last 28 days of treatment were 2 to 4 times higher at the 100 mg dose than at the 50 mg dose (ranges, 17%-25% vs 5%- 17%, respectively). This difference was observed for all analysis combinations except the 24-hour rule, IHS algorithm, and baseline frequency ≥1 headache/month (range, 17% vs 12%) and the 24-hour rule, IHS algorithm, and baseline frequency ≥3 headaches/month (range, 20% vs 17%).

Study CAPSS-122 (All Subjects and Subgroups of Subjects 6 to 11 Years Old and 12 to 17 Years Old)

- The 50% responder rate was higher in the last 28 days of treatment than in the last 12 weeks of the DB phase for all subjects (ranges, 63%-72% vs 56%-58%, respectively), for subjects 12 to 17 years old (ranges, 67%-78% vs 59%-62%, respectively), and for subjects 6 to 11 years old (ranges, 59%-66% vs 52%-57%, respectively).
- For all subjects, statistically significant differences between topiramate and placebo were found only in the last 28 days of treatment for the following analysis combinations:
- 24-hour rule, baseline migraine frequency ≥1 headache/month (difference=19%, p=0.0337)
- 24-hour rule, baseline migraine frequency ≥3 headaches/month (difference=21%, p=0.0219)
- 24-hour rule, IHS algorithm, baseline migraine frequency ≥1 headache/month (difference=20%, p=0.0189)
- 24-hour rule, IHS algorithm, baseline migraine frequency ≥3 headaches/month (difference=24%, p=0.0130)
- 48-hour rule, IHS algorithm, baseline migraine frequency ≥3 headaches/month (difference=23%, p=0.0270)
- For subjects 12 to 17 years old, the difference between topiramate and placebo were statistically significant only in the last 28 days of treatment for the combination of 24-hour rule and baseline migraine frequency ≥3 headaches/month (difference=34%, p=0.0381).
- For subjects 6 to 11 years old, there were no statistically significant differences between topiramate and placebo observed for any of the analysis combinations in the last 28 days of treatment or in the last 12 weeks of the DB phase.

The 100% responder rate (100% Reduction in Average Monthly Migraine Attack Rate From Baseline to the Last 28 days of Treatment of the DB Phase)
Study TOPMAT-MIG-3006

- There were no statistically significant differences in 100% responder rates between placebo and topiramate at either the 50 or 100 mg doses and in either the last 28 days of treatment or the last 12 weeks of the DB phase.
- The 100% responder rates were higher at the 100 mg dose (range, 50%-55%) than at the 50 mg dose (range, 31%-43%) in the last 28 days of treatment, but were similar between doses over the last 12 weeks of the DB phase (ranges, 14%-23% at the 50 mg dose and 19%-22% at the 100 mg dose).

Study CAPSS-122 (All Subjects and Subgroups of Subjects 6 to 11 Years Old and 12 to 17 Years Old)

- There were no statistically significant differences between topiramate and placebo in 100% responder rates observed in both the last 28 days of treatment and the last 12 weeks of the DB phase for all subjects, subjects 12 to 17 years old, and subjects 6 to 11 years old.
- Among all subjects, the percentage of 100% responders was more than 3 times greater in the last 28 days of treatment (range, 32%-36%) than in the last 12 weeks of the DB phase (range, 6%-11%).
- The findings in both the last 28 days of treatment and last 12 weeks of the DB phase were similar between subjects 12 to 17 years old and subjects 6 to 11 years old.

Sponsor Conclusions of Sensitivity Analyses

- With few exceptions, the effects of topiramate on the efficacy endpoints observed in the last 28 days of treatment were generally greater than or similar to those observed in the last 12 weeks of the DB phase, and were also greater than observed for the entire DB period of the study, suggesting that the efficacy outcomes were either continuing to improve in the final month of treatment or were either sustained or had not declined over the duration of treatment. There were no discernible trends in the effects of the 24- or 48-hour rule, IHS criteria, or baseline migraine frequency on any of the efficacy endpoints observed in either the last 28 days of treatment or the last 12 weeks of the DB phase.
- In general, with limited exceptions, statistically significant differences between topiramate and placebo were found only at the 100 mg dose in Study TOPMAT-MIG-3006 for all efficacy endpoints except 100% responder rate in both the last 28 days of treatment and the last 12 weeks of the DB phase.
- Statistically significant differences in the percent reduction in average monthly migraine attack rate between topiramate and placebo were observed for the 100 mg dose for 3 of the 8 analysis combinations in the last 28 days and 5 of 8 of the analysis combinations in the last 12 weeks of the DB phase of TOPMAT-MIG-3006.
- In TOPMAT-MIG-3006, the differences between topiramate and placebo in changes in monthly migraine attack rates in the last 28 days of treatment were also statistically significant in the last 12 weeks of the DB phase for the analysis combinations noted. The percent reductions were considerably higher in the last 28 days of treatment in this study indicating that improvement in monthly attack rates was continuing to the end of the treatment period.

- Statistically significant differences between topiramate and placebo in 50% responder rates in the last 28 days of the treatment period were found only at the 100 mg dose in Study TOPMAT-MIG-3006.

  Overall the efficacy outcomes for the 6- to 11-year-old subjects (Study CAPSS-122) tended to be less robust than observed for the older subjects 12 to 17 years old. There were no statistically significantly differences in efficacy outcomes in topiramate vs placebo in this age group; however, when all subjects were combined in this study, there were some analysis combinations that showed statistically significant differences in the last 28 days of treatment for the efficacy endpoints of percent reduction in average monthly migraine attack rate from baseline and the 50% responder rate.

The following tables represent various sensitivity analyses conducted by the sponsor upon my request. These sensitivity analyses focus on results for Study MIG-3006 and for all pediatric patients (6-17 yo) and adolescents (12-17 yo) in CAPSS-122. These sensitivity analyses assessed the effects of several variables on 4 efficacy endpoints (percentage change from baseline in monthly migraine rate, absolute change from baseline in monthly migraine rate, at least 50 % responder rate, 100 % responder rate) for different treatment groups, especially the treatment difference/effect (topiramate – placebo). The several variables include :

- different populations (ITT vs completer);
- different baseline monthly (28 day) migraine attack rates ($\geq$ 1, $\geq$ 3, no baseline rate requirement)
- period for assessing treatment effect of topiramate (whole double-blind trial period, last 12 weeks of double-blind trial, last 28 days of double-blind trial)
- rule for counting migraine attacks (48 hr vs 24 hr)
- counting migraine attacks (using IHS algorithm vs no IHS algorithm)

Table 38 Sensitivity Analyses for Study MIG-3006 for Efficacy Endpoints (Over Last 12 weeks of DB phase; ITT)

	--- Placebo (N=33) ---			---------- TPM 50 mg (N=35) ----------				---------- TPM 100 mg (N=35) ----------				---------- Any TPM (N=70) ----------			
	Base	FV	Delta	Base	FV	Delta	TE (P)	Base	FV	Delta	TE (P)	Base	FV	Delta	TE (P)
%Reduction:															
48, DB,I,B ≥ 1	3.00	1.67	56.20	3.49	1.50	52.02	-4.18(0.7621)	4.00	1.00	65.06	8.86(0.4743)	4.00	1.33	63.10	6.90(0.3911)
48, DB,I,B ≥ 3	4.34	1.67	56.20	4.00	2.00	51.67	-4.53(0.7266)	4.00	1.33	65.86	9.66(0.2877)	4.00	1.67	64.29	8.09(0.2782)
48, DB,-I,B ≥ 1	3.61	2.33	44.44	4.00	2.33	44.64	0.20(0.7975)	4.00	1.00	72.22	27.78(0.0164*)	4.00	1.51	63.69	19.25(0.1871)
48, DB,-I,B ≥ 3	4.00	2.33	44.44	4.91	2.50	49.94	5.50(0.5058)	4.00	1.17	72.78	28.34(0.0077*)	4.00	1.67	65.86	21.42(0.0349*)
24, DB,I,B ≥ 1	3.93	1.67	61.76	4.00	1.50	60.00	-1.76(0.5901)	4.83	1.00	72.05	10.29(0.3254)	4.00	1.33	66.67	4.91(0.2644)
24, DB,I,B ≥ 3	4.57	1.67	50.64	5.00	2.00	66.67	16.03(0.2458)	5.00	1.33	72.22	21.58(0.0353*)	5.00	1.67	67.19	16.55(0.0363*)
24, DB,-I,B ≥ 1	4.31	2.33	49.49	4.00	2.33	45.75	-3.74(0.7733)	4.83	1.00	73.33	23.84(0.0216*)	4.75	1.67	66.67	17.18(0.2099)
24, DB,-I,B ≥ 3	4.83	2.67	44.44	5.21	2.50	55.00	10.56(0.3824)	4.91	1.17	76.25	31.81(0.0061*)	5.00	1.67	67.78	23.34(0.0230*)
Rate Change															
48, DB,I,B ≥ 1	3.92	2.11	-1.82	3.66	1.74	-1.92	-0.10(0.5082)	4.00	1.30	-2.70	-0.88(0.0858)	3.84	1.52	-2.32	-0.50(0.1234)
48, DB,I,B ≥ 3	4.37	2.30	-2.07	4.35	2.16	-2.20	-0.13(0.6199)	4.43	1.45	-2.98	-0.91(0.1540)	4.40	1.76	-2.63	-0.56(0.1781)
48, DB,-I,B ≥ 1	4.09	2.37	-1.72	4.08	2.37	-1.71	0.01(0.9845)	4.25	1.30	-2.95	-1.23(0.0087*)	4.17	1.83	-2.33	-0.61(0.1166)
48, DB,-I,B ≥ 3	4.38	2.59	-1.78	4.82	2.69	-2.13	-0.35(0.6925)	4.46	1.35	-3.11	-1.33(0.0106*)	4.62	1.95	-2.67	-0.89(0.0573)
24, DB,I,B ≥ 1	4.49	2.43	-2.06	4.09	1.90	-2.19	-0.13(0.4625)	4.52	1.47	-3.04	-0.98(0.1012)	4.31	1.68	-2.62	-0.56(0.1222)
24, DB,I,B ≥ 3	4.86	2.74	-2.12	4.96	2.37	-2.60	-0.48(0.3055)	4.97	1.59	-3.37	-1.25(0.0609)	4.97	1.93	-3.03	-0.91(0.0580)
24, DB,-I,B ≥ 1	4.86	2.73	-2.13	4.65	2.64	-2.01	0.12(0.9924)	4.67	1.45	-3.22	-1.09(0.0203*)	4.66	2.04	-2.62	-0.49(0.1497)
24, DB,-I,B ≥ 3	5.17	2.96	-2.20	5.54	2.98	-2.57	-0.37(0.5405)	4.92	1.52	-3.40	-1.20(0.0182*)	5.20	2.17	-3.03	-0.83(0.0543)
50% Responder:															
48, DB,I,B ≥ 1		62			53		-9(0.8708)		77		15(0.8351)		66		4(0.9059)
48, DB,I,B ≥ 3		65			52		-13(0.8576)		81		16(0.8576)		68		3(0.9897)
48, DB,-I,B ≥ 1		45			46		1(1.0000)		83		38(0.0048*)		64		19(0.0874)
48, DB,-I,B ≥ 3		43			50		7(0.6389)		81		38(0.0124*)		67		24(0.0464*)
24, DB,I,B ≥ 1		54			60		6(0.5838)		74		20(0.4305)		67		13(0.2530)
24, DB,I,B ≥ 3		50			62		12(0.2940)		78		28(0.1746)		71		21(0.0984)
24, DB,-I,B ≥ 1		48			49		1(0.9436)		80		32(0.0170*)		64		16(0.1297)
24, DB,-I,B ≥ 3		45			54		9(0.4395)		78		33(0.0245*)		67		22(0.0567)
100% Responder:															
48, DB,I,B ≥ 1		15			23		8(1.0000)		19		4(1.0000)		21		6(0.9512)
48, DB,I,B ≥ 3		5			19		14(0.4762)		19		14(0.4762)		19		14(0.2687)
48, DB,-I,B ≥ 1		12			14		2(1.0000)		20		8(1.0000)		17		5(0.7455)
48, DB,-I,B ≥ 3		7			15		8(0.4630)		22		15(0.4630)		19		12(0.2162)
24, DB,I,B ≥ 1		15			23		8(1.0000)		19		4(1.0000)		21		6(0.9512)
24, DB,I,B ≥ 3		5			19		14(0.3770)		22		17(0.3770)		21		16(0.1392)
24, DB,-I,B ≥ 1		12			14		2(1.0000)		20		8(1.0000)		17		5(0.7455)
24, DB,-I,B ≥ 3		7			15		8(0.4411)		22		15(0.4411)		19		12(0.1954)

% Reduction = Median Percent Reduction in Average Monthly Migraine Attack Rate; Rate Change = Change from Baseline in Average Monthly Attack Rate; Base = Baseline Monthly Migraine Attack Rate; FV = Final Visit Monthly Migraine Attack Rate; Delta = Difference at FV vs Base; TE = Treatment Effect/Difference of TPM - Placebo; P = p Value, 48 or 24 = 48 hour or 24 hour rule; I = IHS criteria applied; -I = IHS criteria not applied; B ≥ 1 or B ≥ 3 = Baseline Monthly Migraine Attack Rate ≥ 1 or ≥ 3.
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Table 39 Sensitivity Analyses for Study CAPSS-122 for Efficacy Endpoints for All Patients (6-17 yo) and Adolescents (12-17 yo) (Over Last 12 weeks of DB phase; ITT)

	----- PLACEBO (N=49) -----			------ TPM 2-3 MG/KG/DAY (N=108) -----				- PLACEBO (AGE 12-17 N=18) --			TPM 2-3 MG/KG/DAY (AGE 12-17 N=49)			
	BASE	FV	DELTA	BASE	FV	DELTA	TE (P)	BASE	FV	DELTA	BASE	FV	DELTA	TE (P)
%REDUCTION:														
48, DB,I,B ≥ 1	3.56	2.05	40.21	4.00	1.87	52.70	12.49(0.4128)	3.00	2.24	40.43	4.00	1.58	60.56	20.13(0.6414)
48, DB,I,B ≥ 3	4.00	2.38	34.53	4.00	2.18	53.81	19.28(0.1160)	3.56	2.95	37.12	4.00	1.64	61.64	24.52(0.6372)
48, DB,-I,B ≥ 1	4.00	2.17	40.43	4.00	1.96	49.14	8.71(0.2203)	4.00	2.80	40.43	4.00	1.90	55.63	15.20(0.4812)
48, DB,-I,B ≥ 3	4.00	2.17	40.43	4.00	1.96	49.77	9.34(0.1766)	4.00	2.80	40.43	4.00	1.84	60.28	19.85(0.3845)
24, DB,I,B ≥ 1	4.00	2.29	39.47	4.00	1.87	52.70	13.23(0.3583)	3.06	2.53	40.84	4.00	1.58	60.56	19.72(0.5098)
24, DB,I,B ≥ 3	5.00	2.59	34.17	4.00	2.29	56.31	22.14(0.1023)	4.50	3.13	37.12	4.00	1.72	61.77	24.65(0.7664)
24, DB,-I,B ≥ 1	5.00	2.64	40.43	4.15	2.07	52.41	11.98(0.1731)	4.50	3.11	42.66	4.00	1.93	60.28	17.62(0.4246)
24, DB,-I,B ≥ 3	5.00	2.64	40.43	5.00	2.23	52.41	11.98(0.1653)	4.50	3.11	42.66	4.00	1.95	60.56	17.90(0.3979)
RATE CHANGE														
48, DB,I,B ≥ 1	3.70	2.33	-1.37	3.79	2.10	-1.70	-0.33(0.3772)	3.85	2.64	-1.22	3.81	1.94	-1.87	-0.65(0.3406)
48, DB,I,B ≥ 3	4.26	2.74	-1.52	4.24	2.24	-2.00	-0.48(0.1749)	4.38	3.13	-1.26	4.21	2.08	-2.12	-0.86(0.5600)
48, DB,-I,B ≥ 1	4.30	2.66	-1.64	4.11	2.27	-1.84	-0.20(0.2849)	4.47	3.06	-1.41	4.08	2.08	-2.00	-0.59(0.2362)
48, DB,-I,B ≥ 3	4.30	2.66	-1.64	4.30	2.32	-1.99	-0.35(0.2723)	4.47	3.06	-1.41	4.34	2.08	-2.26	-0.85(0.3076)
24, DB,I,B ≥ 1	4.18	2.74	-1.44	4.20	2.34	-1.86	-0.42(0.2766)	4.19	3.14	-1.04	4.23	2.18	-2.05	-1.01(0.2689)
24, DB,I,B ≥ 3	4.81	3.22	-1.58	4.64	2.52	-2.13	-0.55(0.1782)	4.81	3.72	-1.09	4.65	2.36	-2.29	-1.20(0.6262)
24, DB,-I,B ≥ 1	4.91	3.08	-1.83	4.69	2.53	-2.16	-0.33(0.2312)	4.97	3.56	-1.40	4.67	2.33	-2.34	-0.94(0.2733)
24, DB,-I,B ≥ 3	4.91	3.08	-1.83	4.86	2.58	-2.27	-0.44(0.2196)	4.97	3.56	-1.40	4.85	2.35	-2.50	-1.10(0.2618)
50% RESPONDER:														
48, DB,I,B ≥ 1		42			50		8(0.4199)		39			57		18(0.5042)
48, DB,I,B ≥ 3		35			51		16(0.1668)		29			59		30(0.5573)
48, DB,-I,B ≥ 1		43			49		6(0.5956)		39			55		16(0.6699)
48, DB,-I,B ≥ 3		43			50		7(0.5204)		39			59		20(0.5337)
24, DB,I,B ≥ 1		42			51		9(0.3485)		39			57		18(0.5042)
24, DB,I,B ≥ 3		34			52		18(0.1149)		29			58		29(0.6382)
24, DB,-I,B ≥ 1		43			52		9(0.3919)		33			59		26(0.2435)
24, DB,-I,B ≥ 3		43			52		9(0.3884)		33			61		28(0.2208)
100% RESPONDER:														
48, DB,I,B ≥ 1		4			6		2(0.9776)		6			4		-2(1.0000)
48, DB,I,B ≥ 3		0			3		3(0.5834)		0			3		3(1.0000)
48, DB,-I,B ≥ 1		0			6		6(0.1799)		0			4		4(1.0000)
48, DB,-I,B ≥ 3		0			4		4(0.3202)		0			5		5(1.0000)
24, DB,I,B ≥ 1		4			6		2(0.9776)		6			4		-2(1.0000)
24, DB,I,B ≥ 3		0			3		3(0.5445)		0			3		3(1.0000)
24, DB,-I,B ≥ 1		0			6		6(0.1799)		0			4		4(1.0000)
24, DB,-I,B ≥ 3		0			4		4(0.3336)		0			4		4(1.0000)

% Reduction = Median Percent Reduction in Average Monthly Migraine Attack Rate; Rate Change = Change From Baseline in Average Monthly Attack Rate; Base = Baseline Monthly Migraine Attack Rate; FV = Final Visit Monthly Migraine Attack Rate; Delta = Difference at FV vs Base; TE = Treatment Effect/Difference of TPM - Placebo; P = P Value, 48 or 24 = 48 Hour or 24 Hour Rule; I = IHS Criteria Applied; -I = IHS Criteria Not Applied; B ≥ 1 Or B ≥ 3 = Baseline Monthly Migraine Attack Rate ≥ 1 or ≥ 3.

Table 40 Sensitivity Analyses for Study CAPSS-122 for Efficacy Endpoints for Young Pediatric Patients (6-11 yo) (Over Last 12 weeks of DB phase; ITT)

	PLACEBO (AGE 6-11 N=31)			TPM 2-3 MG/KG/DAY (AGE 6-11 N=59)			
	BASE	FV	DELTA	BASE	FV	DELTA	TE (P)
%REDUCTION:							
48, DB,I,B ≥ 1	4.00	1.67	45.83	4.00	1.93	52.86	7.03(0.7363)
48, DB,I,B ≥ 3	4.00	2.00	50.00	4.00	2.29	53.33	3.33(0.3805)
48, DB,-I,B ≥ 1	4.00	2.00	46.43	4.00	2.00	52.38	5.95(0.6275)
48, DB,-I,B ≥ 3	4.00	2.00	46.43	4.00	2.17	51.19	4.76(0.6285)
24, DB,I,B ≥ 1	4.00	1.67	42.26	4.00	2.00	54.44	12.18(0.6447)
24, DB,I,B ≥ 3	5.00	2.33	42.26	5.00	2.33	55.56	13.30(0.2420)
24, DB,-I,B ≥ 1	5.00	2.33	46.43	5.00	2.00	55.56	9.13(0.4119)
24, DB,-I,B ≥ 3	5.00	2.33	46.43	5.00	2.33	53.97	7.54(0.3993)
RATE CHANGE							
48, DB,I,B ≥ 1	3.61	1.94	-1.66	3.78	2.05	-1.73	-0.07(0.9450)
48, DB,I,B ≥ 3	4.18	2.26	-1.92	4.26	2.18	-2.08	-0.16(0.6530)
48, DB,-I,B ≥ 1	4.20	2.20	-2.01	4.14	2.24	-1.90	0.11(0.9847)
48, DB,-I,B ≥ 3	4.20	2.20	-2.01	4.28	2.30	-1.97	0.04(0.9962)
24, DB,I,B ≥ 1	4.18	2.28	-1.89	4.18	2.26	-1.92	-0.03(0.8023)
24, DB,I,B ≥ 3	4.80	2.67	-2.13	4.64	2.40	-2.24	-0.11(0.5297)
24, DB,-I,B ≥ 1	4.88	2.55	-2.33	4.70	2.45	-2.26	0.07(0.8097)
24, DB,-I,B ≥ 3	4.88	2.55	-2.33	4.86	2.52	-2.35	-0.02(0.7877)
50% RESPONDER:							
48, DB,I,B ≥ 1		50			53		3(0.8370)
48, DB,I,B ≥ 3		52			55		3(0.8888)
48, DB,-I,B ≥ 1		48			53		5(0.7092)
48, DB,-I,B ≥ 3		48			52		4(0.7095)
24, DB,I,B ≥ 1		43			55		12(0.2309)
24, DB,I,B ≥ 3		42			57		15(0.1212)
24, DB,-I,B ≥ 1		48			56		8(0.4255)
24, DB,-I,B ≥ 3		48			55		7(0.4228)
100% RESPONDER:							
48, DB,I,B ≥ 1		10			14		4(1.0000)
48, DB,I,B ≥ 3		4			13		9(0.7385)
48, DB,-I,B ≥ 1		6			10		4(0.9313)
48, DB,-I,B ≥ 3		6			7		1(1.0000)
24, DB,I,B ≥ 1		10			14		4(1.0000)
24, DB,I,B ≥ 3		4			12		8(0.6573)
24, DB,-I,B ≥ 1		6			10		4(0.9313)
24, DB,-I,B ≥ 3		6			7		1(1.0000)

% Reduction = Median Percent Reduction In Average Monthly Migraine Attack Rate; Rate Change = Change From Baseline in Average Monthly Attack Rate; Base = Baseline Monthly Migraine Attack Rate; FV = Final Visit Monthly Migraine Attack Rate; Delta = Difference at FV vs Base; TE = Treatment Effect/Difference of TPM - Placebo; P = P Value, 48 or 24 = 48 Hour or 24 Hour Rule; I = IHS Criteria Applied; -I = IHS Criteria Not Applied; B ≥ 1 or B ≥ 3 = Baseline Monthly Migraine Attack Rate ≥ 1 or ≥ 3.

Table 41 Sensitivity Analyses for Study MIG-3006 for Efficacy Endpoints Over Different Time Periods (Over Whole Double-Blind Period, Last 12 weeks of DB phase, Last 28 Days of DB phase; ITT Population)

	Whole DB Treatment Period		Last 12 Weeks of DB Treatment		Last 28 Days of DB Treatment	
	ITT TPM (N=35); P (N=33)	Completer TPM (N=30); P (N=26)	ITT TPM (N=35); P (N=33)	Completer TPM (N=30); P (N=26)	ITT TPM (N=35); P (N=33)	Completer TPM (N=30); P (N=26)
% Reduction						
48, DB, I, B > 1	10.66(0.6304)	13.78(0.4622)	8.86(0.4743)	16.02(0.2926)	35.95(0.1874)	39.29(0.0215*)
48, DB, I, B ≥ 3	8.11(0.5606)	16.57(0.4204)	9.66(0.2877)	21.58(0.1401)	29.29(0.1281)	39.29(0.0276*)
48, DB, -I, B ≥ 1	**22.34(0.0984)**	24.28(0.0344*)	27.78(0.0164*)	30.11(0.0052*)	38.57(0.0298*)	50.89(0.0017*)
48, DB, -I, B ≥ 3	22.59(0.1016)	25.88(0.0498*)	28.34(0.0077*)	30.56(0.0023*)	42.56(0.0298*)	51.79(0.0065*)
24, DB, I, B > 1	10.66(0.5906)	16.91(0.4622)	10.29(0.3254)	16.02(0.2047)	33.33(0.1939)	35.95(0.0230*)
24, DB, I, B ≥ 3	20.43(0.2016)	19.69(0.1625)	21.58(0.0353*)	25.37(0.0310*)	**35.95(0.0966)**	38.57(0.0114*)
24, DB, -I, B ≥ 1	20.68(0.1660)	**23.61(0.0968)**	23.84(0.0216*)	32.67(0.0104*)	**38.57(0.0616)**	46.43(0.0068*)
24, DB, -I, B ≥ 3	20.14(0.1358)	**25.26(0.0825)**	31.81(0.0061*)	36.55(0.0024*)	43.75(0.0376*)	50.89(0.0129*)
Rate Change						
48, DB, I, B > 1	-0.64(0.2604)	-0.75(0.2198)	**-0.88(0.0858)**	**-1.04(0.0556)**	-0.95(0.1410)	-1.29(0.0460*)
48, DB, I, B ≥ 3	-0.63(0.3971)	-0.86(0.3746)	-0.91(0.1540)	-1.22(0.1029)	-1.01(0.2092)	-1.36(0.1207)
48, DB, -I, B ≥ 1	-1.01(0.0384*)	-1.25(0.0306*)	-1.23(0.0087*)	-1.50(0.0059*)	-1.13(0.0465*)	-1.56(0.0115*)
48, DB, -I, B ≥ 3	**-1.06(0.0590)**	**-1.41(0.0512)**	-1.33(0.0106*)	-1.73(0.0069*)	**-1.23(0.0607)**	-1.72(0.0265*)
24, DB, I, B ≥ 1	-0.65(0.3681)	-0.78(0.2570)	-0.98(0.1012)	-1.18(0.0411*)	-1.01(0.1826)	-1.41(0.0429*)
24, DB, I, B ≥ 3	-0.85(0.2283)	-1.00(0.2096)	**-1.25(0.0609)**	-1.48(0.0361*)	-1.11(0.1921)	**-1.55(0.0716)**
24, DB, -I, B ≥ 1	-0.79(0.1171)	**-1.00(0.0882)**	-1.09(0.0203*)	-1.35(0.0107*)	-0.91(0.1168)	-1.36(0.0288*)
24, DB, -I, B ≥ 3	-0.83(0.1349)	**-1.18(0.0921)**	-1.20(0.0182*)	-1.63(0.0071*)	**-1.03(0.0998)**	-1.56(0.0396*)
50 % Responder						
48, DB, I, B > 1	15(0.8393)	24(0.5900)	15(0.8351)	23(0.3614)	19(0.7138)	**33(0.0831)**
48, DB, I, B ≥ 3	13(0.8542)	23(0.5349)	16(0.8576)	26(0.2939)	22(0.4827)	34(0.1429)
48, DB, -I, B ≥ 1	27(0.1774)	35(0.1471)	38(0.0048*)	47(0.0013*)	22(0.2372)	37(0.0203*)
48, DB, -I, B ≥ 3	27(0.2748)	35(0.2357)	38(0.0124*)	50(0.0034*)	25(0.2327)	37(0.0372*)
24, DB, I, B ≥ 1	19(0.4404)	28(0.3858)	20(0.4305)	30(0.1783)	16(0.6026)	30(0.2507)
24, DB, I, B ≥ 3	22(0.3739)	32(0.2202)	28(0.1746)	38(0.0771)	19(0.6214)	33(0.2029)
24, DB, -I, B ≥ 1	18(0.4667)	27(0.2246)	32(0.0170*)	44(0.0029*)	16(0.5877)	29(0.1053)
24, DB, -I, B ≥ 3	18(0.5496)	28(0.2877)	33(0.0245*)	47(0.0048*)	20(0.4675)	31(0.1316)
100 % Responder						
48, DB, I, B > 1	-9(0.6386)	-6(1.0000)	4(1.0000)	8(1.0000)	24(0.5663)	37(0.1420)
48, DB, I, B ≥ 3	-5	-6	14(0.4762)	18(0.7500)	30(0.2282)	38(0.1913)
48, DB, -I, B ≥ 1	-6	-4	8(1.0000)	11(0.7990)	27(0.1578)	**37(0.0540)**
48, DB, -I, B ≥ 3	-4	-4	15(0.4630)	17(0.6174)	29(0.1650)	34(0.1582)
24, DB, I, B ≥ 1	-9(0.6386)	-6(1.0000)	4(1.0000)	8(1.0000)	24(0.5663)	37(0.1420)
24, DB, I, B ≥ 3	-1(1.0000)	-1(1.0000)	17(0.3770)	21(0.4898)	29(0.2891)	**41(0.0956)**
24, DB, -I, B ≥ 1	-6	-4	8(1.0000)	11(0.7990)	27(0.1578)	**37(0.0540)**
24, DB, -I, B ≥ 3	-3	-4	15(0.4411)	18(0.5774)	29(0.1282)	35(0.1207)

Note: TPM=100 mg for MIGR-3006; P=Placebo, N=# of Pts; % Reduction = Median Percent Reduction in Average Monthly Migraine Attack Rate; Rate Change = Change from Baseline in Average Monthly Attack Rate; 48 or 24 = 48 hour or 24 hour rule; I = IHS criteria applied; -I = IHS criteria not applied; B ≥ 1 or B ≥ 3 = Baseline Monthly Migraine Attack Rate > 1 or > 3.

Yellow Highlight indicates statistical significance $P \leq 0.05$: 39.29(0.0215*);
Bold indicates close to statistical significance $P > 0.05$ - < 0.10 : **38.57(0.0616)**
Underline indicates trending toward statistical significance $P \geq 0.10$ - < 0.20 : 20.68(0.1660)

Table 42 Sensitivity Analyses for Study CAPSS-122 for Efficacy Endpoints Over Different Time Periods in Adolescents (12-17yo) (Over Whole Double-Blind Period, Last 12 weeks of DB phase, Last 28 Days of DB phase, ITT Population)

	Whole DB Treatment Period		Last 12 Weeks of DB Treatment		Last 28 Days of DB Treatment	
	ITT TPM (N=49); P (N=18)	Completer TPM (N=42); P (N=15)	ITT TPM (N=49); P (N=18)	Completer TPM (N=42); P (N=15)	ITT TPM (N=49); P (N=18)	Completer TPM (N=42); P (N=15)
% Reduction						
48, DB, I, B > 1	20.13(0.6414)	21.21(0.3383)	19.05(0.3686)	24.60(0.1852)	22.79(0.2693)	26.53(0.1908)
48, DB, I, B ≥ 3	24.52(0.6372)	26.00(0.5927)	33.52(0.4413)	24.60(0.4723)	38.10(0.2995)	36.90(0.4092)
48, DB,- I, B ≥ 1	15.20(0.4812)	19.85(0.4103)	15.82(0.3326)	19.53(0.2716)	31.12(0.3457)	30.10(0.2926)
48, DB, -I, B ≥ 3	19.85(0.3845)	22.19(0.3409)	18.59(0.3232)	20.92(0.2756)	31.12(0.3831)	30.10(0.3361)
24, DB, I, B ≥ 1	19.72(0.5098)	20.64(0.2490)	28.47(0.2451)	27.78(0.1046)	35.88(0.1423)	30.10(0.1027)
24, DB, I, B ≥ 3	24.65(0.7664)	30.40(0.6814)	40.76(0.4095)	31.95(0.4004)	41.67(0.2753)	35.88(0.3688)
24, DB,- I, B ≥ 1	17.62(0.4246)	16.20(0.3096)	17.41(0.2364)	23.70(0.1554)	35.88(0.2543)	31.49(0.1813)
24, DB, -I, B ≥ 3	17.90(0.3979)	17.97(0.3510)	22.96(0.2389)	23.70(0.2135)	35.88(0.2033)	31.49(0.1968)
Rate Change						
48, DB, I, B > 1	-0.65(0.3406)	-0.36(0.4679)	-0.73(0.2611)	-0.43(0.3645)	-0.73(0.2422)	-0.58(0.2832)
48, DB, I, B ≥ 3	-0.86(0.5600)	-0.39(0.8060)	-0.93(0.4774)	-0.44(0.6839)	-0.95(0.3737)	-0.66(0.5402)
48, DB,- I, B ≥ 1	-0.59(0.2362)	-0.41(0.3092)	-0.55(0.2952)	-0.35(0.3561)	-0.60(0.2726)	-0.54(0.2718)
48, DB, -I, B ≥ 3	-0.85(0.3076)	-0.60(0.3840)	-0.78(0.3825)	-0.52(0.4512)	-0.85(0.3703)	-0.73(0.3608)
24, DB, I, B ≥ 1	-1.01(0.2689)	-0.58(0.4750)	-1.11(0.2137)	-0.67(0.3858)	-1.13(0.1331)	-0.91(0.2297)
24, DB, I, B ≥ 3	-1.20(0.6262)	-0.53(0.9279)	-1.29(0.5601)	-0.58(0.8229)	-1.32(0.3922)	-0.92(0.6076)
24, DB,- I, B ≥ 1	-0.94(0.2733)	-0.64(0.3958)	-0.94(0.3013)	-0.60(0.4252)	-1.01(0.1985)	-0.90(0.2458)
24, DB, -I, B ≥ 3	-1.10(0.2618)	-0.73(0.4924)	-1.08(0.2900)	-0.67(0.5307)	-1.18(0.1747)	-1.01(0.2931)
50 % Responder						
48, DB, I, B > 1	18(0.5042)	23(0.2452)	16(0.6711)	19(0.4456)	26(0.1835)	29(0.1234)
48, DB, I, B ≥ 3	30(0.5573)	33(0.5020)	26(0.6711)	27(0.7137)	40(0.1872)	41(0.2722)
48, DB,- I, B ≥ 1	16(0.6699)	22(0.3479)	9(0.9684)	14(0.6221)	23(0.2911)	27(0.1680)
48, DB, -I, B ≥ 3	20(0.5337)	26(0.2645)	11(0.8723)	15(0.5664)	24(0.3905)	27(0.2548)
24, DB, I, B ≥ 1	18(0.5042)	23(0.2452)	10(0.9372)	13(0.7038)	**30(0.0525)**	31(0.0478*)
24, DB, I, B ≥ 3	29(0.6382)	31(0.5851)	17(1.0000)	17(1.0000)	39(0.1796)	36(0.2670)
24, DB,- I, B ≥ 1	26(0.2435)	31(0.1034)	11(0.8170)	14(0.6354)	**32(0.0730)**	**32(0.0589)**
24, DB, -I, B ≥ 3	28(0.2208)	32(0.1152)	11(0.8843)	12(0.8091)	34(0.0381*)	**33(0.0579)**
100 % Responder						
48, DB, I, B > 1	-2(1.0000)	2(1.0000)	-2(1.0000)	0(1.0000)	16(0.6512)	19(0.5475)
48, DB, I, B ≥ 3	3(1.0000)	3(1.0000)	-2(1.0000)	-2(1.0000)	24(0.5714)	23(0.7551)
48, DB,- I, B ≥ 1	4(1.0000)	2(1.0000)	-2(1.0000)	-5(1.0000)	15(0.7495)	18(0.5995)
48, DB, -I, B ≥ 3	5(1.0000)	3(1.0000)	-1(1.0000)	-4(1.0000)	17(0.7836)	19(0.6688)
24, DB, I, B ≥ 1	-2(1.0000)	2(1.0000)	-2(1.0000)	0(1.0000)	16(0.6512)	19(0.5475)
24, DB, I, B ≥ 3	3(1.0000)	3(1.0000)	-2(1.0000)	-2(1.0000)	24(0.6335)	22(0.8278)
24, DB,- I, B ≥ 1	4(1.0000)	2(1.0000)	-2(1.0000)	-5(1.0000)	15(0.7495)	18(0.5995)
24, DB, -I, B ≥ 3	4(1.0000)	3(1.0000)	-2(1.0000)	-4(1.0000)	15(0.8407)	18(0.7267)

Note: TPM=100 mg for MIGR-3006; P=Placebo, N=# of Pts; % Reduction = Median Percent Reduction in Average Monthly Migraine Attack Rate; Rate Change = Change from Baseline in Average Monthly Attack Rate; 48 or 24 = 48 hour or 24 hour rule; I = IHS criteria applied; -I = IHS criteria not applied; B ≥ 1 or B ≥ 3 = Baseline Monthly Migraine Attack Rate ≥ 1 or ≥ 3.

Yellow Highlight indicates statistical significance P ≤ 0.05 : 39.29(0.0215*);
Bold indicates close to statistical significance P > 0.05 - < 0.10 : **38.57(0.0616)**
Underline indicates trending toward statistical significance P ≥ 0.10 - < 0.20 : 20.68(0.1660)

Table 43 Sensitivity Analysis for Study MIG-3006 Over Last 12 weeks of DB phase (ITT Population)

	--- Placebo (N=33) ---			---------- TPM 50 mg (N=35) ----------				---------- TPM 100 mg (N=35) ----------				---------- Any TPM (N=70) ----------			
	Base	FV	Delta	Base	FV	Delta	TE (P)	Base	FV	Delta	TE (P)	Base	FV	Delta	TE (P)
%Reduction:															
48, DB,I	3.00	1.33	55.56	3.00	1.33	44.44	-11.12(0.9620)	3.86	1.00	64.29	8.73(0.3503)	3.18	1.33	56.94	1.38(0.4262)
48, DB,-I	3.61	2.33	44.44	4.00	2.33	44.64	0.20(0.7975)	4.00	1.00	72.22	27.78(0.0164*)	4.00	1.51	63.69	19.25(0.1871)
24, DB,I	3.00	1.67	44.44	3.36	1.33	51.67	7.23(0.7960)	4.00	1.00	66.67	22.23(0.2630)	4.00	1.33	60.00	15.56(0.3141)
24, DB,-I	4.31	2.33	49.49	4.00	2.33	45.75	-3.74(0.7733)	4.83	1.00	73.33	23.84(0.0216*)	4.75	1.67	66.67	17.18(0.2099)
Rate Change															
48, DB,I	3.18	1.82	-1.35	3.17	1.63	-1.54	-0.19(0.5756)	3.60	1.20	-2.40	-1.05(0.0556)	3.38	1.41	-1.97	-0.62(0.1176)
48, DB,-I	4.09	2.37	-1.72	4.08	2.37	-1.71	0.01(0.9845)	4.25	1.30	-2.95	-1.23(0.0087*)	4.17	1.83	-2.33	-0.61(0.1166)
24, DB,I	3.62	2.10	-1.52	3.54	1.76	-1.77	-0.25(0.4630)	4.05	1.36	-2.69	-1.17(0.0583)	3.80	1.56	-2.23	-0.71(0.0969)
24, DB,-I	4.86	2.73	-2.13	4.65	2.64	-2.01	0.12(0.9924)	4.67	1.45	-3.22	-1.09(0.0203*)	4.66	2.04	-2.62	-0.49(0.1497)
50% Responder:															
48, DB,I		55			46		-9(0.6464)		71		16(0.4538)		59		4(0.8495)
48, DB,-I		45			46		1(1.0000)		83		38(0.0048*)		64		19(0.0874)
24, DB,I		48			51		3(0.8520)		69		21(0.2303)		60		12(0.2835)
24, DB,-I		48			49		1(0.9436)		80		32(0.0170*)		64		16(0.1297)
100% Responder:															
48, DB,I		15			20		5(0.9103)		20		5(0.9103)		20		5(0.7887)
48, DB,-I		12			14		2(1.0000)		20		8(1.0000)		17		5(0.7455)
24, DB,I		15			20		5(0.9103)		20		5(0.9103)		20		5(0.7887)
24, DB,-I		12			14		2(1.0000)		20		8(1.0000)		17		5(0.7455)

% Reduction = Median Percent Reduction in Average Monthly Migraine Attack Rate; Rate Change = Change from Baseline in Average Monthly Attack Rate; Base = Baseline Monthly Migraine Attack Rate; FV = Final Visit Monthly Migraine Attack Rate; Delta = Difference at FV vs Base; TE = Treatment Effect/Difference of TPM - Placebo; P = p Value, 48 or 24 = 48 hour or 24 hour rule; I = IHS criteria applied; -I = IHS criteria not applied.

Table 44 Sensitivity Analysis for Study CAPSS-122 for All Patients (6-17 yo) and Adolescents (12-17 yo) Over Last 12 weeks of DB phase (ITT Population)

	------ Placebo (N=49) ------			------- TPM 2-3 mg/kg/day (N=108) ------				- Placebo (Age 12-17 N=18) -			-- TPM 2-3 mg/kg/day (Age 12-17 N=49) --			
	Base	FV	Delta	Base	FV	Delta	TE (P)	Base	FV	Delta	Base	FV	Delta	TE (P)
%Reduction:														
48, DB,I	3.11	2.00	47.62	4.00	1.67	55.71	8.09(0.4012)	3.00	2.24	47.62	4.00	1.33	66.67	19.05(0.5432)
48, DB,-I	4.00	2.33	47.62	4.00	1.67	58.33	10.71(0.2491)	4.00	2.60	50.85	4.00	1.33	66.67	15.82(0.3326)
24, DB,I	4.00	2.15	41.67	4.00	1.67	58.57	16.90(0.2877)	3.06	2.67	43.75	4.00	1.33	66.67	22.92(0.4253)
24, DB,-I	5.00	2.33	46.43	4.15	1.67	61.51	15.08(0.1375)	4.50	2.94	49.26	4.00	1.33	66.67	17.41(0.2364)
Rate Change														
48, DB,I	3.63	2.17	-1.46	3.69	1.90	-1.79	-0.33(0.3551)	3.85	2.56	-1.29	3.65	1.75	-1.90	-0.61(0.3027)
48, DB,-I	4.30	2.42	-1.88	4.11	2.07	-2.04	-0.16(0.3738)	4.47	2.81	-1.66	4.08	1.88	-2.21	-0.55(0.2952)
24, DB,I	4.09	2.58	-1.52	4.09	2.11	-1.97	-0.45(0.2507)	4.19	3.10	-1.09	4.06	1.98	-2.08	-0.99(0.2582)
24, DB,-I	4.91	2.84	-2.07	4.69	2.30	-2.39	-0.32(0.2622)	4.97	3.34	-1.62	4.67	2.12	-2.56	-0.94(0.3013)
50% Responder:														
48, DB,I		47			55		8(0.4907)		44			57		13(0.8191)
48, DB,-I		49			56		7(0.5650)		50			59		9(0.9684)
24, DB,I		45			56		11(0.2931)		50			57		7(1.0000)
24, DB,-I		49			58		9(0.3558)		50			61		11(0.8170)
100% Responder:														
48, DB,I		10			11		1(1.0000)		11			8		-3(1.0000)
48, DB,-I		6			7		1(1.0000)		6			4		-2(1.0000)
24, DB,I		10			11		1(1.0000)		11			8		-3(1.0000)
24, DB,-I		6			7		1(1.0000)		6			4		-2(1.0000)

% Reduction = Median Percent Reduction in Average Monthly Migraine Attack Rate; Rate Change = Change from Baseline in Average Monthly Attack Rate; Base = Baseline Monthly Migraine Attack Rate; FV = Final Visit Monthly Migraine Attack Rate; Delta = Difference at FV vs Base; TE = Treatment Effect/Difference of TPM - Placebo; P = p Value, 48 or 24 = 48 hour or 24 hour rule; I = IHS criteria applied; -I = IHS criteria not applied.

The percent reduction from baseline to the last 28 days of the double-blind phase in average monthly migraine attack rate for the ITT analysis set of Study TOPMAT-MIG-3006 is shown in Table 45.

- The median monthly migraine attack rate over the last 28 days of the double-blind phase was lower in the 100 mg/day group (0.00) compared with the 50 mg/day group (1.00) and placebo group (2.00).
- Median percent reduction was greatest in the 100 mg/day group (100%) compared with the 50 mg/day group (65.5%) and placebo group (61.4%).
- The 100 mg/day group was statistically superior to the placebo group after multiple comparison adjustment (p=0.0298). The 50 mg/day group was not statistically different from placebo.

Table 45 **Percent Reduction from Baseline to the Last 28 Days of Double-Blind Phase in Average Monthly Attack Rate (Using 48-Hour Rule): Study TOPMAT-MIG-3006 (Intent-to-Treat Analysis Set)**

Category	Placebo (N=33)	TPM 50 mg/day (N=35)	TPM 100 mg/day (N=35)	Any TPM (N=70)
Baseline				
N	33	35	35	70
Median (Range)	3.61 (1.9;7.5)	4.00 (1.0;7.2)	4.00 (1.9;9.0)	4.00 (1.0;9.0)
Last 28 days of Double-Blind Phase				
N	33	35	35	70
Median (Range)	2.00 (0.0;7.0)	1.00 (0.0;7.0)	0.00 (0.0;5.0)	1.00 (0.0;7.0)
Percent Reduction (%)				
N	33	35	35	70
Median (Range)	61.43 (-66.7;100.0)	65.48 (-69.7;100.0)	100.00 (0.0;100.0)	80.00 (-69.7;100.0)
P-value VS. Placebo		0.6658	0.0298*	0.1059

Percent reduction is the difference between values at baseline and last 28 days of Double-Blind Phase, divided by value at baseline, times 100.
P-values for comparisons relative to placebo are generated by applying an ANCOVA model on ranks that includes subject's stratified age at baseline, treatment group, and analysis center as factors and monthly migraine attack rate during baseline period as a covariate.
P-values for the dose groups are the adjusted p-value according to the Hochberg multiple comparison procedure.
The p-values for the 'Any TPM' group are unadjusted.
* indicates p-value is less than 0.05 (two-sided).
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Reviewer Comments

- *Table 38 shows sensitivity analyses for the ITT population over the last 12 weeks of treatment in MIG-3006. I note the following observations focusing on the treatment difference/effect of the 100 mg topiramate dose :*
    - *All 24 and 48 hour analyses without the IHS algorithm and regardless of baseline migraine rate (i.e., $\geq$ 1 or $\geq$ 3) are statistically significant ($p < 0.05$) for the primary efficacy endpoint (percentage reduction from baseline in monthly*

migraine rate). In addition, one 24 hour analysis with ≥ 3 baseline migraines is statistically significant when the IHS algorithm is applied for counting migraines.

- *All 24 and 48 hour analyses without the IHS algorithm and regardless of baseline migraine rate (i.e., ≥ 1 or ≥ 3) are statistically significant for the key secondary efficacy endpoint (absolute change from baseline in monthly migraine rate) and the ≥ 50 % responder rate.*

- *Altogether these analyses indicate that the most important variable influencing results and preventing statistical significance is the application of the IHS algorithm to baseline and on-treatment migraine counts.*

- *Table 39 shows sensitivity analyses for the ITT population over the last 12 weeks of treatment for the topiramate treatment difference/effect for all pediatric patients (6-17 yo) and all adolescents (12-17 yo) in CAPSS-122. I note the following observations :*

  - *There are no statistically significant ($p < 0.05$) results for any of these sensitivity analyses.*

  - *Numerical treatment differences for all efficacy endpoints (except 100 % responder rate) shown in this table are notably greater for adolescents than for younger patients (6-11 yo) (Table 39).These results tend to argue against a therapeutic benefit of topiramate in these younger pediatric patients.*

  - *For the percentage change from baseline and absolute change from baseline in monthly migraine rate, the p value for the analyses without the IHS algorithm are frequently notably lower than the p values when the IHS algorithm is applied to the analyses for all pediatric patients.*

- *Table 40 shows sensitivity analyses for the ITT population over the last 12 weeks of treatment for the topiramate treatment difference/effect for young pediatric patients (6-11 yo)) in CAPSS-122. I note the following observations :*

  - *There are no statistically significant ($p < 0.05$) results for any of these sensitivity analyses.*

  - *For all the efficacy endpoints (except the 100 % responder rate), p values for 24 hours analyses (regardless of baseline migraine rate or application of IHS algorithm) are usually lower than the respective 48 hour analyses.*

- *Table 41 shows sensitivity analyses for the ITT and completer population s analyzed over different treatment periods in MIG-3006. In essentially all instances, the topiramate treatment difference is greater for the completer population than the ITT population.*

However, I note the following observations focusing on the treatment difference/effect of the 100 mg topiramate dose for the ITT population :

- *For the percentage change from baseline and absolute change from baseline in monthly migraine rate, many sensitivity analyses for the last 12 weeks or last 28 days of treatment became statistically significant ($p < 0.05$) compared to analyses for the whole double-blind treatment period including the titration period. Several completer analyses applying the 48 hour rule and IHS algorithm became statistically significant in the analyses over the last 28 days.*

- *For the percentage change from baseline and absolute change from baseline in monthly migraine rate, sensitivity analyses for the last 12 weeks were frequently statistically significant when the IHS algorithm was not applied regardless of the 24 or 48 hour rule or baseline migraine rate.*

- *Table 42 shows sensitivity analyses for the ITT population of adolescents (12-17 yo) analyzed over different treatment periods in CAPSS-122. Results for the completer population are quite similar to those for the ITT population as are the number of patients in the topiramate and placebo groups. However, I will focus my comments on results of the ITT population for simplicity.*

  - *Overall, the differences in the various, respective sensitivity analyses treatment difference are relatively small in comparing results for the whole double-blind phase, the last 12 weeks of the trial, and the last 28 days of the trial. Nevertheless, the magnitude of the treatment differences for the last 12 weeks is usually greater than that for the whole double-blind period, and the magnitude of the treatment differences for the last 12 weeks is usually greater than that for the last 28 days for all the efficacy endpoints except 100 % responder rate. Whereas there is no clear topiramate treatment difference for 100 % responders for the whole double-blind period and last 12 weeks of the trial, there does appear to be clear and consistent topiramate treatment difference for 100 % responders for the last 28 days analysis.*

  - *Overall, there does not appear to be clear influence of the variables (24 vs 48 hour rule, application or not of IHS algorithm) on the magnitude of treatment differences. However, the magnitude of treatment differences when the baseline migraine rate is ≥ 3 is frequently greater than the magnitude of treatment differences when the baseline migraine rate is only ≥ 1, suggesting an influence of that variable.*

  - *For the ITT population analyzed for results over the last 28 days of the trial, the treatment difference for the percentage reduction in migraine rate from baseline ranges between 23 % to 42 %. The treatment difference for the absolute reduction in migraine rate from baseline ranges between approximately -0.6 to -1.2. The*

treatment difference for ≥ 50 % responders ranges between 23 % to 40 %. The treatment difference for 100 % responders ranges between 15 % to 24 %. None of these noteworthy treatment differences were statistically significant ($p < 0.05$). However, I suspect that the reason for the lack of statistical significance is likely related to fact these subgroups of adolescents were underpowered to show statistical significance. Although the number of patients in the topiramate group was considerable)N-49), there were only 18 patients in the placebo group.

- *Overall, I interpret these results of adolescents in CAPSS-122 as supportive of the results in MIG-3006 indicating that topiramate is effective for migraine prophylaxis in adolescents.*

- *Table 43 shows sensitivity analyses for all 4 efficacy endpoints for the ITT population (without any requirement for baseline monthly migraine rate) over the last 12 weeks of Study MIG-3006.*

  - *The most noteworthy findings in these results are that the treatment difference for the 100 mg topiramate dose is borderline statistically significant ($p < 0.06$ for the 48 hour and 24 hour sensitivity analyses when the IHS algorithm is applied. These p-values include adjustment for multiple doses. However, as Dr. Massie (Primary Statistical Reviewer) noted in his review, this 48 hour result with the IHS algorithm applied is nominally statistically significant with a p value of 0.03 (without Hochberg multiplicity adjustment.*

    The following is abstracted from Dr. Massie's review to support the view that counting migraine according to patient diaries and not according to the IHS algorithm was not a serious concern and does not detract from concluding that topiramate is effective for migraine prophylaxis in adolescents :
    "The primary endpoint based on the percent reduction from baseline over the last 12 weeks based on the subject classification with the 48 hour rule for counting migraines was statistically significant for the high dose, TPM 100 mg, even after making the prespecified Hochberg adjustment for two dose groups. The corresponding analysis of the percent reduction based on the IHS classification was not statistically significant. However, this reviewer found that the reduction from baseline based on the IHS algorithm was nominally significant for the high dose, TPM 100 mg. Two other post-hoc, slightly modified percent reduction analyses done by the reviewer were also nominally significant. Therefore, the change from using the IHS method of migraine classification is not considered a serious issue by this reviewer."

- *Table 44 shows sensitivity analyses for all 4 efficacy endpoints (without any requirement for baseline monthly migraine rate)for the ITT population for all pediatric patients (6-17 yo) and adolescents (12-17yo) over the last 12 weeks of CAPSS-122.*

- *For all efficacy endpoints (except 100 % responders), the topiramate treatment difference for adolescents is greater than that for all patients in almost every analysis. However, in most instances, the p-values for adolescents for these treatment differences are larger than respective p-values for treatment differences in all pediatric patients. I interpret these observations as suggesting greater effects of topiramate in adolescents compared to younger pediatric patients but that the reason for the larger p-values is underpowering. Whereas the N is 108 for topiramate and is 49 for placebo in all pediatric patients, the N is 49 for topiramate and is 18 for placebo in adolescent patients.*

- *For the percent reduction from baseline and the change from baseline in migraine rate, the 48 hour and 24 hour analyses according to the IHS algorithm show larger treatment differences than those when the IHS algorithm is not applied. These results of adolescents in CAPSS-122 further support results of MIG-3006 indicating the therapeutic benefit of topiramate for migraine prophylaxis in adolescents.*

- *Table 45 shows sensitivity analyses for the primary efficacy endpoint for the ITT population (without any requirement for baseline monthly migraine rate) over the last 28 days of Study MIG-3006.*

  - *The median percent reduction from baseline in monthly migraine rate is 100 % for 100 mg and 61 % for placebo. In this analysis, the treatment difference is 39 %, a value that is larger than the treatment difference (28 %) in the primary analysis when results were analyzed over the last 12 weeks of the trial. This result suggest a greater therapeutic benefit after 4 months treatment compared to the average benefit observed in the maintenance period from month 1-4.*

- *Overall, I find all these various sensitivity analyses as supporting the robust findings of efficacy observed in MIG-3006.*

7 Review of Safety

Safety Summary

The sponsor submitted safety analyses that had been conducted previously for topiramate controlled and open-label monotherapy trials that included pediatric patients as young as 6 years old. These safety analyses results were submitted not only for comparison with pediatric migraine safety results but also to help support that safety of topiramate for migraine prophylaxis for adolescents (12-17 yo), and especially to provide more long-term open-label treatment safety experience. Table 46 describes the monotherapy trials.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety was evaluated relative to the migraine indication in placebo-controlled trials (MIG-3006, CAPSS-122, and MIGR-1-3) and in open-label trials (CAPSS-122, and MIGR-1-3) (Table 2). Supportive safety data were also provided for evaluation from controlled and open-label trials of pediatric patients (≥ 6yo) in monotherapy trials for epilepsy (Table 46).

Table 46 Description of Epilepsy Monotherapy Studies Contributing Data to the Safety Summary

Protocol Number(s)	Study Design
Double-Blind	
TOPMAT-EPMN-104	Randomized, double-blind, parallel-group study comparing the safety and efficacy of a low dosage (25 or 50 mg/day based on body weight) and a high dosage (200 or 500 mg/day based on body weight) of topiramate as monotherapy for the treatment of recently diagnosed partial onset epilepsy in adult and pediatric subjects, (≥3 years of age allowed; ≥6 years of age actually enrolled). The study included 4 phases: a retrospective baseline phase (3 months), an open-label treatment phase (7 days), a double-blind treatment phase (variable duration), and a long-term extension (see below).
TOPMAT-EPMN-105	Randomized, double-blind, parallel group study that compared the efficacy and safety of 2 dosages (100 and 200 mg/day) of topiramate monotherapy to standard monotherapy (either carbamazepine 600 mg/day or valproate 1,250 mg/day) in adult and pediatric (≥6 years of age) subjects with newly diagnosed epilepsy. The study included 3 phases: baseline (7 days), double-blind (5-week titration followed by stabilization of variable duration), and blinded crossover extension of variable duration in which subjects could receive the alternative study medication within their treatment branch under blinded conditions.
TOPMAT-EPMN-106	Randomized, double-blind, parallel-group study comparing the safety and efficacy of 2 dosages of topiramate (50 or 400 mg/day) as monotherapy for the treatment of newly diagnosed or recurrent epilepsy in adult or pediatric subjects (lower limit of enrollment was set not by age,[a] but by body weight ≥25 kg, yielding subjects as young as 6 years). The study had 4 phases: baseline (3-month retrospective), open-label treatment (topiramate 25 mg/day for 7 days to ascertain tolerability), double-blind (50 or 400 mg/day, with a 42-day titration period followed by a stabilization period), and long-term extension (see below).
Open-Label	
TOPMAT-EPMN-104, TOPMAT-EPMN-106	Open-label, flexible-length extensions of topiramate monotherapy up to a maximum of 1,600 mg/day for subjects ≥14 years (for subjects <14 years of age, up to 24 mg/kg/day), yielding topiramate exposure maxima of approximately 7 years in TOPMAT-EPMN-104 and 4 years in TOPMAT-EPMN-106.

[a] Except for sites in Norway, where minimum age was 14 years per local requirements.
Source: Table 3 in the Integrated Summary of Safety of topiramate application 20-505/S-042 (20-844/S-036), approved July 2011, as well as clinical study reports for each study.

71.2 Categorization of Adverse Events

Analysis of Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any untoward medical occurrence, such as intercurrent illness or injury, which occurred as new onset or was presented at baseline and worsened during the study during treatment. Adverse events (verbatim terms) were coded using the "TWA92" dictionary, which is a modified version of the World Health Organization Adverse Reactions Terminology (WHOART) dictionary. For purposes of this integrated safety analysis, no events were recoded from the original study databases. The mapping of TEAE terminology is shown from verbatim term (VT) to preferred term (PT) and from PT to VT.

TEAEs were assessed at each study visit. Information recorded for each TEAE included description, dates of onset and resolution (if applicable), investigator safety analysis of patient (mild, moderate, or severe in Study TOPMAT-MIG-3006; and mild, moderate, or marked in Studies TOPMAT-EPMN-104, -105, and -106; CAPSS-122; and TOPMAT-MIGR-001, -002, and -003), investigator, -105, and -106; CAPSS-122; and TOP study medication (not related, doubtful, possible, probable, or very likely), and whether or not the TEAE was serious or treatment limiting.

Only TEAEs are summarized in this integrated document. A TEAE is defined as any AE that was new in onset (ie, after first dose date) or was aggravated in severity or frequency following treatment.

Serious TEAEs (TESAEs) are 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, cancer, or required medical or surgical intervention to prevent permanent sequelae or any of the previously mentioned outcomes.

Listings (i.e., hub tables) of subjects who died, had SAEs, discontinued due to AEs, or had other clinically notable special safety events are provided for the migraine prophylaxis study population (HUB_MIG) and for the epilepsy monotherapy study population (HUB_MONO). Within both of the hub tables, hyperlinks from each subject number will take the reviewer to the patient's narrative.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Although safety data in individual migraine trials of pediatric patients were presented separately, pools of these trials, outlined in Section 7.1.1, were also presented for evaluating all safety parameters/data.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The following shows the various exposures for topiramate treatment in controlled and open-label trials of pediatric patients for migraine prophylaxis. A breakdown is also provided showing

subgroups for adolescents (12-17 yo) and for younger patients (6-11 yo). Because the clinical development program had relatively limited long-term, open-label topiramate exposure for pediatric patients for the migraine indication, the sponsor also provided safety data and exposures for pediatric patients treated with topiramate as monotherapy for epilepsy.

Table 47 Number of Pediatric Subjects Exposed to Topiramate in the Migraine Prophylaxis Studies (Migraine Prophylaxis sNDA 2013: Double-Blind and Open-Label Subjects Analysis Seta)

	All, Age 6-17 Years	Age 6-11 Years	Age 12-17 Years
Double-blind studies	215	59	156
Open-label extension studies[b]	158	66	92
Combined (no. unique subjects)[b]	260	82	178

[a] Included Study CAPSS-122, Study TOPMAT-MIG-3006, and adolescents (aged 12-17 years) from Studies TOPMAT-MIGR-001, -002, and -003.
[b] Subjects randomly assigned to placebo in a double-blind phase could have topiramate exposure if they continued to an open-label phase.

Table 48 Double-Blind Pediatric Migraine Prophylaxis Data Sets

	All, Age 6-17 Years[a]		Age 6-11 Years		Age 12-17 Years	
Double-Blind Studies	Placebo	Topiramate	Placebo	Topiramate	Placebo	Topiramate
CAPSS-122	49	108	31	59	18	49
TOPMAT-MIG-3006	33	70	0	0	33	70
Pooled TOPMAT-MIGR-001,-002, and -003	12	37	0	0	12	37
Pooled TOPMAT-MIGR-001, -002, -003; CAPSS-122; and TOPMAT-MIG-3006	94	215	31	59	63	156

[a] Three subjects were 17 years old at screening and reached 18 years old at randomization. These 3 subjects were counted in the age 12-17 years group.
Source: Pediatric Migraine Prophylaxis Statistical Analysis Plan, Table 2.

Table 49 Open-Label Pediatric Migraine Prophylaxis Data Sets

	Subjects Receiving Topiramate		
Open-Label Studies	Age 6-17 Years	Age 6-11 Years	Age 12-17 Years
CAPSS-122	122	66	56
Pooled TOPMAT-MIGR-001 and -002	36	0	36
Pooled TOPMAT-MIGR-001, -002, and CAPSS-122	158	66	92

Source: Pediatric Migraine Prophylaxis Statistical Analysis Plan, Table 3.

Table 50 Number of Pediatric Subjects Exposed to Topiramate in the Epilepsy Monotherapy Studies (Epilepsy Monotherapy sNDA 2009: Double-Blind and Open-Label Subjects Analysis Seta)

	All, Age 6-15 Years	Age 6-9 Years[b]	Age 10-15 Years
Double-blind studies	245	67	178
Open-label extension studies	153	41	112
Combined (no. unique subjects)	245	67	178

[a] Included Studies TOPMAT-EPMN-104, -105, and -106.
[b] Younger subjects were allowed in 1 of the epilepsy monotherapy studies, but the youngest subject actually enrolled was 6 years of age.

Table 51 Summary of Treatment Dosage in Milligrams for the Pooled Double-Blind Migraine Prophylaxis Studies(Migraine Prophylaxis sNDA 2013: Double-Blind Subjects Analysis Set[a])

	2-3 mg/kg/d	50 mg/d	100 mg/d	200 mg/d	Any TPM
Average Daily Dosage, mg					
All subjects					
N	108	46	48	13	215
Mean	79.12	42.28	75.64	137.08	73.97
Standard deviation	32.778	9.192	18.465	39.200	34.465
Median	72.63	45.35	80.47	149.31	70.83
Minimum	11.3	1.6	14.0	56.7	1.6
Maximum	160.1	48.8	94.2	172.8	172.8
Age 6-11 years					
N	59	-	-	-	59
Mean	66.47	-	-	-	66.47
Standard deviation	29.321	-	-	-	29.321
Median	62.77	-	-	-	62.77
Minimum	11.3	-	-	-	11.3
Maximum	141.2	-	-	-	141.2
Age 12-17 years					
N	49	46	48	13	156
Mean	94.34	42.28	75.64	137.08	76.80
Standard deviation	30.384	9.192	18.465	39.200	35.900
Median	95.32	45.35	80.47	149.31	75.91
Minimum	21.3	1.6	14.0	56.7	1.6
Maximum	160.1	48.8	94.2	172.8	172.8
Maximum Daily Dosage, mg					
All subjects					
N	-[b]	46	48	13	107
Mean	-[b]	50.54	96.88	182.69	87.38
Standard deviation	-[b]	8.315	16.000	38.709	45.346
Median	-[b]	50.00	100.00	200.00	100.00
Minimum	-[b]	25.0	25.0	75.0	25.0
Maximum	-[b]	75.0	125.0	200.0	200.0
Age 6-11 years					
N	-[b]	-	-	-	-
Age 12-17 years					
N	-[b]	46	48	13	107
Mean	-[b]	50.54	96.88	182.69	87.38
Standard deviation	-[b]	8.315	16.000	38.709	45.346
Median	-[b]	50.00	100.00	200.00	100.00
Minimum	-[b]	25.0	25.0	75.0	25.0
Maximum	-[b]	75.0	125.0	200.0	200.0
Minimum Daily Dosage, mg					
All subjects					
N	-[b]	46	48	13	107
Mean	-[b]	13.04	14.58	11.54	13.55
Standard deviation	-[b]	12.626	12.456	12.972	12.514
Median	-[b]	25.00	25.00	0.00	25.00
Minimum	-[b]	0.0	0.0	0.0	0.0
Maximum	-[b]	25.0	25.0	25.0	25.0
Age 6-11 years					
N	-[b]	-	-	-	-
Age 12-17 years					
N	-[b]	46	48	13	107
Mean	-[b]	13.04	14.58	11.54	13.55
Standard deviation	-[b]	12.626	12.456	12.972	12.514
Median	-[b]	25.00	25.00	0.00	25.00
Minimum	-[b]	0.0	0.0	0.0	0.0
Maximum	-[b]	25.0	25.0	25.0	25.0

[a] Included Study CAPSS-122, Study TOPMAT-MIG-3006, and adolescents (aged 12-17 years) from Studies TOPMAT-MIGR-001, -002, and -003.

[b] Maximum and minimum daily dosages were not available in Study CAPSS-122, the only migraine prophylaxis study with subjects aged 6-11 years.

Table 52 Summary of Treatment Dosage in Milligrams Per Kilogram for the Pooled Double-Blind Migraine Prophylaxis Studies (Migraine Prophylaxis sNDA 2013: Double-Blind Subjects Analysis Set[a])

	2-3 mg/kg/d	50 mg/d	100 mg/d	200 mg/d	Any TPM
Average Daily Dosage, mg/kg					
All subjects					
N	108	46	48	13	215
Mean	1.67	0.77	1.34	2.39	1.45
Standard deviation	0.552	0.274	0.481	1.019	0.676
Median	1.77	0.76	1.47	2.35	1.48
Minimum	0.2	0.0	0.2	0.9	0.0
Maximum	3.3	1.6	2.7	4.3	4.3
Age 6-11 years					
N	59	-	-	-	59
Mean	1.76	-	-	-	1.76
Standard deviation	0.596	-	-	-	0.596
Median	1.82	-	-	-	1.82
Minimum	0.2	-	-	-	0.2
Maximum	3.3	-	-	-	3.3
Age 12-17 years					
N	49	46	48	13	156
Mean	1.56	0.77	1.34	2.39	1.33
Standard deviation	0.477	0.274	0.481	1.019	0.669
Median	1.53	0.76	1.47	2.35	1.30
Minimum	0.5	0.0	0.2	0.9	0.0
Maximum	2.2	1.6	2.7	4.3	4.3
Maximum Daily Dosage, mg/kg					
All subjects					
N	-[b]	46	48	13	107
Mean	-[b]	0.92	1.73	3.25	1.57
Standard deviation	-[b]	0.261	0.521	1.152	0.916
Median	-[b]	0.93	1.77	2.95	1.32
Minimum	-[b]	0.4	0.4	1.1	0.4
Maximum	-[b]	1.6	3.0	5.3	5.3
Age 6-11 years					
N	-[b]	-	-	-	-
Age 12-17 years					
N	-[b]	46	48	13	107
Mean	-[b]	0.92	1.73	3.25	1.57
Standard deviation	-[b]	0.261	0.521	1.152	0.916
Median	-[b]	0.93	1.77	2.95	1.32
Minimum	-[b]	0.4	0.4	1.1	0.4
Maximum	-[b]	1.6	3.0	5.3	5.3
Minimum Daily Dosage, mg/kg					
All subjects					
N	-[b]	46	48	13	107
Mean	-[b]	0.25	0.25	0.21	0.24
Standard deviation	-[b]	0.261	0.228	0.249	0.243
Median	-[b]	0.28	0.29	0.00	0.28
Minimum	-[b]	0.0	0.0	0.0	0.0
Maximum	-[b]	0.8	0.8	0.6	0.8
Age 6-11 years					
N	-[b]	-	-	-	-
Age 12-17 years					
N	-[b]	46	48	13	107
Mean	-[b]	0.25	0.25	0.21	0.24
Standard deviation	-[b]	0.261	0.228	0.249	0.243
Median	-[b]	0.28	0.29	0.00	0.28
Minimum	-[b]	0.0	0.0	0.0	0.0
Maximum	-[b]	0.8	0.8	0.6	0.8

[a] Included Study CAPSS-122, Study TOPMAT-MIG-3006, and adolescents (aged 12-17 years) from Studies TOPMAT-MIGR-001, -002, and -003.

[b] Maximum and minimum daily dosages were not available in Study CAPSS-122, which was the only migraine prophylaxis study with subjects aged 6-11 years and the only study with mg/kg dosing.

Table 53 Dose-Duration Topiramate Exposure of Pediatric Migraine Patients in Pooled Double-Blind Trials

Analysis Set: Double Blind Subjects

	Placebo	TPM 2-3 mg/kg/day	TPM 50 mg/day	TPM 100 mg/day	TPM 200 mg/day	Any TPM
ALL SUBJECTS						
TREATMENT DURATION, DAYS						
N	94	108	46	48	13	215
Category, n (%)						
1-179 DAYS (<6 MONTHS)	90 (96)	107 (99)	41 (89)	42 (88)	5 (38)	195 (91)
180-359 DAYS (6 MONTHS - <1 YEAR)	4 (4)	1 (1)	5 (11)	6 (13)	8 (62)	20 (9)
6-11 YEARS						
TREATMENT DURATION, DAYS						
N	31	59				59
Category, n (%)						
1-179 DAYS (<6 MONTHS)	31 (100)	58 (98)				58 (98)
180-359 DAYS (6 MONTHS - <1 YEAR)	0	1 (2)				1 (2)
12-17 YEARS						
TREATMENT DURATION, DAYS						
N	63	49	46	48	13	156
Category, n (%)						
1-179 DAYS (<6 MONTHS)	59 (94)	49 (100)	41 (89)	42 (88)	5 (38)	137 (88)
180-359 DAYS (6 MONTHS - <1 YEAR)	4 (6)	0	5 (11)	6 (13)	8 (62)	19 (12)

Table 54 Duration Topiramate Exposure of Pediatric Migraine Patients in Pooled Double-Blind Trials

Analysis Set: Open Label Subjects

	Any TPM		
	ALL SUBJECTS	6-11 YEARS	12-17 YEARS
TREATMENT DURATION, DAYS			
N	158	66	92
Category, n (%)			
1-179 DAYS (<6 MONTHS)	135 (85)	66 (100)	69 (75)
180-359 DAYS (6 MONTHS - <1 YEAR)	23 (15)	0	23 (25)
Mean	108.2	86.4	123.8
SD	61.73	14.33	76.39
Median	85.0	85.0	85.0
Minimum	8	31	8
Maximum	343	127	343
Total Exposure (subject years)	46.8	15.6	31.2

Table 55 Treatment Duration Summary for the Combined Double-Blind and Open-Label Phases of the Migraine Prophylaxis Studies (Migraine Prophylaxis sNDA 2013: Double-Blind and Open-Label Subjects Analysis Set[a])

	Any Topiramate		
Treatment Duration, Days	All Subjects	Age 6-11 Years	Age 12-17 Years
N	260	82	178
Category, n (%)			
1-179 days (<6 months)	142 (55)	38 (46)	104 (58)
180-359 days (6 months to <1 year)	100 (38)	44 (54)	56 (31)
360-539 days (1 year to <1.5 years)	18 (7)	0	18 (10)
Mean	168.3	157.9	173.2
Standard deviation	103.15	80.91	111.80
Median	127.5	210.0	120.5
Minimum	4	4	7
Maximum	533	253	533
Total exposure, subject-years	119.8	35.4	84.4

[a] Included Study CAPSS-122, Study TOPMAT-MIG-3006, and adolescents (aged 12-17 years) from Studies TOPMAT-MIGR-001, -002, and -003.

Table 56 Dose-Duration Topiramate Exposure of Pediatric Monotherapy Epilepsy Patients in Pooled Double-Blind Trials

Analysis Set: Double Blind Subjects

	TPM 25/50 mg/day					TPM 100 mg/day				
	AGE 6-9	AGE 10-15	AGE >=16	AGE 6-15	TOTAL	AGE 6-9	AGE 10-15	AGE >=16	AGE 6-15	TOTAL
TREATMENT DURATION, DAYS										
N	25	70	264	95	359	7	23	179	30	209
Category, n (%)										
1-179 DAYS (<6 MONTHS)	7 (28)	21 (30)	128 (48)	28 (29)	156 (43)	2 (29)	7 (30)	60 (34)	9 (30)	69 (33)
180-359 DAYS (6 MONTHS - <1 YEAR)	8 (32)	24 (34)	80 (30)	32 (34)	112 (31)	1 (14)	7 (30)	59 (33)	8 (27)	67 (32)
360-539 DAYS (1 YEAR - <1.5 YEARS)	5 (20)	19 (27)	28 (11)	24 (25)	52 (14)	3 (43)	3 (13)	38 (21)	6 (20)	44 (21)
540-719 DAYS (1.5 YEARS - <2 YEARS)	4 (16)	6 (9)	24 (9)	10 (11)	34 (9)	1 (14)	6 (26)	21 (12)	7 (23)	28 (13)
720-1079 DAYS (2 YEARS - <3 YEARS)	1 (4)	0	4 (2)	1 (1)	5 (1)	0	0	1 (1)	0	1 (<1)
Mean	335.0	286.4	224.1	299.2	243.9	363.3	323.0	267.8	332.4	277.1
SD	209.58	180.10	194.53	188.38	195.50	264.94	222.72	187.43	229.03	194.66
Median	353.0	272.5	186.0	315.0	211.0	507.0	279.0	253.0	314.5	254.0
Minimum	26	9	9	9	9	35	21	6	21	6
Maximum	758	691	763	758	763	685	656	729	685	729
Total Exposure (subject years)	22.9	54.9	161.9	77.8	239.8	7.0	20.3	131.2	27.3	158.5

	TPM 200 mg/day					TPM 400 mg/day				
	AGE 6-9	AGE 10-15	AGE >=16	AGE 6-15	TOTAL	AGE 6-9	AGE 10-15	AGE >=16	AGE 6-15	TOTAL
TREATMENT DURATION, DAYS										
N	8	21	167	29	196	20	57	159	77	236
Category, n (%)										
1-179 DAYS (<6 MONTHS)	2 (25)	4 (19)	75 (45)	6 (21)	81 (41)	7 (35)	7 (12)	72 (45)	14 (18)	86 (36)
180-359 DAYS (6 MONTHS - <1 YEAR)	3 (38)	11 (52)	44 (26)	14 (48)	58 (30)	5 (25)	19 (33)	38 (24)	24 (31)	62 (26)
360-539 DAYS (1 YEAR - <1.5 YEARS)	3 (38)	4 (19)	39 (23)	7 (24)	46 (23)	6 (30)	21 (37)	28 (18)	27 (35)	55 (23)
540-719 DAYS (1.5 YEARS - <2 YEARS)	0	2 (10)	8 (5)	2 (7)	10 (5)	2 (10)	10 (18)	14 (9)	12 (16)	26 (11)
720-1079 DAYS (2 YEARS - <3 YEARS)	0	0	1 (1)	0	1 (1)	0	0	7 (4)	0	7 (3)
Mean	276.8	275.3	235.8	275.7	241.7	291.9	371.4	260.4	350.8	289.9
SD	175.80	169.30	183.62	167.93	181.53	204.37	172.49	222.03	183.29	214.04
Median	238.5	267.0	204.0	267.0	228.5	231.0	383.0	197.0	365.0	270.0
Minimum	47	21	3	21	3	12	29	9	12	9
Maximum	503	632	806	632	806	627	627	786	627	786
Total Exposure (subject years)	6.1	15.8	107.8	21.9	129.7	16.0	58.0	113.4	73.9	187.3

	TPM 200/500 mg/day					Total TPM				
	AGE 6-9	AGE 10-15	AGE >=16	AGE 6-15	TOTAL	AGE 6-9	AGE 10-15	AGE >=16	AGE 6-15	TOTAL
TREATMENT DURATION, DAYS										
N	7	7	113	14	127	67	178	882	245	1127
Category, n (%)										
1-179 DAYS (<6 MONTHS)	3 (43)	3 (43)	67 (59)	6 (43)	73 (57)	21 (31)	42 (24)	402 (46)	63 (26)	465 (41)
180-359 DAYS (6 MONTHS - <1 YEAR)	3 (43)	3 (43)	30 (27)	6 (43)	36 (28)	20 (30)	64 (36)	251 (28)	84 (34)	335 (30)
360-539 DAYS (1 YEAR - <1.5 YEARS)	0	1 (14)	9 (8)	1 (7)	10 (8)	17 (25)	48 (27)	142 (16)	65 (27)	207 (18)
540-719 DAYS (1.5 YEARS - <2 YEARS)	0	0	6 (5)	0	6 (5)	7 (10)	24 (13)	73 (8)	31 (13)	104 (9)
720-1079 DAYS (2 YEARS - <3 YEARS)	1 (14)	0	1 (1)	1 (7)	2 (2)	2 (3)	0	14 (2)	2 (1)	16 (1)
Mean	235.1	218.1	190.4	226.6	194.4	307.7	314.4	237.4	312.6	253.7
SD	277.19	154.61	170.93	215.80	175.80	214.48	184.89	194.74	193.00	196.74
Median	210.0	204.0	140.0	207.0	141.0	288.0	314.5	202.5	311.0	225.0
Minimum	17	28	15	17	15	12	9	3	9	3
Maximum	809	471	807	809	809	809	691	807	809	809
Total Exposure (subject years)	4.5	4.2	58.9	8.7	67.6	56.4	153.2	573.3	209.7	782.9

Reviewer Comments

The various tables presented here show that there is a significant exposure at the 100 mg daily dose level (or higher) for pediatric migraine, especially for adolescents (12-17 yo) in controlled trials. Although there was very limited open-label topiramate treatment exposure for migraine trials in pediatric patients, there was reasonably adequate topiramate treatment exposure in controlled and open-label monotherapy trials in pediatric patients including adolescent patients and at the 100 mg daily dose level and also at higher daily dosing levels. These topiramate monotherapy exposures support the safety of long-term migraine prophylaxis with topiramate as relevant exposures.

7.2.2 Explorations for Dose Response

Safety data analyses (i.e., TEAEs, clinical laboratory analytes, and vital signs) were evaluated for dose-response in the MIG-3006 trial (50 mg and 100 mg), the pool of MIGR-1-3 (50 mg, 100 mg, 200 mg), and the pool of all these trials.

7.2.3 Special Animal and/or In Vitro Testing

No applicable.

7.2.4 Routine Clinical Testing

Safety Analyses
Analyses were performed by treatment group, by age subgroup (based on age at enrollment), and overall. In the migraine prophylaxis studies, the pediatric age subgroups were 6 to 11 years and 12 to 17 years. In the epilepsy monotherapy studies, the pediatric age subgroups were 6 to 9 years and 10 to 15 years. Definitions for age subgroups, treatment groups, visit windows, and titration and maintenance periods are provided in the SAPs for migraine prophylaxis and epilepsy monotherapy.

Analyses performed for this safety summary are as follows (though not all studies collected the required data for each analysis):

- Demographics and baseline characteristics (age, race, sex, height, weight, and body mass index [BMI]).
- Extent of exposure to study medication (duration and dosage).
- Treatment-emergent AEs (TEAEs), including:
    - Common AEs (occurring in ≥2% of subjects in any treatment group).
    - In cases where n=1 was ≥2%, common AEs were also analyzed as ≥10% of subjects in any treatment group.
    - In all cases, the ≥2% threshold is presented in the appendices, but the ≥10% threshold is discussed in text.
    - Serious AEs (TESAEs).
    - TEAEs that led to treatment discontinuation.
    - TEAEs reflecting cognitive dysfunction (for the double-blind studies only).
    - TEAEs by time of onset relative to dose titration and attainment of maintenance dose (for the double-blind studies only).
- Clinical laboratory test values (hematology, chemistry, and urinalysis), including summaries of values and change from baseline, shifts based on normal range values, frequency of abnormal and markedly abnormal values, and outlier analysis of treatment-emergent blood urea nitrogen and serum creatinine values with an increase of >50% from baseline (for migraine prophylaxis studies only).
- Vital sign measurements (temperature, blood pressure, pulse, temperature, and respiratory rate), including summaries of values, change from baseline, and frequency of abnormal values.

- Growth parameters, including absolute values and change from baseline in weight, height, and BMI (converted to Z-scores and percentiles), and height velocity values and Z-scores. Height velocity values and Z-score computations were developed with expert consultation, using normative data based from published literature; for more details, see the SAPs for migraine prophylaxis and epilepsy monotherapy.
- Cognitive and mood assessments, in the form of the CANTAB and the Profile of Mood States (POMS), for Study TOPMAT-MIG-3006 only. For each selected CANTAB outcome or POMS factor, change from baseline to double-blind endpoint was analyzed by using an analysis of covariance (ANCOVA) model.

Additional safety analyses were performed, including summaries of prespecified PTs and clinical laboratory data, for the following areas of special safety concern associated with topiramate: growth delay/retardation, metabolic acidosis, hyperammonemia and encephalopathy, oligohidrosis and hyperthermia, renal events (including nephrolithiasis), hepatic injury, and visual AEs. Narratives are provided for all subjects with these events, as well as for subjects with SAEs or treatment-limiting AEs.

The sponsor also presented results of special testing for cognitive function (with CANTAB) and for mood (with POMS).

There are no analyses of ECG parameter data because ECGs were not routinely collected in the migraine trials.

Safety data analyses were evaluated for time-dependency by analyzing data relative to any time in the trial, developing in the titration period, developing in the maintenance period, or developing in the titration period and persisting into the maintenance period with a total duration of at least 7 days.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There was no particular focus on potential TEAEs for similar drugs in the class (i.e., anti-epileptic drug-AED). Topiramate has a relatively unique profile for its pharmacological actions that is not possessed by similar drugs in the AED class with perhaps exception of zonisamide. There were, however, analyses of TEAEs and also testing for cognitive function and mood.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in the migraine pediatric trials.

7.3.2 Nonfatal Serious Adverse Events

The sponsor provided the following summary.

Serious AEs occurred in 2 (2%) of 94 placebo-treated subjects and 6 (3%) of 215 topiramate-treated subjects (Table 57), with frequencies per age group as follows :

- In the age 6 to 11 years group, 0 of 31 placebo-treated subjects and 3 (5%) of 59 topiramate-treated subjects.
- In the age 12 to 17 years group, 2 (3%) of 63 placebo-treated subjects and 3 (2%) of 156 topiramate-treated subjects.
- Of the SAEs shown in, all had been assessed as having no relationship or doubtful relationship to study drug, except for the case of suicide attempt, which was assessed as probably related to study medication by the investigator and possibly related to study medication by the sponsor.

Table 57 Treatment-Emergent Serious Adverse Events (TESAES) in the Pooled Double-Blind Migraine Prophylaxis Studies (Double Blind Subjects Analysis Seta)

		---------- Topiramate ----------				
Age group Body system Preferred term	Placebo (N=94) n (%)[b]	2-3 mg/kg/d (N=108) n (%)[b]	50 mg/d (N=46) n (%)[b]	100 mg/d (N=48) n (%)[b]	200 mg/d (N=13) n (%)[b]	Any TPM (N=215) n (%)[b]
All Subjects	**94**	**108**	**46**	**48**	**13**	**215**
Total, subjects with serious AEs	2 (2)	4 (4)	0	2 (4)	0	6 (3)
Age 6-11 Years	**31**	**59**	**0**	**0**	**0**	**59**
Total, subjects with serious AEs	0	3 (5)	0	0	0	3 (5)
Age 12-17 Years	**63**	**49**	**46**	**48**	**13**	**156**
Total, subjects with serious AEs	2 (3)	1 (2)	0	2 (4)	0	3 (2)
All Subjects						
Body as a whole - general disorders	0	0	0	2 (4)	0	2 (1)
Back pain	0	0	0	1 (2)	0	1 (<1)
Injury	0	0	0	1 (2)	0	1 (<1)
Central and peripheral NS disorders	0	1 (1)	0	0	0	1 (<1)
Migraine	0	1 (1)	0	0	0	1 (<1)
Metabolic and nutritional disorders	1 (1)	0	0	0	0	0
Ketosis	1 (1)	0	0	0	0	0
Psychiatric disorders	0	1 (1)	0	0	0	1 (<1)
Suicide attempt	0	1 (1)	0	0	0	1 (<1)
Resistance mechanism disorders	0	2 (2)	0	0	0	2 (1)
Infection	0	2 (2)	0	0	0	2 (1)
Respiratory system disorders	1 (1)	0	0	0	0	0
Pharyngitis	1 (1)	0	0	0	0	0
Age 6-11 Years						
Body as a whole - general disorders	0	0	0	0	0	0
Back pain	0	0	0	0	0	0
Injury	0	0	0	0	0	0
Central and peripheral NS disorders	0	1 (2)	0	0	0	1 (2)
Migraine	0	1 (2)	0	0	0	1 (2)
Metabolic and nutritional disorders	0	0	0	0	0	0
Ketosis	0	0	0	0	0	0
Psychiatric disorders	0	0	0	0	0	0
Suicide attempt	0	0	0	0	0	0
Resistance mechanism disorders	0	2 (3)	0	0	0	2 (3)
Infection	0	2 (3)	0	0	0	2 (3)
Respiratory system disorders	0	0	0	0	0	0
Pharyngitis	0	0	0	0	0	0
Age 12-17 Years						
Body as a whole - general disorders	0	0	0	2 (4)	0	2 (1)
Back pain	0	0	0	1 (2)	0	1 (1)
Injury	0	0	0	1 (2)	0	1 (1)
Central and peripheral NS disorders	0	0	0	0	0	0
Migraine	0	0	0	0	0	0
Metabolic and nutritional disorders	1 (2)	0	0	0	0	0
Ketosis	1 (2)	0	0	0	0	0
Psychiatric disorders	0	1 (2)	0	0	0	1 (1)
Suicide attempt	0	1 (2)	0	0	0	1 (1)
Resistance mechanism disorders	0	0	0	0	0	0
Infection	0	0	0	0	0	0
Respiratory system disorders	1 (2)	0	0	0	0	0
Pharyngitis	1 (2)	0	0	0	0	0

Serious Adverse Events by Time of Onset
For the double-blind migraine prophylaxis studies, TESAEs are sorted by time of onset in as follows:

- Onset during the titration period
- Onset during titration with persistence into the maintenance period
- Onset during the maintenance period

For the only SAE from Table 57 that was assessed as possibly or probably related to study medication (i.e., for the case of suicide attempt), onset occurred during the titration period.

Open-Label Studies

During the open-label migraine prophylaxis studies, no SAEs occurred.

Reviewer Comments

A total of 6 topiramate-treated pediatric patients experienced TESAEs in all the controlled migraine trials. The incidence of TESAEs was slightly higher with topiramate (3 %) than with placebo (2 %). Most patients (83%) experienced the TESAE in the titration period. One TESAE (injury) had its onset in the titration period and persisted into the maintenance period. The only TESAE occurring in more than one patient was infection that occurred in 2 topiramate patients. TESAEs occurred in the 100 mg and 2-3 mg/kg/day dose groups. Of the 4 patients in the latter dose group, 75 % of these patients were in the younger age group (6-11 yo).

7.3.3 Dropouts and/or Discontinuations

Table 58 shows treatment limiting TEAEs causing study discontinuation by age group.

The sponsor provided the following summary of TEAEs causing study discontinuation.

- For the age 6 to 11 years group, treatment-limiting AEs occurred in 0 of 31 placebo-treated subjects and 4 (7%) of 59 topiramate-treated subjects.
- For the age 12 to 17 years group, treatment-limiting AEs occurred in 5 (8%) of 63 placebo-treated subjects, a frequency higher than the 10 (6%) of 156 topiramate-treated subjects.
- The only treatment-limiting AEs that occurred in more than 1 subject were fatigue, headache, and somnolence; these AEs each occurred in 0 of 94 placebo-treated subjects and 2 (1%) of 215 topiramate-treated subjects. These TEAEs occurred only in the age 12 to 17 years group, not in the age 6 to 11 years group.
- The overall frequency of treatment-limiting TEAEs did not show any clear dose dependency.

Table 58 Treatment-Emergent Adverse Events Leading to Treatment Discontinuation in the Pooled Double-Blind Migraine Prophylaxis Studies (Double Blind Subjects Analysis Seta)

		Topiramate				
Age Group Body System Preferred Term	Placebo (N=94) n (%)[b]	2-3 mg/kg/d (N=108) n (%)[b]	50 mg/d (N=46) n (%)[b]	100 mg/d (N=48) n (%)[b]	200 mg/d (N=13) n (%)[b]	Any TPM (N=215) n (%)[b]
All Subjects	**94**	**108**	**46**	**48**	**13**	**215**
Total, subjects with AEs that led to discontinuation	5 (5)	9 (8)	3 (7)	2 (4)	0	14 (7)
Age 6-11 Years	**31**	**59**	**0**	**0**	**0**	**59**
Total, subjects with AEs that led to discontinuation	0	4 (7)	0	0	0	4 (7)
Age 12-17 Years	**63**	**49**	**46**	**48**	**13**	**156**
Total, subjects with AEs that led to discontinuation	5 (8)	5 (10)	3 (7)	2 (4)	0	10 (6)
All Subjects						
Body as a whole - general disorders	1 (1)	0	1 (2)	1 (2)	0	2 (1)
Fatigue	0	0	1 (2)	1 (2)	0	2 (1)
Fever	1 (1)	0	0	0	0	0
Central and peripheral NS disorders	0	2 (2)	1 (2)	0	0	3 (1)
Headache	0	1 (1)	1 (2)	0	0	2 (1)
Language problems	0	1 (1)	0	0	0	1 (<1)
Gastro-intestinal system disorders	2 (2)	1 (1)	0	0	0	1 (<1)
Abdominal pain	1 (1)	1 (1)	0	0	0	1 (<1)
Constipation	1 (1)	0	0	0	0	0
Metabolic and nutritional disorders	2 (2)	0	0	0	0	0
Hypokalaemia	1 (1)	0	0	0	0	0
Ketosis	1 (1)	0	0	0	0	0
Age 6-11 Years						
Body as a whole - general disorders	0	0	0	0	0	0
Fatigue	0	0	0	0	0	0
Fever	0	0	0	0	0	0
Central and peripheral NS disorders	0	0	0	0	0	0
Headache	0	0	0	0	0	0
Language problems	0	0	0	0	0	0
Gastro-intestinal system disorders	0	1 (2)	0	0	0	1 (2)
Abdominal pain	0	1 (2)	0	0	0	1 (2)
Constipation	0	0	0	0	0	0
Metabolic and nutritional disorders	0	0	0	0	0	0
Hypokalaemia	0	0	0	0	0	0
Ketosis	0	0	0	0	0	0
Age 12-17 Years						
Body as a whole - general disorders	1 (2)	0	1 (2)	1 (2)	0	2 (1)
Fatigue	0	0	1 (2)	1 (2)	0	2 (1)
Fever	1 (2)	0	0	0	0	0
Central and peripheral NS disorders	0	2 (4)	1 (2)	0	0	3 (2)
Headache	0	1 (2)	1 (2)	0	0	2 (1)
Language problems	0	1 (2)	0	0	0	1 (1)
Gastro-intestinal system disorders	2 (3)	0	0	0	0	0
Abdominal pain	1 (2)	0	0	0	0	0
Constipation	1 (2)	0	0	0	0	0
Metabolic and nutritional disorders	2 (3)	0	0	0	0	0
Hypokalaemia	1 (2)	0	0	0	0	0
Ketosis	1 (2)	0	0	0	0	0

Table 58 Treatment-Emergent Adverse Events Leading to Treatment Discontinuation in the Pooled Double-Blind Migraine Prophylaxis Studies (Double Blind Subjects Analysis Seta) (Continued)

		Topiramate				
Age Group Body System Preferred Term	Placebo (N=94) n (%)[b]	2-3 mg/kg/d (N=108) n (%)[b]	50 mg/d (N=46) n (%)[b]	100 mg/d (N=48) n (%)[b]	200 mg/d (N=13) n (%)[b]	Any TPM (N=215) n (%)[b]
All Subjects						
Psychiatric disorders	0	5 (5)	2 (4)	0	0	7 (3)
Anorexia	0	1 (1)	0	0	0	1 (<1)
Anxiety	0	1 (1)	0	0	0	1 (<1)
Depression	0	0	1 (2)	0	0	1 (<1)
Difficulty with concentration/attention	0	1 (1)	0	0	0	1 (<1)
Emotional lability	0	0	1 (2)	0	0	1 (<1)
Nervousness	0	0	1 (2)	0	0	1 (<1)
Paroniria	0	1 (1)	0	0	0	1 (<1)
Somnolence	0	2 (2)	0	0	0	2 (1)
Suicide attempt	0	1 (1)	0	0	0	1 (<1)
Age 6-11 Years						
Psychiatric disorders	0	2 (3)	0	0	0	2 (3)
Anorexia	0	0	0	0	0	0
Anxiety	0	1 (2)	0	0	0	1 (2)
Depression	0	0	0	0	0	0
Difficulty with concentration/attention	0	0	0	0	0	0
Emotional lability	0	0	0	0	0	0
Nervousness	0	0	0	0	0	0
Paroniria	0	1 (2)	0	0	0	1 (2)
Somnolence	0	0	0	0	0	0
Suicide attempt	0	0	0	0	0	0
Age 12-17 Years						
Psychiatric disorders	0	3 (6)	2 (4)	0	0	5 (3)
Anorexia	0	1 (2)	0	0	0	1 (1)
Anxiety	0	0	0	0	0	0
Depression	0	0	1 (2)	0	0	1 (1)
Difficulty with concentration/attention	0	1 (2)	0	0	0	1 (1)
Emotional lability	0	0	1 (2)	0	0	1 (1)
Nervousness	0	0	1 (2)	0	0	1 (1)
Paroniria	0	0	0	0	0	0
Somnolence	0	2 (4)	0	0	0	2 (1)
Suicide attempt	0	1 (2)	0	0	0	1 (1)
All Subjects						
Resistance mechanism disorders	0	1 (1)	0	0	0	1 (<1)
Infection	0	1 (1)	0	0	0	1 (<1)
Skin and appendages disorders	1 (1)	1 (1)	0	0	0	1 (<1)
Rash	1 (1)	0	0	0	0	0
Sweating decreased	0	1 (1)	0	0	0	1 (<1)
Urinary system disorders	0	0	0	1 (2)	0	1 (<1)
Renal calculus	0	0	0	1 (2)	0	1 (<1)
White cell and RES disorders	0	1 (1)	0	0	0	1 (<1)
WBC abnormal NOS	0	1 (1)	0	0	0	1 (<1)
Age 6-11 Years						
Resistance mechanism disorders	0	1 (2)	0	0	0	1 (2)
Infection	0	1 (2)	0	0	0	1 (2)
Skin and appendages disorders	0	0	0	0	0	0
Rash	0	0	0	0	0	0
Sweating decreased	0	0	0	0	0	0
Urinary system disorders	0	0	0	0	0	0
Renal calculus	0	0	0	0	0	0
White cell and RES disorders	0	0	0	0	0	0
WBC abnormal NOS	0	0	0	0	0	0

Table 58 Treatment-Emergent Adverse Events Leading to Treatment Discontinuation in the Pooled Double-Blind Migraine Prophylaxis Studies (Double Blind Subjects Analysis Seta) (Continued)

		Topiramate				
Age Group Body System Preferred Term	Placebo (N=94) n (%)[b]	2-3 mg/kg/d (N=108) n (%)[b]	50 mg/d (N=46) n (%)[b]	100 mg/d (N=48) n (%)[b]	200 mg/d (N=13) n (%)[b]	Any TPM (N=215) n (%)[b]
Age 12-17 Years						
Resistance mechanism disorders	0	0	0	0	0	0
Infection	0	0	0	0	0	0
Skin and appendages disorders	1 (2)	1 (2)	0	0	0	1 (1)
Rash	1 (2)	0	0	0	0	0
Sweating decreased	0	1 (2)	0	0	0	1 (1)
Urinary system disorders	0	0	0	1 (2)	0	1 (1)
Renal calculus	0	0	0	1 (2)	0	1 (1)
White cell and RES disorders	0	1 (2)	0	0	0	1 (1)
WBC abnormal NOS	0	1 (2)	0	0	0	1 (1)

Adverse Events Leading to Discontinuation by Time of Onset

- For subjects receiving topiramate, most treatment-limiting TEAEs, both in children (aged 6-11 years) and adolescents (aged12-17 years) had onset during titration. In adolescents, onset occurred more commonly during early titration than late titration; no early versus late titration data were available for the younger children.
- For the TEAEs of fatigue, headache, and somnolence, (i.e., the only treatment-limiting AEs from that occurred in more than 1 patient each), onset occurred during titration in all cases. One case each of headache and fatigue occurred during early titration; the other cases of headache, fatigue, and somnolence did not qualify as early titration or late titration.

Open-Label Studies

During the open-label migraine prophylaxis studies, only 1 patient experienced TEAEs leading to treatment discontinuation. The treatment-limiting TEAEs were dizziness and difficulty with concentration/attention, which both occurred in Subject MIGR-002-201003, for a total frequency of 1 (1%) of 158 open-label subjects.

Reviewer Comments

The incidence of TEAEs causing study discontinuation was higher with topiramate treatment (7 %) than with placebo (5 %). The incidence of such events was similar for older and younger pediatric patients, Many of these events were isolated to a single patient. Each of three events (headache, fatigue, and somnolence) occurred in more than one patient (i.e., 2 patients). Not surprisingly, most patients (79 %) experienced TEAEs causing study discontinuation in the titration period. I agree with the sponsor that there was no clear dose-dependence of such events.

7.3.4 Significant Adverse Events

No TEAEs are presented nor discussed here. TEAEs that are submission specific primary safety concerns are presented and discussed in the next section.

7.3.5 Submission Specific Primary Safety Concerns

Prior to NDA submission, there was a plan to conduct many analyses of topics considered to be of special interest in the pediatric safety profile of topiramate. These topics are growth delay/retardation, metabolic acidosis, hyperammonemia/encephalopathy, oligohidrosis/hyperthermia, renal events (including nephrolithiasis), hepatic injury, and visual AEs. The information presented below includes summarizes findings of various analyses of programmatically generated tables summarizing selected TEAEs and laboratory data, and comments (as necessary/appropriate) on a clinical assessment of the narratives for special safety events occurring in pediatric subjects (≤ 17 years of age at enrollment into migraine prophylaxis studies; < 16 years of age in epilepsy monotherapy studies).

The following summarizes the sponsor's presentation of information on these issues particularly for pediatric patients in the migraine trials (double-blinded and open-label). Information on these issues for pediatric patients in the monotherapy epilepsy trials is noted when deemed relevant/appropriate.

Growth Delay/Retardation

This section describes the frequency of TEAEs related to growth delay or retardation among pediatric subjects. The following WHOART preferred terms (as prespecified in the SAPs) were searched: growth retarded, feeding disorder neonatal, weight decrease, anorexia, cachexia, and dwarfism. The frequency of clinically significant decreases in body weight or height (i.e., the occurrence of a decrease of 1 unit or more in body weight or height Z-scores from pretreatment baseline to any 2 consecutive postbaseline visits that were at least 14 days apart, or to final visit) are reported, and an analysis of growth abnormalities concurrent with serum bicarbonate abnormalities is presented.

No height or BMI data are available after baseline in the double-blind phases of migraine prophylaxis Study CAPSS-122 or epilepsy monotherapy Studies TOPMAT-EPMN-104 and -105; however, Study TOPMAT-EPMN-104 did have additional height data during its open-label phase.

As stated in the pediatric epilepsy monotherapy ISS, data entry errors were found in some of the study databases, which triggered abnormal growth flags some subjects. These errors consisted of invalid values which in most cases appear to have resulted from failure to apply unit conversion factors. These outliers were not corrected in the data tables that are included in this summary, although their occurrence is noted in the hub tables and subject narratives, where appropriate.

Migraine Prophylaxis Studies

Double-Blind Studies
For the double-blind migraine prophylaxis studies, growth-related TEAEs are summarized for the pooled studies and the individual study-design datasets. The same appendix also shows the frequency of subjects with only growth-related AEs, with only measured growth delays (i.e., change in Z-score of 1 unit or more), with both TEAE and measurement criteria, and with either TEAE or measurement criteria, for the pooled studies and the individual study-design datasets. Growth delay/retardation events sorted by sex in the double-blind migraine prophylaxis studies.

In the double-blind migraine prophylaxis studies,

- All observed growth-related events were by TEAE criteria, not by height or weight measurement criteria.
- The observed growth-related TEAEs were weight decrease and anorexia, which occurred as follows :
    - Weight decrease in 5 (5%) of 94 placebo-treated subjects and 22 (10%) of 215 topiramate-treated subjects, with age-related frequencies as follows :
        - In the age 6 to 11 years group, 1 (3%) of 31 placebo-treated subjects and 5 (8%) of 59 topiramate-treated subjects.
        - In the age 12 to 17 years group, 4 (6%) of 63 placebo-treated subjects and 17 (11%) of 156 topiramate-treated subjects.
    - Anorexia in 6 (6%) of 94 placebo-treated subjects and 25 (12%) of 215 topiramate treated subjects, with age-related frequencies as follows:
        - In the age 6 to 11 years group, 4 (13%) of 31 placebo-treated subjects and 7 (12%) of 59 topiramate-treated subjects.
        - In the age 12 to 17 years group, 2 (3%) of 63 placebo-treated subjects and 18 (12%) of 156 topiramate-treated subjects.
    - Growth-related TEAEs showed some evidence of dose dependence in subjects aged 12 to 17 years, but data were insufficient to evaluate trends for subjects aged 6 to 11 years.
    - All growth-related TEAEs were mild to moderate in severity and were generally not treatment-limiting ,except in 1 case.

Open-Label Studies (With and Without Double-Blind Studies)
For migraine prophylaxis studies, growth-related AEs are summarized for the pooled open-label studies, the individual open-label study-design datasets, and the combined double-blind and open-label studies. The same appendix also shows the frequency of subjects with only growth-related TE AEs, with only measured growth delays (i.e., change in Z-score of 1 unit or more), with both TEAE and measurement criteria, and with either TEAE or measurement criteria, for the pooled open-label studies, the individual open-label study-design datasets, and the combined double-blind and open-label studies. For growth delay/retardation events sorted by sex in the open-label migraine prophylaxis studies.

In the open-label migraine prophylaxis studies,

- Growth-related events occurred in 5 cases by AE criteria, in 3 cases by measured weight criteria, and in no cases by measured height criteria.
- Growth-related events occurred only in the adolescents (age 12-17 years group), not the children (age 6-11 years group.
- The growth-related AEs were anorexia in 3 (2%) of 158 subjects and weight decrease in 2 (1%) of 158 subjects.
- All growth-related AEs were mild to moderate in severity.

Hyperammonemia and Encephalopathy

This section presents the frequency of TEAEs related to hyperammonemia and encephalopathy, including the following WHOART preferred terms that were prespecified in the SAPs : hyperammonemia, encephalopathy, confusion, stupor, coma, and EEG abnormal. For the migraine prophylaxis studies, the frequency is also presented for markedly abnormally high values for serum ammonia (≥1.5 times the upper limit of normal [ULN]), both alone and in combination with related TEAEs. Ammonia levels were not collected in the epilepsy monotherapy studies or in the migraine studies CAPSS-122 or TOPMAT-MIGR-001, -002, or -003; therefore, all ammonia data originated from Study TOPMAT-MIG-3006. Abnormal ammonia values are also presented as Individual Clinically Significant Values (i.e., markedly abnormally increased/elevated).

Migraine Prophylaxis Studies

Double-Blind Studies

For the double-blind migraine prophylaxis studies, TEAEs related to hyperammonemia and encephalopathy are summarized in for the pooled studies and the individual study-design datasets. The same appendix also shows the frequency of subjects with hyperammonemia and encephalopathy events by TEAEs only, by laboratory (ammonia) criteria only, with both TEAE and laboratory criteria, and with either TEAE or laboratory criteria, for Study TOPMAT-MIG-3006; the other studies did not collect ammonia data. Hyperammonemia and encephalopathy events are sorted by sex in the double-blind migraine prophylaxis studies.

In the double-blind migraine prophylaxis studies,

- No AEs related to hyperammonemia or encephalopathy occurred.
- Laboratory events of hyperammonemia in the age 12 to 17 years group in Study TOPMATMIG-3006 were observed in 1 (3%) of 33 placebo-treated subjects and 4 (6%) of 70 topiramate-treated subjects; no ammonia data were available for younger subjects.

Open-Label Studies (With and Without Double-Blind Studies)

None of the open-label studies assessed serum ammonia. No TEAEs related to hyperammonemia or encephalopathy occurred during the open-label migraine prophylaxis studies:
Therefore, the numbers of events for the combined double-blind and open-label studies matched the numbers for the double-blind phases alone. For hyperammonemia and encephalopathy events in the open-label migraine prophylaxis studies are sorted by sex.

Oligohidrosis and Hyperthermia

This section presents the frequency of TEAEs related to oligohidrosis and hyperthermia, with WHOART preferred terms as listed in the migraine prophylaxis SAP and the epilepsy monotherapy SAP.

Migraine Prophylaxis Studies

Double-Blind Studies

For the double-blind migraine prophylaxis studies, Appendix 5.4.1 shows the frequency of TEAEs related to oligohidrosis and hyperthermia for the pooled studies and for the individual study-design datasets. For oligohidrosis and hyperthermia events are sorted by sex in the double-blind migraine prophylaxis studies

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In the double-blind migraine prophylaxis studies, AEs related to oligohidrosis and hyperthermia were as follows :

- Overall, these AEs were reported for 1 (1%) of 94 placebo-treated subjects and 5 (2%) of 215 topiramate-treated subjects.
- In the topiramate-treated subjects, these AEs included hot flushes, skin disorder, skin dry, sweating decreased, and sweating increased; each of these occurred in 1 subject, and all occurred in the age 12 to 17 years group.

Open-Label Studies (With and Without Double-Blind Studies)

In the migraine prophylaxis studies, no TEAEs related to oligohidrosis and hyperthermia occurred. Therefore, the numbers of TEAEs in the combined double-blind and open-label studies matched the numbers in the double-blind phases alone. Oligohidrosis and hyperthermia TEAEs are sorted by sex in the migraine prophylaxis studies.

Renal Events, Including Nephrolithiasis

This section describes the frequency of renal AEs with WHOART preferred terms as prespecified in the SAPs (bladder calculus, hematuria, renal calculus, renal failure acute, renal pain, and urine abnormal) as well as the frequency of markedly abnormally high values for serum creatinine (>1.6 times the ULN), both alone and in combination with AEs. See also Individual Clinically Significant Values, for blood urea nitrogen and creatinine results.

Migraine Prophylaxis Studies

Double-Blind Studies

For the double-blind migraine prophylaxis studies, renal AEs are summarized for the pooled studies and the individual study-design datasets. The same appendix also shows the frequency of subjects with renal events by TEAEs only, by laboratory (creatinine) criteria only, with both TEAE and laboratory criteria, and with either TEAE or laboratory criteria, for the pooled studies and the individual study-design datasets. Renal events are sorted by sex in the double-blind migraine prophylaxis studies.

For the double-blind migraine prophylaxis studies, renal events were as follows :

- One TEAE (renal calculus) occurred in a topiramate-treated subject in the age 12 to 17 years group; see Narrative MIG-3006-101021 for more information.
- No cases of markedly abnormal values for serum creatinine occurred.

Open-Label Studies (With and Without Double-Blind Studies)
During the open-label migraine prophylaxis studies, no renal AEs or laboratory events occurred. Therefore, the numbers of renal events in the combined double-blind and open-label studies matched the numbers in the double-blind phases alone. Renal events are sorted by sex in the open-label migraine prophylaxis studies.

Hepatic Injury
This section describes the frequency of hepatic injury-related AEs, with WHOART preferred terms as listed in the migraine prophylaxis SAP and the epilepsy monotherapy SAP as well as the frequency of markedly abnormally high values for aspartate aminotransferase (AST, also called serum glutamic oxaloacetic transaminase, SGOT), alanine aminotransferase (ALT, also called alanine transaminase or serum glutamic pyruvic transaminase, SGPT), or total bilirubin. Markedly abnormally high thresholds were set as $\geq 3 \times$ ULN for AST (SGOT), $\geq 3 \times$ ULN for ALT (SGPT), and ≥ 41 μmol/L for bilirubin. The frequencies of laboratory abnormalities are presented both alone and in combination with TEAEs. See also Individual Clinically Significant Values.

Migraine Prophylaxis Studies
During the double-blind migraine prophylaxis studies, no hepatic injury TEAEs or laboratory events occurred.

Open-Label Studies
During the open-label migraine prophylaxis studies, shown in the same appendix, no subjects had any of the prespecified hepatic laboratory events, and 1 subject (an 8-year-old boy) had a hepatic injury TEAE. The event was a case of elevated ALT (SGPT), which did not meet the criterion of $\geq 3 \times$ ULN but was reported as a TEAE, and was assessed as possibly related (by the investigator) and doubtfully related (by the sponsor) to study medication. Hepatic injury events are sorted by sex in the migraine prophylaxis studies.

Visual Adverse Events
This section presents the frequency of TEAEs related to the visual system, with WHOART preferred terms as listed in the migraine prophylaxis SAP and the epilepsy monotherapy SAP.
Migraine Prophylaxis Studies
Double-Blind Studies
For the double-blind migraine prophylaxis studies, Appendix 5.7.1 shows the frequency of visual TEAEs for the pooled studies and the individual study-design datasets. Visual events sorted by sex in the double-blind migraine prophylaxis studies.

- Visual TEAEs were reported for 8 (9%) of 94 placebo-treated subjects, a frequency higher than the 11 (5%) of 215 topiramate-treated subjects.

- The frequency of visual AEs was similar between the topiramate-treated subjects aged 6 to 11 years and those aged 12 to 17 years.
- Each of the reported visual TEAEs occurred in the placebo group at frequencies that were equal to or higher than frequencies in the Any TPM group; these AEs were conjunctivitis, eye abnormality, eye pain, and vision abnormal.

Open-Label Studies
For the migraine prophylaxis studies, Appendix 5.7.1 shows the frequency of visual AEs for the pooled open-label studies, the individual open-label study-design datasets, and the combined double-blind and open-label studies.

- Visual events are sorted by sex in the open-label migraine prophylaxis studies. Visual TEAEs were reported for 5 (3%) of 158 subjects, with a frequency that was similar between subjects aged 6 to 11 years and those aged 12 to 17 years.
- Visual TEAEs were conjunctivitis (n=2), eye pain (n=2), and vision abnormal (n=1).

Reviewer Comments

I conclude that all these various of TEAEs of special interest did not show any new or significant safety signals or information other than what is known about topiramate's safety profile, particularly in pediatric patients.

Cognitive Dysfunction
Adverse Events Reflecting Cognitive Dysfunction
TEAEs reflecting cognitive dysfunction were prespecified in the SAPs and included the following WHOART preferred terms: cognitive problems NOS (not otherwise specified), coma, confusion, difficulty with concentration/attention, difficulty with memory NOS, electroencephalogram (EEG) abnormal, encephalopathy, language problems, muscle contractions involuntary, psychomotor slowing, speech disorders/related speech problems, and stupor.

For the double-blind migraine prophylaxis studies, TEAEs reflecting cognitive dysfunction are shown for the pooled studies and the individual study-design datasets. Cognitive AEs in the pooled studies also are shown in Table 59.

- In topiramate-treated subjects, cognitive TEAEs were slightly more frequent in children (aged 6-11 years) than in adolescents (aged 12-17 years), as follows :
- In children, cognitive TEAEs occurred in 0 of 31 placebo-treated subjects and 7 (12%) of 59 topiramate-treated subjects.
- In adolescents, cognitive TEAEs occurred in 3 (5%) of 63 placebo-treated subjects and 11 (7%) of 156 topiramate-treated subjects.
- The most common cognitive TEAE was difficulty with concentration/attention, occurring as follows (Table 59):
    - In children (aged 6-11 years), 0 of 31 placebo-treated subjects and 3 (5%) of 59 topiramate-treated patients.

  - In adolescents (aged 12-17 years), 1 (2%) of 63 placebo-treated subjects and 5 (3%) of 156 topiramate-treated subjects.
- Cognitive TEAEs occurred most often in isolation in both age groups (Table 59).
- Cognitive TEAEs were generally not treatment-limiting; of 18 topiramate-treated patients with cognitive TEAEs, only 1 patient discontinued due to the cognitive TEAEs (difficulty with concentration/attention and language problems, along with the noncognitive treatment-limiting TEAE of fatigue).

Table 59 Cognitive TEAEs by Preferred Term for the Pooled Double-Blind Migraine Prophylaxis Studies (Double Blind Subjects Analysis Seta)

		Topiramate				
Age Group Preferred Term	Placebo (N=94) n (%)	2-3 mg/kg/d (N=108) n (%)	50 mg/d (N=46) n (%)	100 mg/d (N=48) n (%)	200 mg/d (N=13) n (%)	Any TPM (N=215) n (%)
All Subjects	**94**	**108**	**46**	**48**	**13**	**215**
Total, subjects with cognitive AEs	3 (3)	11 (10)	1 (2)	1 (2)	5 (38)	18 (8)
Cognitive problems NOS	1 (1)	1 (1)	0	0	0	1 (<1)
Difficulty with concentration/attention	1 (1)	5 (5)	0	1 (2)	2 (15)	8 (4)
Difficulty with memory NOS	1 (1)	3 (3)	0	0	1 (8)	4 (2)
Language problems	1 (1)	2 (2)	0	0	2 (15)	4 (2)
Muscle contractions involuntary	0	0	0	0	1 (8)	1 (<1)
Psychomotor slowing	0	2 (2)	1 (2)	0	1 (8)	4 (2)
Age 6-11 Years	**31**	**59**	**0**	**0**	**0**	**59**
Total, subjects with cognitive AEs	0	7 (12)	0	0	0	7 (12)
Cognitive problems NOS	0	1 (2)	0	0	0	1 (2)
Difficulty with concentration/attention	0	3 (5)	0	0	0	3 (5)
Difficulty with memory NOS	0	1 (2)	0	0	0	1 (2)
Language problems	0	1 (2)	0	0	0	1 (2)
Muscle contractions involuntary	0	0	0	0	0	0
Psychomotor slowing	0	2 (3)	0	0	0	2 (3)
Age 12-17 Years	**63**	**49**	**46**	**48**	**13**	**156**
Total, subjects with cognitive AEs	3 (5)	4 (8)	1 (2)	1 (2)	5 (38)	11 (7)
Cognitive problems NOS	1 (2)	0	0	0	0	0
Difficulty with concentration/attention	1 (2)	2 (4)	0	1 (2)	2 (15)	5 (3)
Difficulty with memory NOS	1 (2)	2 (4)	0	0	1 (8)	3 (2)
Language problems	1 (2)	1 (2)	0	0	2 (15)	3 (2)
Muscle contractions involuntary	0	0	0	0	1 (8)	1 (1)
Psychomotor slowing	0	0	1 (2)	0	1 (8)	2 (1)
All Subjects	**94**	**108**	**46**	**48**	**13**	**215**
Number of subjects with cognitive AEs	3 (3)	11 (10)	1 (2)	1 (2)	5 (38)	18 (8)
Occurring in isolation	2 (2)	9 (8)	1 (2)	1 (2)	4 (31)	15 (7)
Occurring in pairs only	1 (1)	2 (2)	0	0	0	2 (1)
Occurring in triples	0	0	0	0	1 (8)	1 (<1)
Age 6-11 Years	**31**	**59**	**0**	**0**	**0**	**59**
Number of subjects with cognitive AEs	0	7 (12)	0	0	0	7 (12)
Occurring in isolation	0	6 (10)	0	0	0	6 (10)
Occurring in pairs only	0	1 (2)	0	0	0	1 (2)
Occurring in triples	0	0	0	0	0	0
Age 12-17 years	**63**	**49**	**46**	**48**	**13**	**156**
Number of subjects with cognitive AEs	3 (5)	4 (8)	1 (2)	1 (2)	5 (38)	11 (7)
Occurring in isolation	2 (3)	3 (6)	1 (2)	1 (2)	4 (31)	9 (6)
Occurring in pairs only	1 (2)	1 (2)	0	0	0	1 (1)
Occurring in triples	0	0	0	0	1 (8)	1 (1)

Cognitive TEAEs by Time of Onset

For most cognitive TEAEs in the double-blind migraine prophylaxis studies, onset occurred during the titration period; these cognitive TEAEs were not sorted for early versus late titration. Of subjects in the Any TPM group, 4% had cognitive TEAEs with onset in titration and persistence into the maintenance period; this proportion was similar between children (aged 6 11 years) and adolescents (aged 12-17 years).

Cognitive Dysfunction As Per CANTAB Testing

The sponsor provided the following summary regarding CANTAB testing.

Cambridge Neuropsychological Test Automated Battery Outcomes
For the double-blind migraine prophylaxis study TOPMAT-MIG-3006, CANTAB outcomes are shown as descriptive statistics and as change from baseline and as a comparison of treatment differences at baseline. The CANTAB outcomes also are shown in Table 60. Point-by point responses to questions sent from the DNP to the sponsor on 6 June 2012, entitled "Questions/Issues Related to Analyses of Cognitive Testing in MIG-3006," were provided.

The sponsor noted that the CANTAB outcomes should be interpreted with caution, because Study TOPMAT-MIG-3006 was neither powered nor designed to evaluate treatment differences in these outcomes, and also because the results indicated significant differences among groups at baseline in Paired Associates Learning (PAL) first trial memory score (p=0.028) and in total number of unique words about food (p=0.015).

Of the CANTAB analyses shown in Table 60, the following had significant ($p < 0.05$) endpoint results, after having no significant differences among groups at baseline.

- In the topiramate 100 mg/day group versus placebo, a reduction in SSP total errors indicated some improvement from baseline to endpoint in visual memory (p=0.040), after having no statistically significant differences among groups at baseline (p=0.179).
- In the topiramate 100 mg/day group versus placebo, statistically significant increases in scores (indicating slowing) were observed from baseline to endpoint in the following:
- Reaction Time Information (RTI) 5-choice reaction time (p=0.028), after no differences at baseline (p=0.617).
- PRM mean correct latency (p=0.027), after no differences at baseline (p=0.711).
- RVP mean latency (p=0.040), after no differences at baseline (p=0.289).

These changes in RTI, PRM, and RVP may indicate some topiramate-related impairment in psychomotor reaction times.

- In the topiramate 50 mg/day group versus placebo, outcomes for the total number of unique words were as follows :
- Number of words about animals was decreased from baseline to endpoint (p=0.013), after having no statistically significant differences among groups at baseline (p=0.655). This result could have indicated some decrease in verbal fluency, perhaps attributable to mild psychomotor slowing. (However, no similar significant difference was noted for this outcome in the topiramate 100 mg/day group.)
- Number of words about foods showed a statistically significant deficit at baseline (p=0.015), but showed no statistically significant decrease from baseline to endpoint (p=0.786); this outcome may complicate any interpretations of overall verbal fluency.

Table 60 Summary of Change From Baseline to Endpoint in Cambridge Neuropsychological Test Automated Battery Outcome Measurements for the Double-Blind Study TOPMAT-MIG-3006 (Migraine Prophylaxis sNDA 2013: Double-Blind Subjects Analysis Set)

Change from Baseline at Endpoint	Placebo (N=33)	TPM 50 mg/d (N=35)	TPM 100 mg/d (N=35)
PAL Total Errors Adjusted[a]			
N	30	29	27
Mean (SD)	-2.80 (14.075)	-1.93 (3.712)	-0.19 (6.397)
Median (range)	-0.50 (-56.0;27.0)	-2.00 (-9.0;4.0)	1.00 (-22.0;12.0)
Least-squares mean change[b]	-1.21	-2.22	-2.23
P-value, minus placebo[b]		0.547	0.562
Difference of least-squares means (SE)[b]		-1.01 (1.675)	-1.03 (1.764)
95% confidence interval		(-4.35;2.32)	(-4.54;2.49)
PAL Total Trials Adjusted[a]			
N	30	29	27
Mean (SD)	-1.00 (2.560)	-0.93 (1.710)	-0.04 (2.915)
Median (range)	-1.00 (-8.0;3.0)	-1.00 (-5.0;2.0)	0.00 (-12.0;5.0)
Least-squares mean change[b]	-0.68	-0.86	-0.56
P-value, minus placebo[b]		0.678	0.798
Difference of least-squares means (SE)[b]		-0.18 (0.444)	0.12 (0.466)
95% confidence interval		(-1.07;0.70)	(-0.81;1.05)
PAL Stages Completed[a]			
N	30	29	27
Mean (SD)	0.03 (0.320)	0.00 (0.000)	0.00 (0.000)
Median (range)	0.00 (-1.0;1.0)	0.00 (0.0;0.0)	0.00 (0.0;0.0)
Least-squares mean change[b]	-0.01	0.03	0.02
P-value, minus placebo[b]		0.192	0.286
Difference of least-squares means (SE)[b]		0.04 (0.029)	0.03 (0.030)
95% confidence interval		(-0.02;0.10)	(-0.03;0.09)
RTI 5-Choice Reaction Time, msec			
N	30	29	28
Mean (SD)	-3.53 (37.359)	-5.78 (38.210)	33.72 (95.953)
Median (range)	6.45 (-108.4;65.6)	-4.90 (-88.7;57.8)	5.14 (-82.6;378.6)
Least-squares mean change[b]	-4.77	-1.04	30.48
P-value, minus placebo[b]		0.811	0.028
Difference of least-squares means (SE)[b]		3.73 (15.575)	35.25 (15.722)
95% confidence interval		(-27.26;34.73)	(3.96;66.53)
RTI Five-Choice Movement Time, msec			
N	30	29	28
Mean (SD)	-25.26 (134.171)	5.57 (89.771)	4.38 (147.068)
Median (range)	-1.77 (-387.4;294.6)	15.36 (-232.4;244.8)	-0.61 (-238.5;511.5)
Least-squares mean change[b]	-14.18	10.58	3.89
P-value, minus placebo[b]		0.422	0.562
Difference of least-squares means (SE)[b]		24.76 (30.650)	18.07 (31.043)
95% confidence interval		(-36.23;85.76)	(-43.71;79.85)
PRM Percentage Correct, %			
N	30	29	28
Mean (SD)	-0.14 (7.215)	2.44 (9.417)	1.64 (6.741)
Median (range)	0.00 (-12.5;20.8)	0.00 (-29.2;20.8)	0.00 (-12.5;20.8)
Least-squares mean change[b]	0.20	1.87	1.84
P-value, minus placebo[b]		0.372	0.386
Difference of least-squares means (SE)[b]		1.66 (1.855)	1.63 (1.875)
95% confidence interval		(-2.03;5.35)	(-2.10;5.37)
PRM Mean Correct Latency, msec			
N	30	29	28
Mean (SD)	-132.74 (256.491)	-76.28 (285.867)	51.30 (360.564)
Median (range)	-128.80 (-817.3;271.2)	-84.86 (-959.3;457.2)	5.68 (-704.6;812.1)
Least-squares mean change[b]	-128.24	-54.59	47.64
P-value, minus placebo[b]		0.341	0.027
Difference of least-squares means (SE)[b]		73.64 (76.873)	175.87 (77.908)
95% confidence interval		(-79.34;226.62)	(20.83;330.91)

Table 60 Summary of Change From Baseline to Endpoint in Cambridge Neuropsychological Test Automated Battery Outcome Measurements for the Double-Blind Study TOPMAT-MIG-3006 (Migraine Prophylaxis sNDA 2013: Double-Blind Subjects Analysis Set) (Continued)

Change from Baseline at Endpoint	Placebo (N=33)	TPM 50 mg/d (N=35)	TPM 100 mg/d (N=35)
SSP Span Length			
N	29	29	28
Mean (SD)	0.31 (1.442)	0.62 (1.147)	0.25 (1.076)
Median (range)	0.00 (-4.0;3.0)	1.00 (-1.0;3.0)	0.00 (-2.0;3.0)
Least-squares mean change[b]	0.28	0.54	0.42
P-value, minus placebo[b]		0.367	0.629
Difference of least-squares means (SE)[b]		0.26 (0.284)	0.14 (0.290)
95% confidence interval		(-0.31;0.82)	(-0.44;0.72)
SSP Total Errors			
N	30	29	28
Mean (SD)	1.40 (7.587)	-2.76 (6.277)	-3.68 (8.718)
Median (range)	1.00 (-18.0;18.0)	-2.00 (-19.0;11.0)	-2.50 (-21.0;9.0)
Least-squares mean change[b]	-0.08	-2.06	-3.47
P-value, minus placebo[b]		0.222	0.040
Difference of least-squares means (SE)[b]		-1.98 (1.610)	-3.39 (1.620)
95% confidence interval		(-5.19;1.22)	(-6.61;-0.16)
RVP Mean Latency, msec			
N	30	29	28
Mean (SD)	-87.90 (230.147)	10.90 (61.069)	22.97 (95.621)
Median (range)	-25.80 (-915.5;96.1)	-5.75 (-76.0;228.0)	5.21 (-188.0;353.1)
Least-squares mean change[b]	-51.22	-8.36	1.15
P-value, minus placebo[b]		0.088	0.040
Difference of least-squares means (SE)[b]		42.86 (24.855)	52.37 (25.067)
95% confidence interval		(-6.60;92.33)	(2.49;102.26)
RVP A			
N	30	29	28
Mean (SD)	-0.0061 (0.02425)	-0.0025 (0.02086)	-0.0005 (0.02163)
Median (range)	0.0000 (-0.066;0.045)	0.0000 (-0.074;0.045)	0.0000 (-0.056;0.049)
Least-squares mean change[b]	-0.0039	-0.0025	0.0003
P-value, minus placebo[b]		0.802	0.454
Difference of least-squares means (SE)[b]		0.0014 (0.00555)	0.0042 (0.00559)
95% confidence interval		(-0.0096;0.0124)	(-0.0069;0.0153)
Total Number of Unique Words, Food			
N	31	29	31
Mean (SD)	-1.52 (4.959)	-0.41 (3.418)	-3.65 (4.550)
Median (range)	-2.00 (-10.0;10.0)	0.00 (-8.0;5.0)	-4.00 (-11.0;8.0)
Least-squares mean change[b]	-1.33	-1.05	-2.67
P-value, minus placebo[b]		0.786	0.199
Difference of least-squares means (SE)[b]		0.28 (1.041)	-1.34 (1.035)
95% confidence interval		(-1.79;2.35)	(-3.40;0.72)
Total Number of Unique Words, Animals			
N	31	29	31
Mean (SD)	0.13 (3.819)	-2.97 (4.633)	-1.52 (4.603)
Median (range)	1.00 (-7.0;10.0)	-3.00 (-15.0;6.0)	-1.00 (-11.0;6.0)
Least-squares mean change[b]	-0.33	-2.57	-1.50
P-value, minus placebo[b]		0.013	0.180
Difference of least-squares means (SE)[b]		-2.24 (0.878)	-1.17 (0.862)
95% confidence interval		(-3.99;-0.49)	(-2.88;0.55)

PAL = paired associates learning; PRM = pattern recognition memory; SSP = spatial span; RTI = reaction time information; RVP = rapid visual processing; RVP A = an RVP measure of sensitivity to errors; SE = standard error; SD = standard deviation.

[a] An outlier from the topiramate 100 mg/day group was eliminated from PAL test parameters because of abnormal values (0 PAL stages completed at baseline, with baseline values of 177 and 50 in PAL total errors adjusted and PAL total trials adjusted, respectively); the elimination of this outlier did not change the interpretation of the PAL analysis results.

[b] P-values and least squares means were derived based on analysis of covariance (ANCOVA) model with treatment, stratified age at baseline (12-14 years; 15-17 years), and analysis center (US; Argentina and Brazil; Europe and Israel) as factors and baseline scores as a covariate. Nominal unadjusted p-values are presented.

Source: tcantab01_db_m3006_1.rtf generated by dcantab01_db_m3006.sas, 15MAR2013 13:41.

Reviewer Comments

- *The incidence of cognitive adverse reactions was increased in TOPAMAX®-treated patients (7 %) vs placebo (4 %) in pooled, double-blind placebo-controlled studies in which adolescent patients (12 to 17 years) were randomized to placebo or one of several fixed daily doses of TOPAMAX® (50 mg, 100 mg, 200 mg), The incidence of cognitive adverse reactions was also increased in a placebo-controlled study of pediatric patients (6—16 years) treated with 2-3 mg/kg/day of TOPAMAX®(10 %) vs placebo treatment (2 %). The risk for cognitive adverse reactions was dose-dependent and was also greater in younger patients (6-11 years) than in older patients (12-17 years). The most common cognitive adverse reaction in all these trials was difficulty with concentration/attention, Cognitive adverse reactions most commonly developed in the titration period and sometimes persisted into the maintenance period. These adverse reactions typically occurred in isolation as single type of cognitive adverse reaction. In some patients, a cognitive adverse reaction (e.g., difficulty with concentration/attention or language problems) led to study discontinuation.*

- *A consult has been obtained by the DNP to request a review of the results of the CANTAB and POMS testing and to ascertain if the consultant (Dr. Peter Como), who is a neurospsychologist agrees with the sponsor's interpretation of results. Dr. Como's main conclusion is that the CANTAB results suggested that topiramate caused psychomotor slowing and also decreased verbal fluency, findings that are well recognized as adverse reactions of topiramate both in the label as per various descriptions in TEAE tables and also according to the published literature. I believe that these CANTAB findings (i.e., psychomotor slowing and decreased verbal fluency) should be described in the label.*

Mood Testing with POMS

Profiles of Mood States Outcomes
For the double-blind migraine prophylaxis study TOPMAT-MIG-3006, POMS outcomes were shown as descriptive statistics and as change from baseline and as a comparison of treatment differences at baseline. The lack of available normative data for the POMS test in adolescents was described.

- Significant between-group differences at baseline were noted in several POMS parameters, including total mood disturbance (p=0.019) and 2 of its subscale components, the depression/dejection factor (p=0.002) and the confusion/bewilderment factor (p=0.003); these indicated worse mood disturbance in the placebo group.
- The baseline disadvantage of the placebo group may partially explain why that group had the largest improvement in total mood disturbance score from baseline to endpoint.
- Overall, POMS outcomes indicated no significant changes from baseline to endpoint for topiramate-treated groups versus the placebo group.

Reviewer Comments

There are no statistically significant results for topiramate (vs placebo) for the POMS testing as change from baseline. Although there were some statistically significant baseline differences in some scores at baseline, baseline results were included in the analyses as covariate.

Metabolic Acidosis

This section discusses the frequency of TEAEs related to metabolic acidosis and musculoskeletal development, including the following WHOART preferred terms as prespecified in the SAPs: acidosis, acidosis lactic, hyperventilation, cardiac failure, renal calculus, hypothyroidism, hypophosphataemia, hypercalcinuria, hyperchloremia, fracture pathological, osteoporosis, osteomalacia, skeletal pain, bone disorder, and bone development abnormal. This section also presents results for various threshold outlier abnormalities of serum bicarbonate reflecting different severities of metabolic acidosis.

Migraine Prophylaxis Studies
Double-Blind Studies
For the double-blind migraine prophylaxis studies, AEs related to metabolic acidosis are summarized for the pooled studies and the individual study design datasets. The same appendix also shows the frequency of subjects with events related to metabolic acidosis by TEAEs only, by laboratory (bicarbonate) criteria only, with both AE and laboratory criteria, and with either TEAE or laboratory criteria, for the pooled studies and the individual study-design datasets.
In the double-blind migraine prophylaxis studies, Serum bicarbonate was measured only in MIG-3006 and MIGR-1-3.

- TEAEs related to metabolic acidosis were reported for 0 of 94 placebo-treated subjects and 2 (1%) of 215 topiramate-treated subjects; these events were 1 case of hyperventilation and 1 case of renal calculus, both of which occurred in the age 12 to 17 years group.
- Laboratory events related to metabolic acidosis (i.e., serum bicarbonate value < 17 mEq/L) in the age 12 to 17 years group were observed in 1 (2%) of 63 placebo-treated subjects and 9 (6%) of 156 topiramate-treated subjects. These events appeared to be dose-dependent occurring in 4%, 8%, and 23% of the 50, 100, and 200 mg/day groups, respectively. As stated in the footnotes of that table, the denominators for the percentages were defined as the number of subjects from the corresponding age and treatment group; however, note that Study CAPSS-122 did not record bicarbonate data. No bicarbonate data were available for younger subjects.
- No subjects met both laboratory and TEAE criteria for metabolic acidosis.

Open-Label Studies (With and Without Double-Blind Studies)
In the open-label migraine prophylaxis studies,

- No TEAEs related to metabolic acidosis occurred.
- Laboratory events related to metabolic acidosis (i.e., serum bicarbonate value < 17 mEq/L) in the age 12 to 17 years group were observed in 9 (10%) of 92 patients.

Serum Bicarbonate Analyses

Metabolic acidosis, that is defined by decreased serum bicarbonate (in the absence of chronic respiratory alkalosis), is a Warning and Precaution in the topiramate (TOPAMAX) label. Metabolic acidosis is related to topiramate's pharmacological action as a carbonic anhydrase inhibitor. The following tables shows the incidence of various serum bicarbonate abnormalities according to specified thresholds for various time perspectives including any visit, final visit, final visit and any previous post-baseline visit, 2 consecutive visits, and at 2 consecutive visits of the final visit (a perspective that we have previously referred to as "persistent"). These time perspective results for various bicarbonate abnormality thresholds are shown for MIG-3006, MIGR-1-3, and the pool of these trials.

Table 61 Treatment Emergent Serum Bicarbonate Values < 20 mEq/L for Study MIG-3006

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	Placebo n (%)	TPM 50 mg/day n (%)	TPM 100 mg/day n (%)	Any TPM n (%)
All Subjects	33	35	35	70
At Any Visit	1 (3.0)	17 (48.6)	13 (37.1)	30 (42.9)
At Final Visit	1 (3.0)	8 (22.9)	6 (17.1)	14 (20.0)
At Final Visit and Any Previous Post-Baseline Visit	0	6 (17.1)	4 (11.4)	10 (14.3)
At 2 Consecutive Visits	0	7 (20.0)	6 (17.1)	13 (18.6)
At 2 Consecutive Visits or Final Visit	1 (3.0)	9 (25.7)	8 (22.9)	17 (24.3)

Table 62 Treatment Emergent Serum Bicarbonate Values < 20 mEq/L for Pool of Studies MIGR-001,-002,-003

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	Placebo n (%)	TPM 50 mg/day n (%)	TPM 100 mg/day n (%)	TPM 200 mg/day n (%)	Any TPM n (%)
All Subjects	11	11	13	13	37
At Any Visit	4 (36.4)	6 (54.5)	6 (46.2)	11 (84.6)	23 (62.2)
At Final Visit	2 (18.2)	5 (45.5)	5 (38.5)	10 (76.9)	20 (54.1)
At Final Visit and Any Previous Post-Baseline Visit	1 (9.1)	3 (27.3)	0	7 (53.8)	10 (27.0)
At 2 Consecutive Visits	2 (18.2)	3 (27.3)	0	7 (53.8)	10 (27.0)
At 2 Consecutive Visits or Final Visit	3 (27.3)	5 (45.5)	5 (38.5)	10 (76.9)	20 (54.1)

Table 63 Treatment Emergent Serum Bicarbonate Values < 20 mEq/L for Pool of Studies MIG-3006 and MIGR-001,-002,-003

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	Placebo n (%)	TPM 50 mg/day n (%)	TPM 100 mg/day n (%)	TPM 200 mg/day n (%)	Any TPM n (%)
All Subjects	44	46	48	13	107
At Any Visit	5 (11.4)	23 (50.0)	19 (39.6)	11 (84.6)	53 (49.5)
At Final Visit	3 (6.8)	13 (28.3)	11 (22.9)	10 (76.9)	34 (31.8)
At Final Visit and Any Previous Post-Baseline Visit	1 (2.3)	9 (19.6)	4 (8.3)	7 (53.8)	20 (18.7)
At 2 Consecutive Visits	2 (4.5)	10 (21.7)	6 (12.5)	7 (53.8)	23 (21.5)
At 2 Consecutive Visits or Final Visit	4 (9.1)	14 (30.4)	13 (27.1)	10 (76.9)	37 (34.6)

Table 64 Treatment Emergent Serum Bicarbonate Values < 17 mEq/L for Study MIG-3006

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	Placebo n (%)	TPM 50 mg/day n (%)	TPM 100 mg/day n (%)	Any TPM n (%)
All Subjects	33	35	35	70
At Any Visit	0	1 (2.9)	1 (2.9)	2 (2.9)
At Final Visit	0	1 (2.9)	1 (2.9)	2 (2.9)
At Final Visit and Any Previous Post-Baseline Visit	0	0	0	0
At 2 Consecutive Visits	0	0	0	0
At 2 Consecutive Visits or Final Visit	0	1 (2.9)	1 (2.9)	2 (2.9)

Table 65 Treatment Emergent Serum Bicarbonate Values < 17 mEq/L for Pool of Studies MIGR-001,-002,-003

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	Placebo n (%)	TPM 50 mg/day n (%)	TPM 100 mg/day n (%)	TPM 200 mg/day n (%)	Any TPM n (%)
All Subjects	11	11	13	13	37
At Any Visit	1 (9.1)	1 (9.1)	3 (23.1)	3 (23.1)	7 (18.9)
At Final Visit	0	1 (9.1)	3 (23.1)	2 (15.4)	6 (16.2)
At Final Visit and Any Previous Post-Baseline Visit	0	0	0	1 (7.7)	1 (2.7)
At 2 Consecutive Visits	0	0	0	1 (7.7)	1 (2.7)
At 2 Consecutive Visits or Final Visit	0	1 (9.1)	3 (23.1)	2 (15.4)	6 (16.2)

Table 66 Treatment Emergent Serum Bicarbonate Values < 17 mEq/L for Pool of Studies MIG-3006 and MIGR-001,-002,-003

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	Placebo n (%)	TPM 50 mg/day n (%)	TPM 100 mg/day n (%)	TPM 200 mg/day n (%)	Any TPM n (%)
All Subjects	44	46	48	13	107
At Any Visit	1 (2.3)	2 (4.3)	4 (8.3)	3 (23.1)	9 (8.4)
At Final Visit	0	2 (4.3)	4 (8.3)	2 (15.4)	8 (7.5)
At Final Visit and Any Previous Post-Baseline Visit	0	0	0	1 (7.7)	1 (0.9)
At 2 Consecutive Visits	0	0	0	1 (7.7)	1 (0.9)
At 2 Consecutive Visits or Final Visit	0	2 (4.3)	4 (8.3)	2 (15.4)	8 (7.5)

Table 67 Treatment Emergent Serum Bicarbonate Values < 17 mEq/L With a Decrease from Baseline > 5 mEq/L When Baseline ≥ 20 mEq/L for Study MIG-3006

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	Placebo n (%)	TPM 50 mg/day n (%)	TPM 100 mg/day n (%)	Any TPM n (%)
All Subjects	33	35	35	70
At Any Visit	0	1 (2.9)	1 (2.9)	2 (2.9)
At Final Visit	0	1 (2.9)	1 (2.9)	2 (2.9)
At Final Visit and Any Previous Post-Baseline Visit	0	0	0	0
At 2 Consecutive Visits	0	0	0	0
At 2 Consecutive Visits or Final Visit	0	1 (2.9)	1 (2.9)	2 (2.9)

Table 68 Treatment Emergent Serum Bicarbonate Values <17 mEq/L With a Decrease from Baseline > 5 mEq/L When Baseline ≥ 20 mEq/L for Pool of Studies MIGR-001,-002,-003

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	Placebo n (%)	TPM 50 mg/day n (%)	TPM 100 mg/day n (%)	TPM 200 mg/day n (%)	Any TPM n (%)
All Subjects	11	11	13	13	37
At Any Visit	1 (9.1)	0	2 (15.4)	0	2 (5.4)
At Final Visit	0	0	2 (15.4)	0	2 (5.4)
At Final Visit and Any Previous Post-Baseline Visit	0	0	0	0	0
At 2 Consecutive Visits	0	0	0	0	0
At 2 Consecutive Visits or Final Visit	0	0	2 (15.4)	0	2 (5.4)

Table 69 Treatment Emergent Serum Bicarbonate Values <17 mEq/L With a Decrease from Baseline > 5 mEq/L When Baseline ≥ 20 mEq/L for Pool of Studies MIG-3006 and MIGR-001,-002,-003

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	Placebo n (%)	TPM 50 mg/day n (%)	TPM 100 mg/day n (%)	TPM 200 mg/day n (%)	Any TPM n (%)
All Subjects	44	46	48	13	107
At Any Visit	1 (2.3)	1 (2.2)	3 (6.3)	0	4 (3.7)
At Final Visit	0	1 (2.2)	3 (6.3)	0	4 (3.7)
At Final Visit and Any Previous Post-Baseline Visit	0	0	0	0	0
At 2 Consecutive Visits	0	0	0	0	0
At 2 Consecutive Visits or Final Visit	0	1 (2.2)	3 (6.3)	0	4 (3.7)

Reviewer Comments

- *The sponsor presented analyses regarding TEAEs that might be related to metabolic acidosis. However, it is important to recognize that metabolic acidosis is a laboratory based diagnosis. At a minimum, the diagnosis requires documenting a decreased serum bicarbonate value below the normal reference range in the absence of chronic respiratory alkalosis. There is also some question whether some patients have chronic metabolic acidosis without a decreased serum bicarbonate because the metabolic acidosis is a dynamic process compensated by an increase in serum bicarbonate (from a decreased value to a normal value) by a buffering process from bone. Considering that metabolic acidosis is a laboratory based diagnosis, it is not possible to diagnose metabolic acidosis on the basis of TEAEs because many patients with metabolic acidosis are frequently asymptomatic (even with sometimes more severe metabolic acidosis) and if symptomatic, the symptoms are nonspecific and similar to symptoms produced by a variety of disorders/diseases.*

- *Although the previous tables (Table 61- Table 69) provide serum bicarbonate abnormalities indicating various severities of metabolic acidosis according to different bicarbonate thresholds and time perspectives, my comments will focus on abnormalities at 2 consecutive visits or the final visit (i.e., "persistent" perspective) in the pools of the adolescent migraine trials unless otherwise noted. The highest incidence of any abnormality is usually at any visit and the frequency at the final visit is typically lower and usually the lowest incidence of the all the time perspectives.*

- *The topiramate treatment difference incidence (topiramate % – placebo %) of "persistent" metabolic acidosis (operationally defined as a serum bicarbonate of < 20 mEq/L) is 21 % for 50 mg, 18 % for 100 mg, and 68 % for 200 mg. These results indicate a clear dose-dependence but it is noteworthy the such a considerable percentage of patients exhibit this abnormality at the lowest daily dose of 50 mg.*

- *The topiramate treatment difference incidence of "persistent" more severe metabolic acidosis (i.e., < 17 mEq/L) is 4 % for 50 mg, 8 % for 100 mg, and 15 % for 200 mg. These results indicate a clear dose-dependence this more severe representation of metabolic acidosis.*

- *The topiramate treatment difference incidence of the most severe "persistent" metabolic acidosis (i.e., < 17 mEq/L and > 5 mEq/L decrease from baseline when baseline serum bicarbonate is ≥ 20 mEq/L)) is 2 % for 50 mg, 4 % for 100 mg, and 0 % for 200 mg. Although the 100 mg dose suggests a dose-dependent effect relative to the 50 mg dose, there are no cases for the 200 mg dose. However, it is possible that the absence of showing a dose-dependent increased incidence at the 200 mg dose is related to the fact that there were relatively few patients (N=13 patients compared to 46-48 patients in the other 2 lower dose groups) in that highest dose group and none exhibited this severe abnormality.*

- *Refer also to Section 7.4.2 Laboratory Findings also shows outlier results for decreases of serum bicarbonate below the lower limit of the reference range and also for markedly abnormally decreased outliers.*

- *Overall, these results show that adolescents treated with topiramate for migraine prophylaxis exhibit metabolic acidosis frequently and with various degrees of severity. This information should be described in the label for comparison with the incidence of metabolic acidosis in other adult and pediatric indications.*

Ammonia/Hyperammonemia

Hyperammonemia and encephalopathy is a Warning and Precaution in the topiramate (TOPAMAX) label. The following tables present abnormalities (i.e., elevations) in serum ammonia from different time perspectives in MIG-3006, the only pediatric migraine trial that prospectively collected serum ammonia at baseline and throughout treatment.

Table 70 Incidence of Abnormal Serum Ammonia in MIG-3006 At Any Visit and Final Visit in MIG-3006

Analysis Set: Double Blind Subjects in Mig-3006 (12-17 Years Old)
Lab Tests: Ammonia (umol/L)

Time Flag	Placebo n (%)	TPM 50 mg/day n (%)	TPM 100 mg/day n (%)	Any TPM n (%)
DB Baseline	33	35	35	70
Abnormal High	0	0	0	0
Abnormal Low	0	0	0	0
Any Visit	33	35	35	70
Abnormal High	3 (9.1)	5 (14.3)	9 (25.7)	14 (20.0)
Abnormal Low	12 (36.4)	10 (28.6)	11 (31.4)	21 (30.0)
DB Endpoint	33	35	35	70
Abnormal High	0	3 (8.6)	1 (2.9)	4 (5.7)
Abnormal Low	7 (21.2)	5 (14.3)	8 (22.9)	13 (18.6)

Table 71 Incidence of Markedly Abnormal Serum Ammonia in MIG-3006 Over Time

Analysis Set: Double Blind Subjects
Lab Tests: Ammonia (umol/L)

Age Group / Time Interval Flag	Placebo n (%)	TPM 50 mg/day n (%)	TPM 100 mg/day n (%)	Any TPM n (%)
All Subjects				
DB Month 2	27	29	26	55
Markedly Abnormal High	1 (3.7)	0	0	0
DB Month 3	28	29	27	56
Markedly Abnormal High	0	0	1 (3.7)	1 (1.8)
DB Month 4	24	28	26	54
Markedly Abnormal High	1 (4.2)	0	2 (7.7)	2 (3.7)
12-17 Years				
DB Month 2	27	29	26	55
Markedly Abnormal High	1 (3.7)	0	0	0
DB Month 3	28	29	27	56
Markedly Abnormal High	0	0	1 (3.7)	1 (1.8)
DB Month 4	24	28	26	54
Markedly Abnormal High	1 (4.2)	0	2 (7.7)	2 (3.7)

Reviewer Comments

- *The topiramate treatment difference incidence (topiramate % – placebo %) of hyperammonemia (relative to the upper limit of "normal" in the reference range) was dose-dependently increased at any visit for 50 mg (5 %) and 100 mg (*17 %) (Table 70). *At the final visit, the treatment difference was 9 % for 50 mg and 3 % for 100 mg.*

- *Table 71 shows the incidence of markedly abnormally (i.e., ≥ 50 % above upper limit of normal reference range) increased serum ammonia over the trial. Whereas the topiramate treatment difference of markedly abnormally increased serum ammonia is increased at 4% at month 3 and 4, this treatment difference incidence at any visit was 6 %*

- *Refer also to Section 7.4.2 Laboratory Findings also shows outlier results for increases of ammonia levels above the upper limit of the reference range and also for markedly abnormally increased outliers.*

BUN and Creatinine

The sponsor was asked to conduct special analyses for serum BUN and creatinine assessing the incidence of increases that were > 50 % above the baseline value in individual patients in Study MIG-3006, CAPSS-122, MIGR-1-3, and the pool of all of these trials.

Table 72 Incidence of Serum BUN Increase > 50 % Above Baseline in MIG-3006

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	Placebo n (%)	TPM 50 mg/day n (%)	TPM 100 mg/day n (%)	Any TPM n (%)
All Subjects	33	35	35	70
At Any Visit	8 (24.2)	5 (14.3)	8 (22.9)	13 (18.6)
At Final Visit	1 (3.0)	1 (2.9)	4 (11.4)	5 (7.1)

Table 73 Incidence of Serum BUN Increase > 50 % Above Baseline in Pool of MIGR-001,-002,-003

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	Placebo n (%)	TPM 50 mg/day n (%)	TPM 100 mg/day n (%)	TPM 200 mg/day n (%)	Any TPM n (%)
All Subjects	11	11	13	13	37
At Any Visit	1 (9.1)	1 (9.1)	4 (30.8)	4 (30.8)	9 (24.3)
At Final Visit	0	0	2 (15.4)	2 (15.4)	4 (10.8)

Table 74 Incidence of Serum BUN Increase > 50 % Above Baseline in CAPSS-122

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	Placebo n (%)	TPM 2-3 mg/kg/day n (%)
All Subjects	41	82
At Any Visit	3 (7.3)	10 (12.2)
At Final Visit	3 (7.3)	10 (12.2)
6-11 Years	25	41
At Any Visit	2 (8.0)	5 (12.2)
At Final Visit	2 (8.0)	5 (12.2)
12-17 Years	16	41
At Any Visit	1 (6.3)	5 (12.2)
At Final Visit	1 (6.3)	5 (12.2)

Table 75 Incidence of Serum BUN Increase > 50 % Above Baseline in Pooled Pediatric Migraine Trials (MIG-3006, CAPSS-122, MIGR-001,-002,-003)

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	Placebo n (%)	TPM 2-3 mg/kg/day n (%)	TPM 50 mg/day n (%)	TPM 100 mg/day n (%)	TPM 200 mg/day n (%)	Any TPM n (%)
All Subjects	85	82	46	48	13	189
At Any Visit	12 (14.1)	10 (12.2)	6 (13.0)	12 (25.0)	4 (30.8)	32 (16.9)
At Final Visit	4 (4.7)	10 (12.2)	1 (2.2)	6 (12.5)	2 (15.4)	19 (10.1)
6-11 Years	25	41	0	0	0	41
At Any Visit	2 (8.0)	5 (12.2)	0	0	0	5 (12.2)
At Final Visit	2 (8.0)	5 (12.2)	0	0	0	5 (12.2)
12-17 Years	60	41	46	48	13	148
At Any Visit	10 (16.7)	5 (12.2)	6 (13.0)	12 (25.0)	4 (30.8)	27 (18.2)
At Final Visit	2 (3.3)	5 (12.2)	1 (2.2)	6 (12.5)	2 (15.4)	14 (9.5)

Table 76 Incidence of Serum Creatinine Increase > 50 % Above Baseline in MIG-3006

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	Placebo n (%)	TPM 50 mg/day n (%)	TPM 100 mg/day n (%)	Any TPM n (%)
All Subjects	33	35	35	70
At Any Visit	1 (3.0)	2 (5.7)	3 (8.6)	5 (7.1)
At Final Visit	1 (3.0)	1 (2.9)	1 (2.9)	2 (2.9)

Table 77 Incidence of Serum Creatinine Increase > 50 % Above Baseline in Pool of MIGR-001,-002,-003

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	Placebo n (%)	TPM 50 mg/day n (%)	TPM 100 mg/day n (%)	TPM 200 mg/day n (%)	Any TPM n (%)
All Subjects	11	11	13	13	37
At Any Visit	1 (9.1)	0	0	1 (7.7)	1 (2.7)
At Final Visit	0	0	0	0	0

Table 78 Incidence of Serum Creatinine Increase > 50 % Above Baseline in CAPSS-122

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	Placebo n (%)	TPM 2-3 mg/kg/day n (%)
All Subjects	41	82
At Any Visit	2 (4.9)	7 (8.5)
At Final Visit	2 (4.9)	7 (8.5)
6-11 Years	25	41
At Any Visit	0	3 (7.3)
At Final Visit	0	3 (7.3)
12-17 Years	16	41
At Any Visit	2 (12.5)	4 (9.8)
At Final Visit	2 (12.5)	4 (9.8)

Table 79 Incidence of Serum Creatinine Increase > 50 % Above Baseline in Pooled Pediatric Migraine Trials (MIG-3006, CAPSS-122, MIGR-001,-002,-003)

Analysis Set: Double Blind Subjects

Age Group Analysis Visits	Placebo n (%)	TPM 2-3 mg/kg/day n (%)	TPM 50 mg/day n (%)	TPM 100 mg/day n (%)	TPM 200 mg/day n (%)	Any TPM n (%)
All Subjects	85	82	46	48	13	189
At Any Visit	4 (4.7)	7 (8.5)	2 (4.3)	3 (6.3)	1 (7.7)	13 (6.9)
At Final Visit	3 (3.5)	7 (8.5)	1 (2.2)	1 (2.1)	0	9 (4.8)
6-11 Years	25	41	0	0	0	41
At Any Visit	0	3 (7.3)	0	0	0	3 (7.3)
At Final Visit	0	3 (7.3)	0	0	0	3 (7.3)
12-17 Years	60	41	46	48	13	148
At Any Visit	4 (6.7)	4 (9.8)	2 (4.3)	3 (6.3)	1 (7.7)	10 (6.8)
At Final Visit	3 (5.0)	4 (9.8)	1 (2.2)	1 (2.1)	0	6 (4.1)

Reviewer Comments

- *Table 72 - Table 75 show the incidence of BUN increases of at least 50 % or more in the various pediatric migraine trials (including pools of trials) according to treatment. Most notably, pooled results of all these trials in Table 75 shows a dose-dependent increase in the incidence of these outliers at 100 mg and 200 mg at any visit and also at the final visit. In addition, there is an increase in the incidence of such outliers for 2-3 mg/kg/day of topiramate (vs placebo) at the final visit. A closer examination of results of CAPSS-122 by itself reveals similar increases in the incidence of these outliers with 2-3 mg/kg/day topiramate at any visit and the final visit in both subgroups (younger and older) of pediatric patients.*

- *Table 76 - Table 79 show the incidence of serum creatinine increases of at least 50 % or more in the various pediatric migraine trials (including pools of trials) according to treatment. Most notably, pooled results of all these trials in Table 79 shows a dose-dependent small increase in the incidence of these outliers at 100 mg and 200 mg at any visit. In addition, there is an increase in the incidence of such outliers for 2-3 mg/kg/day of topiramate (vs placebo) at any visit and the final visit. A closer examination of results*

of CAPSS-122 by itself (Table 78) reveals increases in the incidence of these outliers with 2-3 mg/kg/day topiramate any visit and the final visit in both subgroups (younger and older) of pediatric patients.

- *These analyses show that topiramate treatment is associated with an increased risk for outliers who exhibit at least a 50 % or more increase from baseline in serum BUN and creatinine compared to such outliers in the placebo group. This increased risk for these BUN outliers is dose-dependent at any visit and the final visit, and this increased risk for creatinine outliers is dose-dependent at any visit.*

- *Refer also to Section 7.4.2 Laboratory Findings also shows outlier results for increases of serum BUN and creatinine above the upper limit of the reference range and also for markedly abnormally increased outliers.*

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Frequency of Common Adverse Events
Treatment-emergent adverse events (TEAEs) occurring in at least 10% of subjects in any of the treatment groups are shown in randomized, double-blinded, placebo-controlled trials is shown in Table 80.

The sponsor provided the following summary.

- Overall, TEAEs were reported for 68 (72%) of 94 placebo-treated subjects and 176 (82%) of 215 topiramate-treated subjects.
- In the age 6 to 11 years group, TEAEs were reported for 27 (87%) of 31 placebo-treated subjects and 50 (85%) of 59 topiramate-treated subjects.
- In the age 12 to 17 years group, TEAEs were reported for 41 (65%) of 63 placebo-treated subjects and 126 (81%) of 156 topiramate-treated subjects.
- When TEAEs that occurred in at least 10% of subjects in any of the treatment groups were considered as a pooled "Any Topiramate" group (Any TPM) against placebo for subjects aged 6 to 17 years,
- TEAEs that occurred more commonly in the Any TPM group than the placebo group were as follows: influenza-like symptoms, language problems, paresthesia, gastroenteritis, weight decrease, anorexia, difficulty with concentration/attention, somnolence, infection viral, rhinitis, sinusitis, and upper respiratory tract infection. The TEAEs that occurred in at least 10% of subjects in the Any TPM group and that occurred at least twice as frequently in the Any TPM group as the placebo group were paresthesia, anorexia, and weight decrease as described below :

  Paresthesia:

- Overall, paresthesia occurred in 3 (3%) of 94 placebo-treated subjects and 32 (15%) of 215 topiramate-treated subjects.
- In the age 6 to 11 years group, paresthesia occurred in 0 of 31 placebo-treated subjects and 4 (7%) of 59 topiramate-treated subjects.
- In the age 12 to 17 years group, paresthesia occurred in 3 (5%) of 63 placebo-treated subjects and 28 (18%) of 156 topiramate-treated subject.
- Paresthesia showed some evidence of dose dependence in subjects aged 12 to 17 years; data in subjects aged 6 to 11 years were insufficient to evaluate dose dependence.

Anorexia:

- Overall, anorexia occurred in 6 (6%) of 94 placebo-treated subjects and 25 (12%) of 215 topiramate-treated subjects.
- In the age 6 to 11 years group, anorexia occurred more commonly in the placebo group (4 [13%] of 31 subjects) than in the Any TPM group (7 [12%] of 59 subjects)
- In the age 12 to 17 years group, anorexia occurred in 2 (3%) of 63 placebo-treated subjects and 18 (12%) of 156 topiramate-treated subjects. Anorexia showed evidence of dose dependence in subjects aged 12 to 17 years; data in subjects aged 6 to 11 years were insufficient to evaluate dose dependence.

Weight decrease :

- Overall, weight decrease occurred in 5 (5%) of 94 placebo-treated subjects and 22 (10%) of 215 topiramate-treated subjects.
- In the age 6 to 11 years group, weight decrease occurred in 1 (3%) of 31 placebo-treated subjects and 5 (8%) of 59 topiramate-treated subjects.
- In the age 12 to 17 years group, weight decrease occurred in 4 (6%) of 63 placebo-treated subjects and 17 (11%) of 156 topiramate-treated subjects.
- Weight decrease showed evidence of dose dependence in subjects aged 12 to 17 years; data in subjects aged 6 to 11 years were insufficient to evaluate dose

Table 80 Treatment-Emergent Adverse Events in at Least 10% of Patients in Any Treatment Group for the Pooled Double-Blind Migraine Prophylaxis Studies (Double-Blind Subjects Analysis Set)

		Topiramate				
Age Group Body System Preferred Term	Placebo (N=94) n (%)[b]	2-3 mg/kg/d (N=108) n (%)[b]	50 mg/d (N=46) n (%)[b]	100 mg/d (N=48) n (%)[b]	200 mg/d (N=13) n (%)[b]	Any TPM (N=215) n (%)[b]
All Subjects	94	108	46	48	13	215
Total, subjects with adverse events	68 (72)	93 (86)	34 (74)	37 (77)	12 (92)	176 (82)
Age 6-11 Years	31	59	0	0	0	59
Total, subjects with adverse events	27 (87)	50 (85)	0	0	0	50 (85)
Age 12-17 Years	63	49	46	48	13	156
Total, subjects with adverse events	41 (65)	43 (88)	34 (74)	37 (77)	12 (92)	126 (81)
All Subjects (Continued)						
Body as a whole - general disorders	30 (32)	35 (32)	9 (20)	14 (29)	4 (31)	62 (29)
Fatigue	10 (11)	7 (6)	3 (7)	4 (8)	2 (15)	16 (7)
Influenza-like symptoms	2 (2)	8 (7)	0	1 (2)	0	9 (4)
Injury	11 (12)	8 (7)	4 (9)	5 (10)	1 (8)	18 (8)
Central and peripheral NS disorders	11 (12)	21 (19)	14 (30)	16 (33)	5 (38)	56 (26)
Language problems	1 (1)	2 (2)	0	0	2 (15)	4 (2)
Paraesthesia	3 (3)	9 (8)	9 (20)	9 (19)	5 (38)	32 (15)
Age 6-11 Years (Continued)						
Body as a whole - general disorders	10 (32)	16 (27)	0	0	0	16 (27)
Fatigue	4 (13)	2 (3)	0	0	0	2 (3)
Influenza-like symptoms	1 (3)	3 (5)	0	0	0	3 (5)
Injury	4 (13)	5 (8)	0	0	0	5 (8)
Central and peripheral NS disorders	2 (6)	11 (19)	0	0	0	11 (19)
Language problems	0	1 (2)	0	0	0	1 (2)
Paraesthesia	0	4 (7)	0	0	0	4 (7)
Age 12-17 Years (Continued)						
Body as a whole - general disorders	20 (32)	19 (39)	9 (20)	14 (29)	4 (31)	46 (29)
Fatigue	6 (10)	5 (10)	3 (7)	4 (8)	2 (15)	14 (9)
Influenza-like symptoms	1 (2)	5 (10)	0	1 (2)	0	6 (4)
Injury	7 (11)	3 (6)	4 (9)	5 (10)	1 (8)	13 (8)
Central and peripheral NS disorders	9 (14)	10 (20)	14 (30)	16 (33)	5 (38)	45 (29)
Language problems	1 (2)	1 (2)	0	0	2 (15)	3 (2)
Paraesthesia	3 (5)	5 (10)	9 (20)	9 (19)	5 (38)	28 (18)
Gastrointestinal system disorders	20 (21)	29 (27)	9 (20)	13 (27)	3 (23)	54 (25)
Abdominal pain	10 (11)	11 (10)	3 (7)	7 (15)	2 (15)	23 (11)
Gastroenteritis	4 (4)	10 (9)	1 (2)	1 (2)	0	12 (6)
Metabolic and nutritional disorders	8 (9)	13 (12)	3 (7)	2 (4)	5 (38)	23 (11)
Weight decrease	5 (5)	13 (12)	3 (7)	2 (4)	4 (31)	22 (10)
Psychiatric disorders	15 (16)	32 (30)	13 (28)	9 (19)	6 (46)	60 (28)
Anorexia	6 (6)	14 (13)	4 (9)	5 (10)	2 (15)	25 (12)
Difficulty with concentration/attention	1 (1)	5 (5)	0	1 (2)	2 (15)	8 (4)
Somnolence	4 (4)	9 (8)	1 (2)	3 (6)	2 (15)	15 (7)
Age 6-11 Years (Continued)						
Gastrointestinal system disorders	6 (19)	15 (25)	0	0	0	15 (25)
Abdominal pain	4 (13)	5 (8)	0	0	0	5 (8)
Gastroenteritis	2 (6)	7 (12)	0	0	0	7 (12)
Metabolic and nutritional disorders	1 (3)	5 (8)	0	0	0	5 (8)
Weight decrease	1 (3)	5 (8)	0	0	0	5 (8)
Psychiatric disorders	8 (26)	17 (29)	0	0	0	17 (29)
Anorexia	4 (13)	7 (12)	0	0	0	7 (12)
Difficulty with concentration/attention	0	3 (5)	0	0	0	3 (5)
Somnolence	3 (10)	5 (8)	0	0	0	5 (8)

Table 80 Treatment-Emergent Adverse Events in at Least 10% of Patients in Any Treatment Group for the Pooled Double-Blind Migraine Prophylaxis Studies (Double-Blind Subjects Analysis Set) (Continued)

		Topiramate				
Age Group Body System Preferred Term	Placebo (N=94) n (%)[b]	2-3 mg/kg/d (N=108) n (%)[b]	50 mg/d (N=46) n (%)[b]	100 mg/d (N=48) n (%)[b]	200 mg/d (N=13) n (%)[b]	Any TPM (N=215) n (%)[b]
Age 12-17 Years (Continued)						
Gastrointestinal system disorders	14 (22)	14 (29)	9 (20)	13 (27)	3 (23)	39 (25)
Abdominal pain	6 (10)	6 (12)	3 (7)	7 (15)	2 (15)	18 (12)
Gastroenteritis	2 (3)	3 (6)	1 (2)	1 (2)	0	5 (3)
Metabolic and nutritional disorders	7 (11)	8 (16)	3 (7)	2 (4)	5 (38)	18 (12)
Weight decrease	4 (6)	8 (16)	3 (7)	2 (4)	4 (31)	17 (11)
Psychiatric disorders	7 (11)	15 (31)	13 (28)	9 (19)	6 (46)	43 (28)
Anorexia	2 (3)	7 (14)	4 (9)	5 (10)	2 (15)	18 (12)
Difficulty with concentration/attention	1 (2)	2 (4)	0	1 (2)	2 (15)	5 (3)
Somnolence	1 (2)	4 (8)	1 (2)	3 (6)	2 (15)	10 (6)
All Subjects (Continued)						
Resistance mechanism disorders	7 (7)	9 (8)	2 (4)	4 (8)	3 (23)	18 (8)
Infection viral	2 (2)	3 (3)	2 (4)	4 (8)	2 (15)	11 (5)
Otitis media	3 (3)	4 (4)	0	0	1 (8)	5 (2)
Respiratory system disorders	33 (35)	44 (41)	16 (35)	18 (38)	5 (38)	83 (39)
Pharyngitis	15 (16)	12 (11)	2 (4)	3 (6)	0	17 (8)
Rhinitis	4 (4)	4 (4)	3 (7)	3 (6)	1 (8)	11 (5)
Sinusitis	7 (7)	11 (10)	4 (9)	2 (4)	2 (15)	19 (9)
Upper respiratory tract infection	13 (14)	21 (19)	12 (26)	11 (23)	3 (23)	47 (22)
Age 6-11 Years (Continued)						
Resistance mechanism disorders	4 (13)	6 (10)	0	0	0	6 (10)
Infection viral	0	2 (3)	0	0	0	2 (3)
Otitis media	3 (10)	3 (5)	0	0	0	3 (5)
Respiratory system disorders	16 (52)	22 (37)	0	0	0	22 (37)
Pharyngitis	7 (23)	4 (7)	0	0	0	4 (7)
Rhinitis	3 (10)	2 (3)	0	0	0	2 (3)
Sinusitis	1 (3)	6 (10)	0	0	0	6 (10)
Upper respiratory tract infection	5 (16)	10 (17)	0	0	0	10 (17)
Age 12-17 Years (Continued)						
Resistance mechanism disorders	3 (5)	3 (6)	2 (4)	4 (8)	3 (23)	12 (8)
Infection viral	2 (3)	1 (2)	2 (4)	4 (8)	2 (15)	9 (6)
Otitis media	0	1 (2)	0	0	1 (8)	2 (1)
Respiratory system disorders	17 (27)	22 (45)	16 (35)	18 (38)	5 (38)	61 (39)
Pharyngitis	8 (13)	8 (16)	2 (4)	3 (6)	0	13 (8)
Rhinitis	1 (2)	2 (4)	3 (7)	3 (6)	1 (8)	9 (6)
Sinusitis	6 (10)	5 (10)	4 (9)	2 (4)	2 (15)	13 (8)
Upper respiratory tract infection	8 (13)	11 (22)	12 (26)	11 (23)	3 (23)	37 (24)

Table 81 **TEAEs (≥ 2 % Rounded Off Incidence in Any TPM Group and Greater Than Incidence in Placebo) in Pooled Migraine Trials (MIG-3006, MIGR-001,-002,-003) in Adolescents (12-17 yo) (Yellow Highlight Indicates TPM % ≥ 5 % Greater Than Placebo %)**

	Placebo	TPM 50 mg/day	TPM 100 mg/day	TPM 200 mg/day	Any TPM
Body System for TEAE	(N=45)	(N=46)	(N=48)	(N=13)	(N=107)
Preferred Term for TEAE	n (%)	n (%)	n (%)	n (%)	n (%)
12-17 YEARS	45	46	48	13	107
TOTAL NO. SUBJECTS WITH ADVERSE EVENTS	26 (58)	34 (74)	37 (77)	12 (92)	83 (78)
BODY AS A WHOLE - GENERAL DISORDERS	11 (24)	9 (20)	14 (29)	4 (31)	27 (25)
ALLERGIC REACTION	0	1 (2)	0	0	1 (1)
ALLERGY	0	0	2 (4)	1 (8)	3 (3)
FATIGUE	3 (7)	3 (7)	4 (8)	2 (15)	9 (8)
FEVER	1 (2)	2 (4)	3 (6)	0	5 (5)
INFLUENZA-LIKE SYMPTOMS	0	0	1 (2)	0	1 (1)
LEG PAIN	0	1 (2)	1 (2)	1 (8)	3 (3)
PALLOR	0	1 (2)	0	0	1 (1)
SYNCOPE	0	1 (2)	1 (2)	0	2 (2)
CENTR & PERIPH NERV SYST DISORDERS	7 (16)	14 (30)	16 (33)	5 (38)	35 (33)
DIZZINESS	2 (4)	2 (4)	3 (6)	0	5 (5)
HEADACHE	1 (2)	1 (2)	2 (4)	1 (8)	4 (4)
HYPERKINESIA	0	0	1 (2)	0	1 (1)
HYPOAESTHESIA	0	1 (2)	0	0	1 (1)
LANGUAGE PROBLEMS	1 (2)	0	0	2 (15)	2 (2)
MUSCLE CONTRACTIONS INVOLUNTARY	0	0	0	1 (8)	1 (1)
NEURALGIA	0	1 (2)	0	0	1 (1)
PARAESTHESIA	3 (7)	9 (20)	9 (19)	5 (38)	23 (21)
TREMOR	0	0	1 (2)	0	1 (1)
ENDOCRINE DISORDERS	0	1 (2)	0	1 (8)	2 (2)
HYPERTHYROIDISM	0	0	0	1 (8)	1 (1)
SIALOADENITIS	0	1 (2)	0	0	1 (1)
GASTRO-INTESTINAL SYSTEM DISORDERS	9 (20)	9 (20)	13 (27)	3 (23)	25 (23)
ABDOMINAL PAIN	4 (9)	3 (7)	7 (15)	2 (15)	12 (11)
CONSTIPATION	0	0	1 (2)	0	1 (1)
DIARRHOEA	0	1 (2)	1 (2)	1 (8)	3 (3)
GASTRITIS	0	1 (2)	1 (2)	0	2 (2)
NAUSEA	2 (4)	2 (4)	4 (8)	0	6 (6)
STOMATITIS	0	1 (2)	0	0	1 (1)
TOOTH CARIES	0	0	1 (2)	0	1 (1)
VOMITING	1 (2)	0	2 (4)	0	2 (2)
HEARING AND VESTIBULAR DISORDERS	0	1 (2)	0	0	1 (1)
EARACHE	0	1 (2)	0	0	1 (1)
HEART RATE AND RHYTHM DISORDERS	0	0	1 (2)	0	1 (1)
ARRHYTHMIA VENTRICULAR	0	0	1 (2)	0	1 (1)
METABOLIC AND NUTRITIONAL DISORDERS	4 (9)	3 (7)	2 (4)	5 (38)	10 (9)
OEDEMA PHARYNX	0	0	0	1 (8)	1 (1)
WEIGHT DECREASE	1 (2)	3 (7)	2 (4)	4 (31)	9 (8)
MUSCULO-SKELETAL SYSTEM	0	1 (2)	3 (6)	0	4 (4)

	Placebo	TPM 50 mg/day	TPM 100 mg/day	TPM 200 mg/day	Any TPM
Body System for TEAE	(N=45)	(N=46)	(N=48)	(N=13)	(N=107)
Preferred Term for TEAE	n (%)	n (%)	n (%)	n (%)	n (%)
DISORDERS					
ARTHRALGIA	0	1 (2)	0	0	1 (1)
ARTHRITIS	0	0	1 (2)	0	1 (1)
HAEMARTHROSIS	0	0	1 (2)	0	1 (1)
MYALGIA	0	0	1 (2)	0	1 (1)
PLATELET,BLEEDING & CLOTTING DISORDERS	0	1 (2)	1 (2)	1 (8)	3 (3)
EPISTAXIS	0	1 (2)	1 (2)	1 (8)	3 (3)
PSYCHIATRIC DISORDERS	6 (13)	13 (28)	9 (19)	6 (46)	28 (26)
ANOREXIA	2 (4)	4 (9)	5 (10)	2 (15)	11 (10)
ANXIETY	0	0	0	1 (8)	1 (1)
DEPRESSION	0	2 (4)	0	0	2 (2)
DIFFICULTY WITH CONCENTRATION/ATTENTION	0	0	1 (2)	2 (15)	3 (3)
DIFFICULTY WITH MEMORY NOS	1 (2)	0	0	1 (8)	1 (1)
EMOTIONAL LABILITY	0	1 (2)	0	0	1 (1)
INSOMNIA	1 (2)	4 (9)	1 (2)	0	5 (5)
MOOD PROBLEMS	2 (4)	1 (2)	1 (2)	1 (8)	3 (3)
NERVOUSNESS	0	2 (4)	1 (2)	0	3 (3)
PSYCHOMOTOR SLOWING	0	1 (2)	0	1 (8)	2 (2)
SOMNOLENCE	1 (2)	1 (2)	3 (6)	2 (15)	6 (6)
REPRODUCTIVE DISORDERS, FEMALE	2 (4)	0	1 (2)	0	1 (1)
DYSMENORRHOEA	0	0	1 (2)	0	1 (1)
RESISTANCE MECHANISM DISORDERS	3 (7)	2 (4)	4 (8)	3 (23)	9 (8)
INFECTION	0	1 (2)	0	0	1 (1)
INFECTION VIRAL	2 (4)	2 (4)	4 (8)	2 (15)	8 (7)
OTITIS MEDIA	0	0	0	1 (8)	1 (1)
RESPIRATORY SYSTEM DISORDERS	10 (22)	16 (35)	18 (38)	5 (38)	39 (36)
ASTHMA	0	0	2 (4)	0	2 (2)
COUGHING	0	3 (7)	1 (2)	0	4 (4)
HYPERVENTILATION	0	1 (2)	0	0	1 (1)
LARYNGITIS	0	0	0	1 (8)	1 (1)
PNEUMONIA	0	1 (2)	2 (4)	0	3 (3)
RESPIRATORY DISORDER	0	0	1 (2)	0	1 (1)
RHINITIS	1 (2)	3 (7)	3 (6)	1 (8)	7 (7)
SINUSITIS	1 (2)	4 (9)	2 (4)	2 (15)	8 (7)
UPPER RESP TRACT INFECTION	5 (11)	12 (26)	11 (23)	3 (23)	26 (24)
SKIN AND APPENDAGES DISORDERS	2 (4)	6 (13)	5 (10)	1 (8)	12 (11)
ACNE	0	0	1 (2)	0	1 (1)
DERMATITIS FUNGAL	0	1 (2)	0	0	1 (1)
DERMATITIS LICHENOID	0	1 (2)	0	0	1 (1)
NAIL DISORDER	0	1 (2)	1 (2)	0	2 (2)
PARONYCHIA	0	1 (2)	0	0	1 (1)
PRURITUS	0	1 (2)	1 (2)	0	2 (2)
RASH ERYTHEMATOUS	0	0	0	1 (8)	1 (1)
SKIN DISORDER	0	0	1 (2)	0	1 (1)
SKIN DRY	0	1 (2)	0	0	1 (1)
SWEATING INCREASED	0	1 (2)	0	0	1 (1)
SPECIAL SENSES OTHER, DISORDERS	1 (2)	1 (2)	3 (6)	1 (8)	5 (5)
TASTE PERVERSION	1 (2)	1 (2)	3 (6)	1 (8)	5 (5)

	Placebo	TPM 50 mg/day	TPM 100 mg/day	TPM 200 mg/day	Any TPM
Body System for TEAE	(N=45)	(N=46)	(N=48)	(N=13)	(N=107)
Preferred Term for TEAE	n (%)	n (%)	n (%)	n (%)	n (%)
URINARY SYSTEM DISORDERS	1 (2)	3 (7)	1 (2)	0	4 (4)
FACE OEDEMA	0	1 (2)	0	0	1 (1)
RENAL CALCULUS	0	0	1 (2)	0	1 (1)
URINARY TRACT INFECTION	1 (2)	2 (4)	1 (2)	0	3 (3)
VISION DISORDERS	5 (11)	4 (9)	4 (8)	0	8 (7)
CONJUNCTIVITIS	2 (4)	3 (7)	2 (4)	0	5 (5)
WHITE CELL AND RES DISORDERS	0	2 (4)	0	0	2 (2)
GRANULOCYTOPENIA	0	1 (2)	0	0	1 (1)
LEUKOCYTOSIS	0	1 (2)	0	0	1 (1)
LYMPHOCYTOSIS	0	1 (2)	0	0	1 (1)
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.					

Table 82 Incidence of Most Common TEAEs by WHO-ART Body System and Preferred Term in CAPSS-122 (Evaluable-for-Safety Population)

	Topiramate (N=108)		Placebo (N=49)	
WHO-ART System Organ Class/ Preferred Term[b]	n	(%)	n	(%)
Body As A Whole - General Disorders				
Fatigue	7	(6.5)	6	(12.2)
Fever	6	(5.6)	2	(4.1)
Influenza-Like Symptoms	8	(7.4)	2	(4.1)
Injury	8	(7.4)	6	(12.2)
Centr & Periph Nerv Syst Disorders				
Headache	5	(4.6)	3	(6.1)
Paraesthesia	9	(8.3)	0	(0.0)
Gastro-Intestinal System Disorders				
Abdominal Pain	11	(10.2)	6	(12.2)
Gastroenteritis	10	(9.3)	3	(6.1)
Nausea	6	(5.6)	3	(6.1)
Metabolic And Nutritional Disorders				
Weight Decrease	11	(10.2)	2	(4.1)
Psychiatric Disorders				
Anorexia	14	(13.0)	4	(8.2)
Somnolence	9	(8.3)	3	(6.1)
Resistance Mechanism Disorders				
Otitis Media	5	(4.6)	4	(8.2)
Respiratory System Disorders				
Coughing	3	(2.8)	3	(6.1)
Pharyngitis	12	(11.1)	10	(20.4)
Sinusitis	11	(10.2)	6	(12.2)
Upper Resp Tract Infection	21	(19.4)	8	(16.3)
Grand Total				
Subjects With At Least 1 AE	91	(84.3)	40	(81.6)

Time of Onset of Common Adverse Events
For subjects receiving topiramate :

- Onset of TEAEs occurred slightly more frequently during titration than during maintenance . Onset during early titration was more common than onset during late titration. For subjects in the Any TPM group, 41% (46% of adolescents aged 12-17 years, 29% of children aged 6-11 years) had AEs with onset during titration that persisted into maintenance. Overall, AE onset patterns were approximately similar between children (aged 6-11 years) and adolescents (aged 12-17 years); however, no early or late titration data were available for children.

- The TEAEs of paresthesia, anorexia, and weight decrease (i.e., the TEAEs that occurred in ≥ 10% of patients in the Any TPM group and that occurred at least twice as frequently in the Any TPM group as the placebo group had onset during titration in most cases, with onset occurring more commonly during early titration than late titration, and persisting into maintenance in approximately half of cases.

Reviewer Comments

- *Table 80 shows the pooled incidence of TEAEs in all the Double-Blinded, Pediatric Migraine Prophylaxis Trials according to treatment group when any group (even placebo) had a frequency ≥ 10 %. Because I am also presenting more comprehensive TEAEs for the pool of MIG-3006 and MIGR-1-3 (Table 81) and CAPSS-122 (Table 82) separately, I will focus my comments on these other tables. I have also summarized sponsor observations of most common TEAEs shown in Table 80 immediately prior to this table.*

- *Table 81 shows results for the pool of MIG-3006 and MIGR-1-3. Yellow highlighting emphasizes any topiramate group with an incidence that was at least 5 % greater than the respective incidence for placebo. The following TEAEs had a large treatment difference such as an incidence for any topiramate group at the 200 mg dose that was at least 10 % greater than the incidence for placebo (shown in descending order of treatment difference) : paresthesia, weight decrease, difficulty with concentration/attention, language problems, somnolence, sinusitis, upper respiratory tract infection, anorexia, and viral infection.*

- *Many TEAEs (Table 81) exhibited a topiramate dose-response . In many instances (but not all), the dose-response relationship was demonstrated a progressive increase in the incidence of a TEAE with each larger dose. The following TEAEs appear to be dose-dependent : allergy, fatigue, leg pain, headache, language problems, paresthesia, hyperthyroidism, abdominal pain, diarrhea, pharyngeal edema, weight decrease, epistaxis, anorexia, difficulty with concentration/memory, mood problems, psychomotor slowing, somnolence, viral infection, otitis media, laryngitis, rhinitis, sinusitis, and taste perversion.*

- *Some previous analyses of pediatric patients treated with topiramate have suggested that pediatric patients treated with topiramate are at increased risk for various infections. This analysis (Table 81) shows an increased risk for various infections including : viral infection, otitis media, rhinitis, sinusitis, and upper respiratory tract infection. Consideration should be given to creating a separate section in the Warnings and Precautions section of the topiramate label describing this increased risk for infections in pediatric patients.*

- *TEAEs with a treatment difference (topiramate % - placebo %) of 10 % or greater have been considered as being caused by topiramate. I believe that such TEAEs shown here in Table 81 are also caused by topiramate.*

- *Based upon results shown in Table 81, I recommend that the label describe the most common TEAEs as those occurring in the 100 mg topiramate dose group (because this would be the only approved dose for adolescents) when the incidence is at least 4 % or more greater than the placebo group incidence and the 100 mg topiramate dose group is composed of at least 2 patients. With this treatment difference threshold/criterion for most common adverse reactions, the following TEAEs are the most common adverse reactions (shown in descending order of treatment difference incidence) : paresthesia, upper respiratory tract infection, anorexia, abdominal pain, somnolence allergy, fever, somnolence, viral infection, asthma, pneumonia, and taste perversion. I also believe that these adverse reactions are caused by topiramate.*

  Many of the adverse reactions that were more frequent with topiramate than with placebo and that were seemingly caused by topiramate developed in the titration period. A significant proportion of these events developing in the titration period persisted into the maintenance phase and had a total duration of 7 or more days.

- *Many of these "most common" TEAEs for the 100 mg dose group in adolescents are similar to the "most common" TEAEs list for that same dose in adults in the controlled migraine trials when the same threshold (treatment difference $\geq$ 4 %) is applied. This list of "most common" TEAEs in adults (shown in descending order of treatment difference) includes : paresthesia, somnolence, weight decrease, taste perversion, diarrhea, difficulty with memory, nausea, difficulty with concentration/attention, mood problems, language problems, and fatigue. Thus, paresthesia, language problems, difficulty with concentration/attention, weight decrease, and anorexia were included in "most common" lists in adolescents and adults. Overall, the safety profile in adolescents for all TEAEs was quite similar to that for adults for migraine prophylaxis.*

- *The safety profile based upon all TEAEs in adolescents in controlled migraine trials was also relatively similar to the safety profile for adults and pediatric patients in all the controlled epilepsy trials. Of interest, paresthesia, anorexia, weight decrease, and difficulty with concentration/attention are included in "most common" adverse reactions*

list for adolescents in migraine trials and for adults and pediatric patients in all epilepsy trials.

- *Table 82 shows TEAEs in CAPSS-122. Treatment differences of at least 5 % or greater were observed for paresthesia, weight decrease, and anorexia, TEAEs clearly attributed to topiramate. There were several other TEAEs that occurred more frequently in the topiramate group than the placebo group but with a smaller treatment difference including fever, gastroenteritis, somnolence, and upper respiratory tract infection.*

  Several TEAEs exhibited noteworthy treatment differences (topiramate % - placebo %) for developing in the titration period. These TEAEs included paresthesia, weight decrease, anorexia, difficulty with concentration/attention, abdominal pain, somnolence, sinusitis, and upper respiratory tract infection.

7.4.2 Laboratory Findings

In general, central tendency analyses of clinical laboratory analyses were not very informative. Consequently, I am presenting outlier tables for low or high abnormalities (relative to the normal reference range) and markedly abnormal low or high values when the abnormality has the possibility of clinical significance. For example, a "low" value for serum alkaline phosphatase would ordinarily have no clinical significance and thus a low alkaline phosphatase would not be presented.

The tables presented are summary tables created by the reviewer based upon review of the sponsor's outlier tables. Incidence in these tables is highlighted in yellow when the topiramate treatment difference (topiramate % - placebo %) is ≥ 5 %.

Table 83 Incidence (Rounded Off %) of Abnormal Hematology Results in Placebo-Controlled Pediatric Migraine Trials

Analyte and Trial(s)	Time Perspective	Placebo	TPM 50 mg	TPM 100 mg	TPM 200 mg	TPM 2-3 mg/kg	TPM Any Dose
Low Neutrophils							
CAPSS-122, MIGR-1-3 (6-17 yo)	Any Visit	0	4	0	0	0	3
	Final Visit	0	4	0	0	0	3
\CAPSS-122 (6-11)	Any Visit	0				7	7
	Final Visit	0				7	7
High Neutrophils							
MIG-3006, CAPSS-122, MIGR-1-3	Any Visit	1	5	2	2	0	3
	Final Visit	0	5	2	0	0	3
High Lymphocytes							
CAPSS-122 (6-11)	Any Visit	12				32	32
	Final Visit	12				29	29
CAPSS-122	Any Visit	16				22	22

Analyte and Trial(s)	Time Perspective	Placebo	TPM 50 mg	TPM 100 mg	TPM 200 mg	TPM 2-3 mg/kg	TPM Any Dose
	Final Visit	16				21	21
High Platelets							
MIG-3006, CAPSS-122, MIGR-1-3	Any Visit	8	4	13	15	23	10
	Final Visit	6	4	7	10	23	7
MIG-3006	Any Visit	12	15	14			15
	Final Visit	6	6	11			9
MIGR-1-3	Any Visit	0	9	15	23		16
	Final Visit	0	9	8	23		14
High Eosinophils							
CAPSS-122 (6-11)	Any Visit	0				10	10
	Final Visit	0				10	10
Low Hematocrit							
CAPSS-122 (6-11)	Any Visit	0				10	10
	Final Visit	0				10	10
CAPSS-122	Any Visit	2				5	5
	Final Visit	2				5	5
Low Total RBC							
CAPSS-122 (6-11)	Any Visit	4				7	7
	Final Visit	4				7	7
Low Total WBC							
CAPSS-122 (6-11)	Any Visit	0				10	10
	Final Visit	0				10	10

Table 84 Incidence (Rounded Off %) of Markedly Abnormal Hematology Results in Placebo-Controlled Pediatric Migraine Trials

Analyte and Trial(s)	Time Perspective	Placebo	TPM 50 mg	TPM 100 mg	TPM 200 mg	TPM 2-3 mg/kg	TPM Any Dose
Eosinophils							
CAPSS-122	Any Visit	0				2	2
	Final Visit	0				2	2
CAPSS-122 (6-11 yo)	Any Visit	0				5	5
	Final Visit	0				5	5

Table 85 Incidence (Rounded Off %) of Abnormal Chemistry Results in Placebo-Controlled Pediatric Migraine Trials

Analyte and Trial(s)	**Time Perspective**	**Placebo**	**TPM 50 mg**	**TPM 100 mg**	**TPM 200 mg**	**TPM 2-3 mg/kg**	**TPM Any Dose**
High Alkaline Phosphatase							
MIG-3006	Any Visit	9	14	26			20
	Final Visit	0	9	3			6
CAPSS-122 (6-11 yo)	Any Visit	10				23	23
	Final Visit	10				11	11
MIG-3006, CAPSS-122 (12-17 yo),	Any Visit	3	6	7	0	0	4
	Final Visit	2	2	4	0	0	2

Analyte and Trial(s)	Time Perspective	Placebo	TPM 50 mg	TPM 100 mg	TPM 200 mg	TPM 2-3 mg/kg	TPM Any Dose
MIGR-1-3							
MIGR-1-3	Any Visit	0	9	0	0		3
	Final Visit	0	9	0	0		3
CAPSS-122	Any Visit	6				15	15
	Final Visit	6				7	7
CAPSS-122 (12-17 yo)	Any Visit	0				6	6
	Final Visit						
Low Bicarbonate							
MIG-3006, MIGR-1-3	Any Visit	16	59	58	31		55
	Final Visit	7	33	38	31		35
MIGR-1-3	Any Visit	9	36	31	31		32
	Final Visit	0	0	31	31		22
High Ammonia							
MIG-3006	Any Visit	9	14	26			20
	Final Visit	0	9	3			6
High Chloride							
MIG-3006, MIGR-1-3	Any Visit	2	11	25	39		21
	Final Visit	2	4	8	15		8
MIGR-1-3	Any Visit	9	18	31	39		30
	Final Visit	9	9	8	15		11
High BUN							
MIG-3006, CAPSS-122 (12-17 yo), MIGR-1-3	Any Visit	0	2	4	8	0	3
	Final Visit	0	0	0	0	0	0
High Creatinine							
MIG-3006, CAPSS-122, MIGR-1-3	Any Visit	6	11	11	10	0	10
	Final Visit	5	11	0	6	0	6
CAPSS-122 (6-11 yo)	Any Visit	0				15	15
	Final Visit	0				15	15
MIG-3006, CAPSS-122 (12-17 yo), MIGR-1-3	Any Visit	8	7	11	10	0	9
	Final Visit	7	7	0	6	0	4
CAPSS-122	Any Visit	5				11	11
	Final Visit	5				11	11
High Creatine Kinase							
MIG-3006	Any Visit	9	14	14			14
	Final Visit	0	6	6			6
Low Phosphorus							
MIG-3006	Any Visit	6	14	0			7
	Final Visit	0	11	0			6
Low Potassium							
MIG-3006, MIGR-1-3	Any Visit	0	2	2	0		2
	Final Visit	0	0	0	0		0
MIG-3006,	Any Visit	0	3	3			3
	Final Visit	0	0	0			0

Analyte and Trial(s)	Time Perspective	Placebo	TPM 50 mg	TPM 100 mg	TPM 200 mg	TPM 2-3 mg/kg	TPM Any Dose
High Total Protein							
MIG-3006, MIGR-1-3	Any Visit	2	9	6	15		8
	Final Visit	2	2	2	0		2
MIGR-1-3	Any Visit	0	9	0	15		8
	Final Visit	0	9	0	0		3
High Uric Acid							
MIG-3006, CAPSS-122 (12-17 yo)	Any Visit	2	14	11		5	10
	Final Visit	2	3	9		5	5
MIG-3006,	Any Visit	3	14	11			13
	Final Visit	3	3	9			6
CAPSS-122	Any Visit	2				4	
	Final Visit	2				4	
High ALT							
CAPSS-122	Any Visit	2				4	4
	Final Visit	0				2	2
CAPSS-122 (12-17 yo)	Any Visit	0				4	4
	Final Visit	0				2	2
High SGOT							
	Any Visit	2				4	4
	Final Visit	0				0	0
High AST							
MIG-3006, CAPSS-122 (12-17 yo), MIGR-1-3	Any Visit	2	4	0	6	0	3
	Final Visit	2	0	0	0	0	0
CAPSS-122 (12-17 yo),	Any Visit	0				4	4
	Final Visit	0				0	0
High GGT							
MIG-3006	Any Visit	3	3	11			7
	Final Visit	3	0	6			3

Table 86 Incidence (Rounded Off %) of Markedly Abnormal Chemistry Results in Placebo-Controlled Pediatric Migraine Trials

Analyte and Trial(s)	Time Perspective	Placebo	TPM 50 mg	TPM 100 mg	TPM 200 mg	TPM 2-3 mg/kg	TPM Any Dose
High Ammonia							
MIG-3006	Any Visit	3	0	9			4
	Final Visit	0	0	0			0
Low Bicarbonate							
MIG-3006	Any Visit	0	3	3			3
	Final Visit	0	3	3			3
MIG-3006, MIGR-1-3	Any Visit	2	2	6	0		4
	Final Visit	0	2	6	0		4

MIGR-1-3	Any Visit	9	0	15	0		5
	Final Visit	0	0	15	0		5
High Chloride							
MIG-3006, MIGR-1-3	Any Visit	2	2	2	8		3
	Final Visit	2	0	0	8		1
MIG-3006	Any Visit	0	3	3			3
	Final Visit	0	0	0			0

Reviewer Comments

An increased risk for abnormalities (value outside normal reference range) in several clinical laboratory analytes measured in blood has been observed during topiramate treatment of pediatric patients (6-17 years) in controlled trials for migraine prophylaxis compared to placebo-treated patients. Abnormally increased results were observed for creatinine, BUN, alkaline phosphatase, total protein, uric acid, gamma glutamyl transferase, creatine kinase, chloride, ammonia, eosinophils, platelets, and lymphocytes. Abnormally decreased results were observed for phosphorus, bicarbonate, hematocrit, total white blood count and neutrophils. In some instances, abnormalities were also observed at the end of the trial at the final visit and the changes were considered markedly abnormal. Abnormalities in some hematology analytes (i.e., increased eosinophils and decreased total while blood count and neutrophils) occurred predominantly or exclusively in younger pediatric patients (6-11 years).

7.4.3 Vital Signs

All trials collected sitting vital sign measurements, except study TOPMAT-MIG-3006 that did not specify a position for vital sign measurement.

In general, central tendency analyses of vital sign (blood pressure and pulse) analyses were not very informative. Consequently, I am presenting outlier tables for low or high outliers (relative to various thresholds that the DNP recommended to the sponsor.

The tables presented here are summary outlier tables created by the reviewer based upon review of the sponsor's outlier tables. Outlier results are presented for systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse for any visit and for final visit for different trial analyses when the topiramate incidence is greater than the placebo incidence and the topiramate treatment group is composed of at least 2 patients.

For the following vital sign outlier tables, yellow highlights indicate topiramate incidence > placebo incidence **and bold indicates topiramate treatment difference (vs placebo) ≥ 10 %.**

Table 87 Incidence (Rounded Off %) of SBP Outlier Results in Placebo-Controlled Pediatric Migraine Trials

(Decrease or Increase = Change from Baseline; Yellow Highlight indicates TPM % > Placebo %; Bold indicates TPM Treatment Difference at Least 10 % Greater Than Placebo)

SBP Outlier and Trial(s)	Time Perspective	Placebo	TPM 50 mg	TPM 100 mg	TPM 200 mg	TPM 2-3 mg/kg	TPM Any Dose
SBP < 90 for ≥ 10 yo							
MIG-3006, CAPSS-122 MIGR-1-3	Any Visit	6	9	13	15	9	10
	Final Visit	5	2	0	8	1	1
MIG-3006, CAPSS-122 (12-17 yo) MIGR-1-3	Any Visit	3	9	**13**	**15**	8	10
	Final Visit	3	4	4	8	0	3
MIG-3006	Any Visit	3	6	**14**			10
	Final Visit	3	0	0			0
MIGR-1-3	Any Visit	8	**18**	8	15		14
	Final Visit	8	9	0	8		5
CAPSS-122 (12-17 yo)	Any Visit	0				8	8
	Final Visit	0				0	0
CAPSS-122 (6-11 yo)	Any Visit	3				5	5
	Final Visit	10				2	2
SBP Decrease ≥ 10							
MIG-3006, CAPSS-122, MIGR-1-3	Any Visit	36	41	**48**	**62**	44	45
	Final Visit	15	24	23	**31**	19	22
MIG-3006	Any Visit	33	**46**	**46**			**46**
	Final Visit	15	**26**	23			24
MIGR-1-3	Any Visit	33	27	**54**	**62**		**49**
	Final Visit	8	**18**	**23**	**31**		**24**
CAPSS-122	Any Visit	39				44	44
	Final Visit	16				19	19
CAPSS-122 (6-11 yo)	Any Visit	32				**45**	**45**
	Final Visit	13				17	17
SBP Decrease ≥ 20							
MIG-3006, CAPSS-122, MIGR-1-3	Any Visit	12	17	18	**31**	12	14
	Final Visit	5	7	6	8	3	5
MIG-3006, CAPSS-122 (12-17 yo) MIGR-1-3	Any Visit	38	41	**48**	**62**	43	46
	Final Visit	16	24	23	**31**	20	23
CAPSS-122 (12-17 yo)	Any Visit	11				14	14
	Final Visit	6				2	2
MIGR-1-3	Any Visit	0	9	8	**31**		**16**
	Final Visit	0	0	8	8		5

SBP Outlier and Trial(s)	Time Perspective	Placebo	TPM 50 mg	TPM 100 mg	TPM 200 mg	TPM 2-3 mg/kg	TPM Any Dose
CAPSS-122	Any Visit	8				12	12
	Final Visit	2				3	3
CAPSS-122 (6-11 yo	Any Visit	7				10	10
	Final Visit	0				3	3
SBP > 130 for ≥ 10 yo							
MIG-3006, CAPSS-122 MIGR-1-3	Any Visit	6	11	8	8	7	8
	Final Visit	2	4	4	8	0	2
MIGR-1-3	Any Visit	0	**18**	8	8		**11**
	Final Visit	0	0	0	8		3
SBP Increase ≥ 10							
MIGR-1-3	Any Visit	33	**82**	15	23		38
	Final Visit	0	**27**	**15**	8		**16**
SBP Increase ≥ 20							
MIGR-1-3	Any Visit	8	**18**	15	8		14
	Final Visit	0	0	8	8		5

Table 88 Incidence (Rounded Off %) of DBP Outlier Results in Placebo-Controlled Pediatric Migraine Trials

(Decrease or Increase = Change from Baseline; Yellow Highlight indicates TPM % > Placebo %; Bold indicates TPM Treatment Difference at Least 10 % Greater Than Placebo)

DBP Outlier and Trial(s)	Time Perspective	Placebo	TPM 50 mg	TPM 100 mg	TPM 200 mg	TPM 2-3 mg/kg	TPM Any Dose
DBP < 50 for ≥ 10 yo							
MIG-3006, CAPSS-122 MIGR-1-3	Any Visit	7	0	4	**31**	6	6
	Final Visit	4	0	0	0	3	1
MIG-3006, CAPSS-122 (12-17 yo) MIGR-1-3	Any Visit	3	0	4	**31**	4	5
	Final Visit	2	0	0	0	2	1
MIG-3006	Any Visit	8	0	8	**31**		14
	Final Visit	0	0	0	0		0
CAPSS-122 (12-17 yo)	Any Visit	0				4	4
	Final Visit	0				2	2
DBP Decrease ≥ 7							
MIG-3006, CAPSS-122, MIGR-1-3	Any Visit	45	46	35	**85**	44	45
	Final Visit	25	28	15	**53**	22	23
MIG-3006,	Any Visit	41	46	35	**85**	45	46

DBP Outlier and Trial(s)	Time Perspective	Placebo	TPM 50 mg	TPM 100 mg	TPM 200 mg	TPM 2-3 mg/kg	TPM Any Dose
CAPSS-122 (12-17 yo) MIGR-1-3	Final Visit	21	28	15	**54**	22	24
MIG-3006	Any Visit	43	**54**	34			44
	Final Visit	30	31	20			26
MIGR-1-3	Any Visit	25	18	**39**	**85**		**49**
	Final Visit	8	**18**	0	**54**		**24**
CAPSS-122 (12-17 yo)	Any Visit	50				45	45
	Final Visit	11				**22**	**22**
DBP Decrease ≥ 10							
MIG-3006, CAPSS-122, MIGR-1-3	Any Visit	36	**46**	27	**85**	36	39
	Final Visit	19	24	13	**46**	12	17
MIG-3006, CAPSS-122 (12-17 yo) MIGR-1-3	Any Visit	35	**46**	27	**85**	39	41
	Final Visit	18	24	13	**46**	12	19
MIG-3006	Any Visit	39	40	26			37
	Final Visit	24	26	17			21
MIGR-1-3	Any Visit	17	**36**	**31**	**85**		**51**
	Final Visit	8	18	0	**46**		**22**
CAPSS-122 (12-17 yo)	Any Visit	39				39	39
	Final Visit	11				12	12
DBP Decrease ≥ 20							
MIG-3006, CAPSS-122 MIGR-1-3	Any Visit	6	15	10	8	4	8
	Final Visit	3	9	6	8	2	5
MIG-3006, CAPSS-122 (12-17 yo) MIGR-1-3	Any Visit	6	15	10	8	2	9
	Final Visit	3	9	6	8	0	5
MIG-3006	Any Visit	12	14	11			13
	Final Visit	6	9	9			9
MIGR-1-3	Any Visit	0	**18**	8	8		**11**
	Final Visit	0	9	0	8		5
DBP > 80 for ≥ 10 yo							
MIG-3006, CAPSS-122 MIGR-1-3	Any Visit	6	**17**	**19**	0	8	12
	Final Visit	1	4	8	0	5	5
MIG-3006, CAPSS-122 (12-17 yo)	Any Visit	10	17	19	0	18	17
	Final Visit	2	4	8	0	10	7

DBP Outlier and Trial(s)	Time Perspective	Placebo	TPM 50 mg	TPM 100 mg	TPM 200 mg	TPM 2-3 mg/kg	TPM Any Dose
MIGR-1-3							
MIG-3006	Any Visit	9	11	17			14
	Final Visit	0	6	9			7
MIGR-1-3	Any Visit	0	**36**	**23**	0		**19**
	Final Visit	0	0	8	0		3
CAPSS-122	Any Visit	6				8	8
	Final Visit	2				5	5
CAPSS-122 (12-17 yo)	Any Visit	17				18	18
	Final Visit	6				10	10
DBP Increase ≥ 7							
CAPSS-122 (6-11 yo)	Any Visit	39				47	47
	Final Visit	23				19	19
MIG-3006, CAPSS-122 (12-17 yo) MIGR-1-3	Any Visit	40	35	42	31	**59**	44
	Final Visit	18	29	15	8	20	17
MIG-3006	Any Visit	33	29	40			34
	Final Visit	21	17	14			16
MIGR-1-3	Any Visit	42	**55**	46	31		43
	Final Visit	8	**27**	15	8		16
CAPSS-122	Any Visit	43				**52**	**52**
	Final Visit	20				20	20
CAPSS-122 (6-11 yo)	Any Visit	39				47	47
	Final Visit	23				19	19
CAPSS-122 (12-17 yo)	Any Visit	50				59	59
	Final Visit	17				20	20
DBP Increase ≥ 10							
MIG-3006, CAPSS-122, MIGR-1-3	Any Visit	27	26	27	31	**41**	34
	Final Visit	16	11	13	8	15	13
CAPSS-122 (6-11)	Any Visit	26				**36**	**36**
	Final Visit	19				12	12
MIG-3006, CAPSS-122 (12-17 yo) MIGR-1-3	Any Visit	27	26	27	31	**47**	33
	Final Visit	14	11	13	8	18	14
MIG-3006	Any Visit	21	20	26			23
	Final Visit	15	9	11			10
MIGR-1-3	Any Visit	33	**46**	31	31		35
	Final Visit	8	**18**	15	8		14
CAPSS-122	Any Visit	29				**41**	**41**
	Final Visit	18				15	15
CAPSS-122 (6-11 yo)	Any Visit	26				**36**	**36**
	Final Visit	19				12	12

DBP Outlier and Trial(s)	Time Perspective	Placebo	TPM 50 mg	TPM 100 mg	TPM 200 mg	TPM 2-3 mg/kg	TPM Any Dose
CAPSS-122 (12-17 yo)	Any Visit	33				**47**	**47**
	Final Visit	17				18	18
DBP Increase ≥ 20							
MIG-3006, CAPSS-122, MIGR-1-3	Any Visit	7	9	2	8	9	8
	Final Visit	4	4	0	0	3	2
MIG-3006, CAPSS-122 (12-17 yo) MIGR-1-3	Any Visit	8	9	2	8	14	8
	Final Visit	3	4	0	0	2	2
MIGR-1-3	Any Visit	8	**18**	8	8		11
	Final Visit	8	9	0	0		3
CAPSS-122	Any Visit	6				9	9
	Final Visit	6				3	3
CAPSS-122 (12-17 yo)	Any Visit	6				14	14
	Final Visit	6				2	2

Decreases or Increases are Changes from Baseline

Table 89 Incidence (Rounded Off %) of Pulse Outlier Results in Placebo-Controlled Pediatric Migraine Trials (Decrease or Increase = Change from Baseline; Yellow Highlight indicates TPM % > Placebo %; Bold indicates TPM Treatment Difference at Least 10 % Greater Than Placebo)

Pulse Outliers and Trial(s)	Time Perspective	Placebo	TPM 50 mg	TPM 100 mg	TPM 200 mg	TPM 2-3 mg/kg	TPM Any Dose
Pulse Decrease ≥ 15 BPM							
MIG-3006, CAPSS-122, MIGR-1-3	Any Visit	17	**28**	10	**31**	24	22
	Final Visit	5	9	6	**23**	8	9
CAPSS-122 (6-11 yo)	Any Visit	19				22	22
	Final Visit	3				3	3
MIG-3006, CAPSS-122 (12-17), MIGR-1-3	Any Visit	16	**28**	10	**31**	**27**	22
	Final Visit	6	9	6	**23**	14	11
MIG-3006	Any Visit	24	26	14			20
	Final Visit	12	9	9			9
MIGR-1-3	Any Visit	8	**36**	0	**31**		**22**
	Final Visit	0	9	0	**23**		**11**
CAPSS-122	Any Visit	14				**24**	**24**
	Final Visit	2				8	8
CAPSS-122 (6-11 yo)	Any Visit	19				22	22
	Final Visit	3				3	3
CAPSS-122 (12-17 yo)	Any Visit	6				**27**	**27**
	Final Visit	0				**14**	**14**

Pulse Outliers and Trial(s)	Time Perspective	Placebo	TPM 50 mg	TPM 100 mg	TPM 200 mg	TPM 2-3 mg/kg	TPM Any Dose
Pulse Decrease ≥ 30 BPM							
MIG-3006, CAPSS-122, MIGR-1-3	Any Visit	1	0	2	8	3	2
	Final Visit	0	0	0	0	1	1
MIG-3006, CAPSS-122 (12-17), MIGR-1-3	Any Visit	2	0	2	8	4	3
	Final Visit	0	0	0	0	2	1
CAPSS-122	Any Visit	0				3	3
	Final Visit	0				1	1
CAPSS-122 (12-17 yo)	Any Visit	0				4	4
	Final Visit	0				2	2
Pulse Increase ≥ 15 BPM							
MIG-3006, CAPSS-122, MIGR-1-3	Any Visit	28	37	31	15	25	29
	Final Visit	14	17	10	0	8	10
MIG-3006, CAPSS-122 (12-17), MIGR-1-3	Any Visit	23	**37**	31	15	31	31
	Final Visit	11	17	10	0	6	10
MIG-3006	Any Visit	27	34	23			29
	Final Visit	12	11	6			9
MIGR-1-3	Any Visit	17	**46**	**54**	15		**38**
	Final Visit	8	**36**	**23**	0		**19**
CAPSS-122 (12-17 yo)	Any Visit	22				31	31
	Final Visit	11				6	6
Pulse Increase ≥ 30 BPM							
MIG-3006, CAPSS-122, MIGR-1-3	Any Visit	4	4	13	0	3	5
	Final Visit	0	2	2	0	0	1
CAPSS-122 (6-11 yo)	Any Visit	3				5	5
	Final Visit	0				0	0
MIG-3006, CAPSS-122 (12-17), MIGR-1-3	Any Visit	5	4	13	0	0	5
	Final Visit	0	2	2	0	0	1
MIG-3006	Any Visit	3	3	11			7
	Final Visit	0	0	3			1
MIGR-1-3	Any Visit	8	9	15	0		8
	Final Visit	0	9	0	0		3
CAPSS-122 (6-11 yo)	Any Visit	3				5	5
	Final Visit	0				0	0

Reviewer Comments

Changes (increases and decreases) from baseline in vital signs (systolic blood pressure, diastolic blood pressure, pulse) occurred more frequently in pediatric patients (6-17 years) treated with various daily doses of topiramate (50 mg, 100 mg, 200 mg, 2-3 mg/kg) than in patients treated with placebo in controlled trials for migraine prophylaxis. These changes were commonly mild-modest for systolic blood pressure (≥ 20 mm Hg), diastolic blood pressure (10 ≥ mm Hg), and pulse (≥ 15 BPM), were often dose-related, and were most frequent at the 200 mg dose level. The most notable changes were SBP < 90 mm Hg, DBP < 50 mm Hg, SBP or DBP increases or decreases ≥ 20 mm Hg, and pulse increases or decreases ≥ 30 beats per minute. When a position was specified for measurement of vital signs in a trial, measurements were made in a sitting position. Systematic collection of orthostatic vital signs has not been conducted.

7.4.4 Electrocardiograms (ECGs)

Not applicable because ECGs were not routinely collected in pediatric migraine trials.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose-dependency of TEAEs was addressed in the earlier various analyses of adverse events particularly in section 7.4.1 (Common Adverse Events) for the controlled trial and open-label trials.

Dose-dependency of other safety parameters (i.e., clinical laboratory analytes and vital signs) was addressed in the respective sections in which these data analyses were presented.

7.5.2 Time Dependency for Adverse Events

Time-dependency of adverse events was addressed in the earlier various analyses of adverse events particularly in section 7.4.1 (Common Adverse Events) for the controlled trial and open-label trials. Time-dependency was considered from the perspective of having a TEAE onset at any time in the trial, onset in the titration period, onset in the maintenance period, and onset in the titration period and persisting into the maintenance period and having a total duration of at least 7 days.

Time-dependency of other safety parameters (i.e., clinical laboratory analytes and vital signs) was addressed in the respective sections in which these data analyses were presented.

7.5.3 Drug-Demographic Interactions

The sponsor conducted subgroup analyses for age and gender for all safety analyses.

Reviewer Comments

There were no noteworthy subgroup findings in these numerous analyses.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Not applicable.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable.

7.6.2 Human Reproduction and Pregnancy Data

Not applicable.

7.6.3 Pediatrics and Assessment of Effects on Growth

The sponsor presented growth analyses from other topiramate trials for other indications in pediatric patients. There were no significant growth analyses for pediatric patients treated with topiramate for migraine because there long-term growth data necessary for appropriate analytes were not available.

Reviewer Comments

There were not clear, noteworthy observations from the epilepsy pediatric data analyses. However, it is important to recognize that pediatric trials (with the exception of the long-term open-label, infant/toddler topiramate treatment experience) have not been conducted with special protocol provisions for collecting adequate height measurements. The current Topamax label notes some delayed growth data for infant/toddlers during long-term, open-label treatment

but these data were uncontrolled and it is not possible to conclude definitively that topiramate treatment was responsible for the delay growth observations in infants/toddlers.

Because the effects of topiramate (especially in view of its strong potential for causing metabolic acidosis that can delay/retard growth, a long-term, controlled safety trial in pediatric patients (2-15 yo) is being conducted to assess effects of topiramate on growth (and other safety interests : bones, kidney stones, cognitive effects).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The sponsor did not present any new information on topiramate regarding overdose, drug abuse potential, withdrawal and rebound.

The following information shown immediately below here in italics is presented in the Topamax (topiramate) label regarding overdose

"Overdoses of TOPAMAX□ have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbance, blurred vision, diplopia, mentation impaired, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. The clinical consequences were not severe in most cases, but deaths have been reported after poly-drug overdoses involving TOPAMAX□. Topiramate overdose has resulted in severe metabolic acidosis [see Warnings and Precautions (5.4)].

A patient who ingested a dose between 96 and 110 g topiramate was admitted to a hospital with a coma lasting 20 to 24 hours followed by full recovery after 3 to 4 days. In acute TOPAMAX® overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has been shown to adsorb topiramate in vitro. Treatment should be appropriately supportive. Hemodialysis is an effective means of removing topiramate from the body."

The following information shown immediately below here in italics is presented in the Topamax (topiramate) label regarding abuse potential, dependence, and Topamax as a controlled substance.

"The abuse and dependence potential of TOPAMAX has not been evaluated in human studies.

TOPAMAX has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

TOPAMAX (topiramate) is not a controlled substance."

Because topiramate is an anti-epileptic drug (AED)/anticonvulsant and can have an effect of seizure threshold, it is generally recommended that patients treated with topiramate taper the

dose of topiramate gradually over an extended period of time (instead of abruptly discontinuing topiramate) to reduce the chance of experiencing a withdrawal seizure.

7.7 Additional Submissions / Safety Issues

The sponsor did not submit a typical 4 Month Safety Update (4MSU) consisting of additional safety data in patients in ongoing trials because there were no ongoing trials of pediatric patients at the time of the Safety Update submission. Instead the sponsor submitted an additional review of postmarketing data.

Reviewer Comments

There were no significant new, noteworthy findings in this material submitted.

8 Postmarket Experience

The sponsor submitted a review of postmarketing data in pediatric patients.

Reviewer Comments

There were no significant new, noteworthy findings in this material submitted.

9 Appendices

9.1 Literature Review/References

The sponsor submitted a comprehensive review of the published literature in pediatric patients.

Reviewer Comments

There were no significant new, noteworthy findings in this material submitted.

9.2 Labeling Recommendations

I have revised the Topamax (topiramate) label in the following respects relative to inserting primarily information from this pediatric migraine prophylaxis NDA :

- Revisions as appropriate on the first page of highlights
- Updating metabolic acidosis acidosis data from adolescent migraine experience
- Updating cognitive dysfunction section of in Warnings and Precautions (section 5) regarding cognitive adverse reactions and dose and time dependent effects of topiramate on these adverse reactions
- Updating section on hyperammonemia regarding laboratory outliers
- Requested sponsor to provide new table for TEAEs in Adverse Reaction section 6 for pool of MIG-3006 and MIGR-1-3 trials
- (b) (4)
- Asked sponsor to insert results of CANTAB testing in the label regarding effects of topiramate on cognitive function in adolescents
- Asked sponsor to insert tables showing efficacy of topiramate on primary efficacy endpoint and on important secondary efficacy endpoint (change from baseline in absolute monthly migraine rate) in MIG-3006
- Asked sponsor to revise language in section 17 Patient Counseling to command language (b) (4)
- Inserted description of clinical laboratory outlier abnormalities in pediatric migraine controlled trials
- Inserted descriptions of information from pediatric, controlled migraine trials in section 8 (Pediatric subsection)
- Inserted summary descriptions of vital signs (blood pressure and pulse) outliers for increases and decrease from baseline from pediatric migraine controlled trials
- Revised section on visual field defects in Warnings and Precautions (section 5)

A revised Topamax (topiramate) label including the revisions outlined above here was sent to the sponsor.

Labeling negotiations for the inclusion of the adolescent migraine indication in the currently approved Topamax label were ongoing at the time that this review was filed.

In addition, the Division of Medical Policies and Procedures (DMPP) has recently completed a consult focused on the Patient Information labeling and has offered recommendations that will need to be conveyed to the Applicant. A consult from the Office of Prescription Drug Promotion (OPDP) is also still outstanding.

The Agency's Study Endpoints and Labeling Division (SEALD) will also need to complete and end-of-cycle review after the label is agreed-upon by both the Applicant and the Division.

9.3 Advisory Committee Meeting

Not applicable. There is no need for an Advisory Committee Meeting.

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/s/

LEONARD P KAPCALA

03/18/2014

Nick,
Here is my final review for your signature. Please let me know if any questions. Thanx.
Len

NICHOLAS A KOZAUER

03/19/2014