U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	20505 (S052)
Drug Name:	Topiramate(Topamax)
Indication(s):	Adolescent Migraine Prophylaxis
Applicant:	Johnson and Johnson
Date(s):	May 28, 2013
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
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Keywords: ANCOVA; ranked analysis

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

The clinical trial efficacy data from study 3006 provided in this application seems to support the efficacy of Topiramate (TPM) 100 mg as migraine prophylaxis for adolescents. The sponsor changed the primary headache classification criteria from the International Headache Society (IHS) algorithm to that of subject's diary classification after a blinded review of the data (see section 3.1.1.5, page 14 for further details). There were 10 randomized subjects that had zero baseline migraines according to IHS classification criteria, which presents a problem for the percent reduction primary endpoint, since dividing by zero results in an undefined percent reduction. This problem could be determined in a blinded data review as suggested by the sponsor. There were no subjects with zero migraines during baseline according to the subject's classification of migraines. 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.

2 INTRODUCTION

2.1 Overview

IND numbers associated with the development of this drug are IND (b) (4) 49640, and 60913 (migraine prophylaxis). NDA 20844 is another new drug application for cross reference involving topiramate.

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.

Table 1 Key Efficacy Studies

Study Design/ Start - completion dates/Region	No. Subjects Age Range	Enrollment Criteria	Study Duration	Study Drug / Dose	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 12 to 17 years of age 10 August 2005 - 29 November 2006 United States, Europe, Israel, South America	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]), 4 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 in the prophylaxis of migraine in pediatric subjects, plus OLE. DB 31 July 2001 - 2 September 2003 OLE 31 July 2001/ 2 January 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 HIS 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-week titration, 12-week maintenance).	TPM titrated to target dosages of 2 to 3 mg/kg/day or until the subject's maximum tolerated dose was achieved, whichever was lower, or matching PBO.	Primary: Number of migraine days per month during DB period vs BL 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, and Overall Global Evaluation.

Note: This was copied from page 12 of the sponsor's clinical overview document

Only study 3006 will be reviewed in detail in this review because Topiramate is already approved for adult migraine prophylaxis and CAPSS-122 was technically not a positive study. Furthermore, the TopMat-Migr 001, 002, and 003 studies pooled together had only the following sample sizes of adolescent subjects N=12, N=11, N=13, and N=13 for placebo, 50 mg TPM, 100 mg TPM, and 200 mg TPM, respectively.

Thirty-one centers participated in study 3006: Argentina (2 centers), Brazil (2 centers), Finland (2 centers), France (5 centers), Israel (2 centers), Norway (2 centers), Romania (3 centers), Spain (4 centers), and the United States (9 centers).

2.2 Data Sources

At the time of review the locations of the primary endpoint raw and derived data, respectively, for the key study, 3006, were as follows.

\\cdsesub1\evsprod\nda020505\0205\m5\datasets\topmat-mig-3006-db\analysis\legacy\datasets\khdrdihs.xpt

\\cdsesub1\evsprod\nda020505\0205\m5\datasets\topmat-mig-3006-db\analysis\legacy\datasets\kmigattk.xpt

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

This reviewer was able to closely reproduce the sponsor's derived migraine rates starting from the raw data provided.

The primary objective of this study was to evaluate the efficacy of 2 dosages of topiramate, 50- and 100 mg per day, compared with placebo in the prevention of migraine attacks in subjects 12 to 17 years of age, as assessed by the percent reduction from prospective baseline to the last 12 weeks of double-blind phase in the monthly migraine attack rate.

3.1.1 Study 3006

DATE STUDY INITIATED:
10 August 2005
DATE STUDY COMPLETED:
29 November 2006

Study TOPMAT-MIG-3006 was a randomized, double-blind, placebo-controlled, parallel-group, 3-arm, fixed dose-ranging study to evaluate the tolerability, safety, and efficacy of topiramate as prophylaxis in subjects, age 12 to 17 years, with episodic migraine headaches with or without aura, based on the proposed International Headache Society (IHS) classification of pediatric migraine.

The study included 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).
The pretreatment phase included a ≤1-week screening period, a 4-week washout period, if needed, with a 2-week taper of disallowed prophylactic migraine medications and 2-week observation period, and a 4-week medication-free, prospective baseline period during which subject headaches were recorded. Eligible subjects with 3 to 12 migraine attacks by subject report during the baseline period (but no more than 14 migraine or non-migraine headache days) were allowed to enter the double-blind treatment phase of the study.
In the double-blind treatment phase, approximately 102 subjects (34 per arm) were to be randomized (1:1:1) by Interactive Voice Response System (IVRS) to 1 of 3 arms, to receive prophylactic study medication orally, twice daily (topiramate titrated up over a 4-week period until the final target dosage [50- or 100 mg-per-day] or the maximum dosage tolerated had been achieved, or placebo). Study medication consisted of topiramate 25 mg tablets or matching placebo. During the 4-week titration period, either a pause, a halt or a dose reduction was allowed for intolerability; during the 12-week double blind maintenance phase, a single dose reduction of study drug was allowed for safety and/ or tolerability concerns.

Efficacy was assessed at each visit by review of the headache and medication record.

3.1.1.1 Study Design and Statistical Methods

Intent-to-treat (ITT) Analysis Set:
The ITT analysis set was the analysis set for the efficacy analysis in the double-blind phase. All randomized subjects who received at least 1 dose of double-blind study medication as recorded on the case report form (CRF) and had at least 1 post-randomization efficacy evaluation (i.e. headache record) in the double-blind phase were included in this analysis set.
Safety Analysis Set:
The all randomized and treated subjects analysis set was the set for the safety analysis in the double-blind phase. It included all randomized subjects who received at least one dose of double-blind study medication as recorded on the CRF.

Classification of Headaches
Classification of migraines includes migraine with aura, migraine without aura, or aura only with rescue medication. Any other type of headache (excluding aura only without rescue medication) is considered a non-migraine headache.
The classification of headaches was to be based on the headache type recorded by subjects in their headache records. An "Aura, no pain" record accompanied by ingestion of rescue medication within 30 minutes of aura onset was to be classified as "migraine – aura only with rescue medication". The classification of headaches used for a sensitivity analysis was to be based on an algorithm following IHS criteria.

Primary Efficacy Variable
The primary efficacy endpoint was the:
· Percent reduction from the prospective baseline period to the last 12 weeks of the double-blind phase in the monthly migraine attack rate, where a single migraine attack included all recurrences of migraine symptoms within 48 hours of onset (i.e., recurrences within 48 hours of the previous counted migraine were not counted as new migraines, as per the 48-hour rule of individual attacks). The classification of headaches was based on the headache type recorded by subjects in their headache records. The monthly migraine attack rate over a period was calculated by the actual migraine attack count, s_m, multiplied by 28, divided by the number of days in the period, n_d; in effect, the monthly migraine attack rate was the migraine attack count normalized to 4-weeks: $28*s_m/n_d$.
The percent reduction was calculated as:
100 * (B - D) / B,
where B was the monthly migraine attack rate over the prospective baseline and D was the rate over the last 12 weeks of the double-blind (DB) phase. Using this calculation, a positive value indicates a reduction from Baseline, while a negative value indicates an increase from Baseline.
If for a subject there are no migraine attacks in the prospective baseline (B=0) then the following imputation rule was to be used for the computation of the percent reduction for that subject:

If B=0 and D=0 (no migraine attacks in both prospective baseline and last 12 weeks of the DB phase) then percent reduction was to be set to zero. If B=0 and D>0 then percent reduction was to be set to –999%, assigning that subject the smallest percent reduction, so the lowest rank.

Responder rate, was a secondary endpoint, for which a responder was defined as a subject with 50% or greater reduction in the monthly migraine attack rate (using 48-hour rule) from the prospective baseline period to the last 12 weeks of DB phase. The Mantel-Haenszel method was to be used to assess the overall association between treatment and responder rates, controlling for the analysis center effect. All secondary endpoints (except responder rate) were to be analyzed using the same ANCOVA model on ranks as for the primary endpoint, using the corresponding baseline variable in the model.

Pooling Strategy for Analysis Centers

To account for study center variability, study center was used as a factor in the statistical models to analyze efficacy data. The study centers were pooled by region. The following regions were defined to group countries with more similar medical practice, patient's care, or cultural background, as well as to comprise a geographical area:

- USA
- Europe and Israel (including Belgium, Finland, France, Norway, Romania, Spain, and Israel)

The primary efficacy endpoint was to be analyzed using an analysis of covariance (ANCOVA) model on ranks that included subjects' stratified age at baseline (i.e., 12 to 14 or 15 to 17 years old), treatment group, and analysis center as factors and monthly migraine attack rate during prospective baseline period as a covariate.

The Hochberg's procedure at the 0.05 level was to be used to address multiplicity. That is, let H_{01} and H_{02} denote the null hypotheses associated to the comparisons of topiramate 50 and 100 mg doses to placebo, respectively, and let the corresponding (unadjusted) p-values based on least squares mean differences be p_1 and p_2, respectively. Let the larger (less statistically significant) of the two p-values be denoted by $p_{(2)}$, and let the corresponding hypothesis be $H_{0(2)}$. Likewise, let the smaller of the two p-values be $p_{(1)}$, and let the corresponding hypothesis be $H_{0(1)}$. If $p_{(2)} \leq 0.05$, which is equivalent to both p-values being less than or equal to 0.05, then we would reject both H_{01} and H_{02}. However, if $p_{(2)} > 0.05$, then we would fail to reject the corresponding null hypothesis $H_{0(2)}$, but we would continue on to examine $p_{(1)}$. If $p_{(1)} \leq 0.025$, then we would reject $H_{0(1)}$.

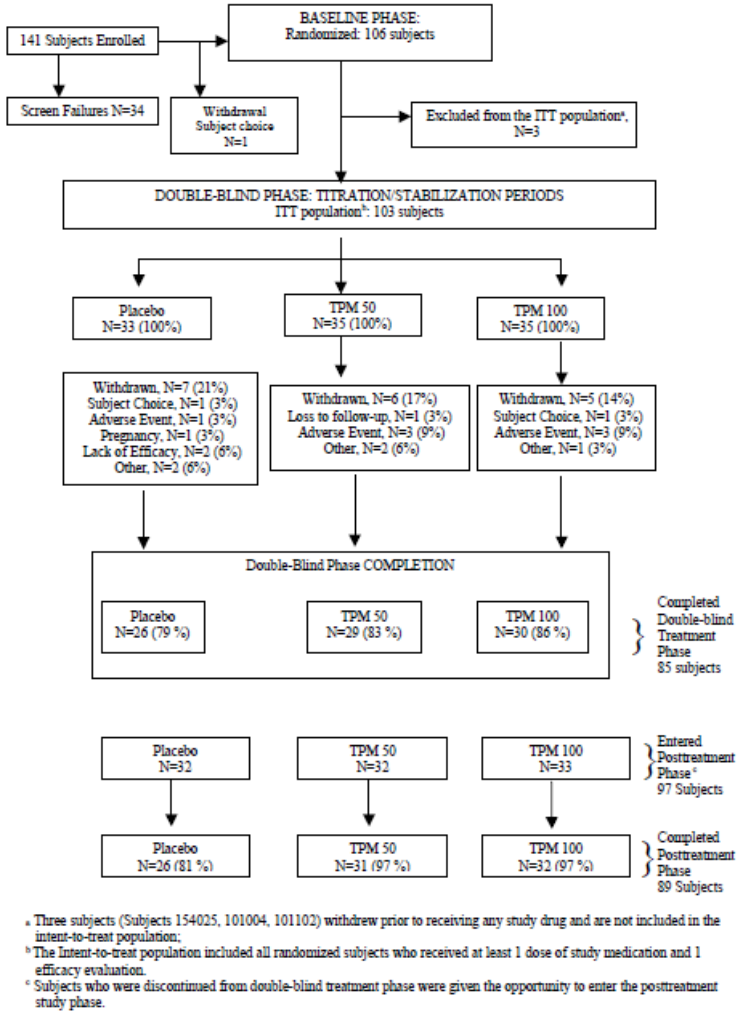
One global and two country-specific amendments to the study protocol significantly impacted the study. Amendment INT-1 (21 July 2006) clarified some statistical procedures and headache definitions. The statistical methods for the primary and secondary efficacy analyses were also revised by replacing the analysis of covariance (ANCOVA) models with ANCOVA models on ranks, keeping the same factors and covariates in the model, in consideration of non-symmetrical distributions for the percent reduction endpoints. For the same reason, in this amendment Hochberg's procedure was specified to be used instead of the originally planned Dunnett's procedure's to adjust the Type I error rate for the comparisons of the topiramate doses to placebo

in the primary endpoint. One hundred six subjects had been enrolled in the study at the time of this amendment. The original protocol was issued on 15 Mar 2005.

3.1.1.2 Patient Disposition

Of the 141 subjects enrolled in this study, 106 were randomly assigned to treatment. Thirty-four subjects were screen failures. Subject 101098 withdrew due to subject choice, after screening but prior to randomization. Of the 106 subjects randomized in this study, 103 subjects received at least 1 dose of study medication. Three subjects (154025, 101004, 101102) withdrew after randomization, but prior to receiving any study drug. All 103 subjects received at least 1 dose of study medication and at least 1 efficacy evaluation; these subjects comprise both the ITT and safety populations. Eighty-five (83%) of the 103 subjects from the ITT and safety populations completed the double-blind phase. Eighty-nine (92%) of 97 subjects who entered the posttreatment phase completed this phase (See flowchart, Figure 1).

Figure 1 Study 3006 Subject Disposition



[a] Three subjects (Subjects 154025, 101004, 101102) withdrew prior to receiving any study drug and are not included in the intent-to-treat population;
[b] The Intent-to-treat population included all randomized subjects who received at least 1 dose of study medication and 1 efficacy evaluation.
[c] Subjects who were discontinued from double-blind treatment phase were given the opportunity to enter the posttreatment study phase.

3.1.1.3 Baseline Demographics and Disease Characteristics

The treatment groups were generally well matched in terms of age, race, weight, and BMI. The median age of all subjects was 14.0 years Overall there was a greater percentage of female subjects (61%) relative to male subjects (39%); this proportion was mirrored in placebo and 50 mg-per-day topiramate-treated groups, but in the 100 mg topiramate group the ratio of female to male subjects was almost 1:1 (49.0% and 51.0%, respectively).
The majority of range: 15.0 - 32.0 kg/m2).

Table 2 Study 3006 Baseline Demographic and Disease Characteristics

Variable	Identification of Statistic other than N(%) or Subgroup (as applicable)	Placebo (N=33)	TPM 50 mg/day (N=35)	TPM 100 mg/day (N=35)	All
Age	Mean (SD)	14.4 (1.7)	14.2 (1.6)	14.2 (1.5)	14.2 (1.6)
Age Group	12-14	17 (51.5)	20 (57.1)	19 (54.3)	56 (54.4)
Age Group	15-17	14 (42.4)	15 (42.9)	15 (42.9)	44 (42.7)
Age Group	>17	2 (6.1)	0 (0.0)	1 (2.9)	3 (2.9)
Baseline Headache Rate Subject Classification/ 48 hour rule	Mean (SD)	4.1 (1.5)	4.1 (1.7)	4.2 (1.6)	4.1 (1.6)
Pooled center	ARGENTINA+BRAZIL	10 (30.3)	9 (25.7)	11 (31.4)	30 (29.1)
Pooled center	EUROPE+ISRAEL	15 (45.5)	16 (45.7)	11 (31.4)	42 (40.8)
Pooled center	UNITED STATES OF AMERICA	8 (24.2)	10 (28.6)	13 (37.1)	31 (30.1)
Race	BLACK	4 (12.1)	2 (5.7)	5 (14.3)	11 (10.7)
Race	OTHER		2 (5.7)	2 (5.7)	4 (3.9)
Race	WHITE	29 (87.9)	31 (88.6)	28 (80.0)	88 (85.4)
Sex	FEMALE	21 (63.6)	25 (71.4)	17 (48.6)	63 (61.2)
Sex	MALE	12 (36.4)	10 (28.6)	18 (51.4)	40 (38.8)

3.1.1.4 Sponsor's Results

The primary efficacy parameter was percent reduction from prospective Baseline to the last 12 weeks of double-blind phase in the monthly migraine attack rate (using 48-Hour Rule); the primary endpoint was based on the classification of headaches recorded by subjects in their headache records.

The 100 mg-per-day topiramate-treated group was statistically superior to the placebo treatment group after multiple comparison adjustment. The 50 mg-per-day topiramate-treated group had similar results to placebo. Median percent reductions for the 50- and 100 mg-per-day topiramate-treated groups, with adjusted p-values for comparison to placebo, were 44.6% (p=0.7975) and 72.2% (p=0.0164), respectively; the median percent reduction for placebo was 44.4% (Table 3). Figure 2 presents descriptive summaries of the percent reduction in the monthly migraine attack rate over time. The box-plots used in Figure 2 have the following characteristics: the lower boundary of the box is the 25th percentile and the higher boundary is the 75th percentile; whiskers above and below the box indicate the 90th and 10th percentiles; the solid line within the box marks the median; outlying data points are extreme values. The medians from Month 1 to Month 4 are connected in this figure. The median percent reduction for the 100 mg-per-day topiramate-treated group for the last 4-weeks is not apparent in the figure, as it has a 100% value.

Prospective baseline median values for monthly migraine attack rate were similar in all treatment groups, though placebo-treated subjects had slightly lower median values (4.0, 4.0 and 3.6 in 50- and 100 mg-per-day topiramate-treated and placebo treatment groups, respectively). The median monthly migraine attack rates over the last 12 weeks of double-blind phase were 2.3, 1.0 and 2.3 in 50- and 100 mg-per-day topiramate-treated and placebo treatment groups, respectively.

Table 3 Percent Reduction From Prospective Baseline to the Last 12 Weeks of Double-Blind Phase in Monthly Migraine Attack Rate (Using 48-Hour Rule)

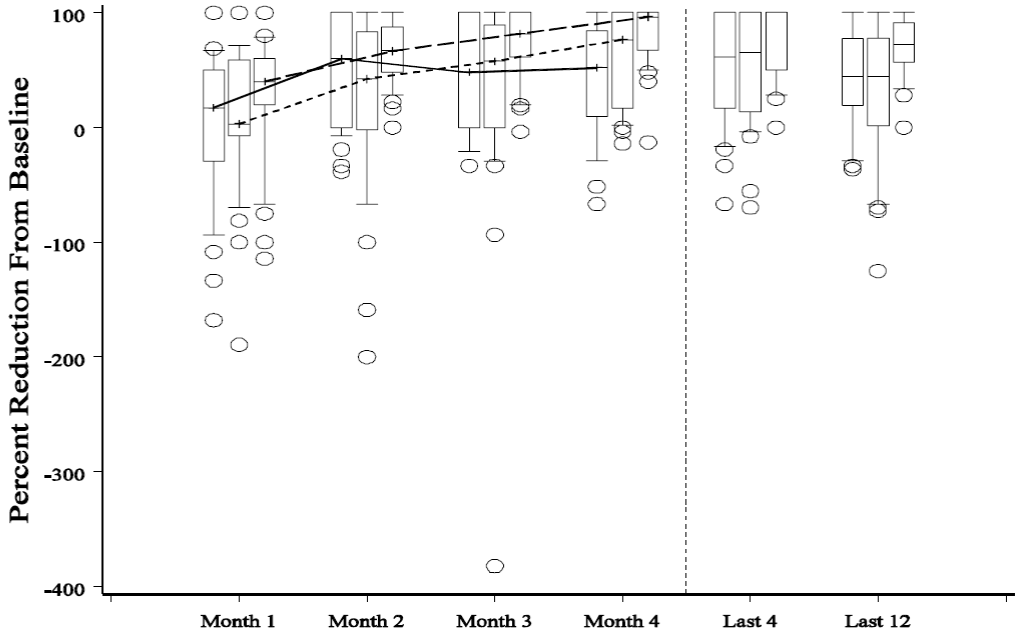
Category	Placebo (N=33)	TPM 50 mg/day (N=35)	TPM 100 mg/day (N=35)
Prospective Baseline Period			
N	33	35	35
Median (Range)	3.6 (1.9;7.5)	4.0 (1.0;7.2)	4.0 (1.9;9.0)
Last 12 Weeks of double-blind Phase			
N	33	35	35
Median (Range)	2.3 (0.0;7.3)	2.3 (0.0;7.0)	1.0 (0.0;4.5)
Percent Reduction (%)[a]			
N	33	35	35
Median (Range)	44.4(-36;100)	44.6(-125;100)	72.2(0.0;100)
P-Value Versus Placebo)[b]		0.7975	0.0164

[a] Percent reduction is the difference between values at baseline and last 12 weeks of double-blind Phase, divided by value at baseline, times 100.

[b] Adjusted P-values for comparisons relative to placebo are generated by first 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 prospective baseline period as a covariate, then adjusting for multiplicity using the Hochberg's multiple comparison procedure.

Note: This table was copied from page 72 of the sponsor's study report

Figure 2 Percent Reduction in Monthly Migraine Attack Rate over Time Using 48 Hour Rule (ITT)



Treatment Group (Left to Right): Placebo TPM 50 mg/day TPM 100 mg/day

Note: Month 1 represents titration and Months 2 to 4 represent maintenance. Last X=Last X weeks of DB.

Note: This figure was copied from page 72 of the sponsor's study report

3.1.1.5 Reviewer's Results

It is important to note that a Statistical Analysis Plan (SAP) for this study was submitted (IND 60,913, SN: 204) to the FDA on 13 September 2006 and this SAP proposed to assess the efficacy endpoints using an algorithm for migraine classification following the revised International Headache Society (IHS) criteria for children and adolescents. This original SAP reflected the original intent for this study, which was to apply the IHS algorithm throughout the study conduct and analysis. It was later determined during a blinded data review by the sponsor that the IHS criteria were not consistently applied by investigators during the prospective baseline to determine eligibility for randomization. Subsequently a revised SAP was sent to the FDA on 30 January 2007 (IND 60,913, SN: 218) that proposed the use of subject-recorded headache type for the primary and secondary analyses. The sponsor claimed this approach ensured consistency with the randomization procedure and with the 3 topiramate migraine prophylaxis clinical studies for adults, which included subjects 12-65 years old. In addition, the revised SAP specified two supplemental analyses based on the IHS headache classification. Both migraine classification methods are evaluated below.

This reviewer's derived data had some discrepancies with the sponsor's derived percent reductions over the last 12 weeks based on the 48 hour rule and subject classification of migraines. The differences between reviewer and sponsor are summarized in Table 4. 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.

Table 4 Differences between Reviewer and Sponsor in Derived Data

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

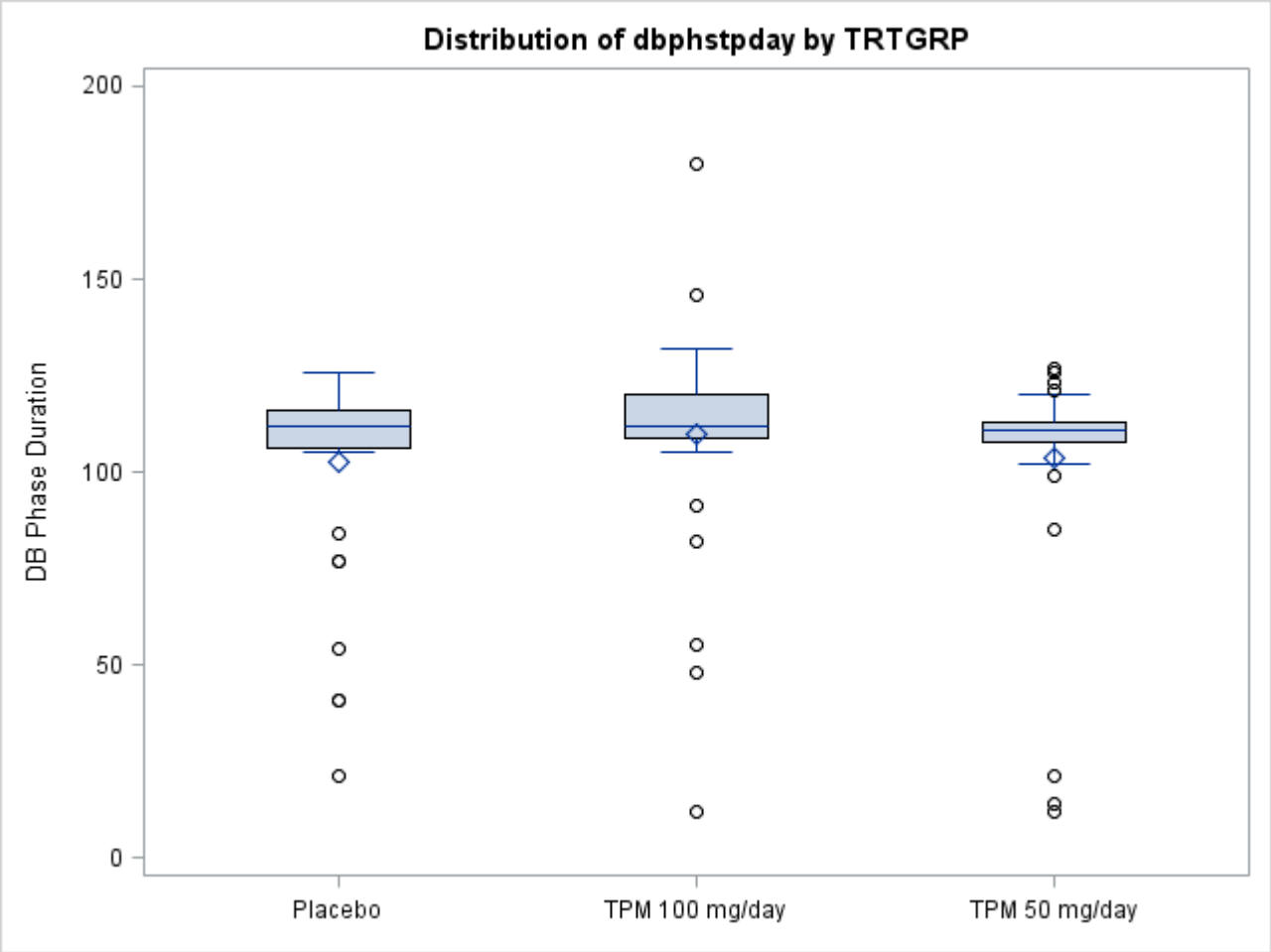
[b]Sponsor has one less migraine than me during Double Blind Phase; had one on dbday 24 (patient had 106 total db days)would be during titration and was first day of last 12 weeks

[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

The mean length of the double blind phase was 102, 103, and 110 days for placebo, 50 mg, and 100 mg, respectively. The median lengths were 112, 111, and 112, respectively. Placebo group lengths of the double blind treatment phase ranged from 21 to 126 days, 50 mg from 12 to 127 days, and 100 mg from 12 to 180 days. Figure 3 shows side-by-side boxplots for each treatment group of the distribution of actual double blind phase treatment period durations.

Figure 3 Distribution of Actual DB Phase Durations by TRTGRP



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.

This reviewer verified the significance of the sponsor's primary analysis of the percent reduction over the last 12 weeks for the TPM 100 mg vs. placebo comparison based on the subject classification of migraines with the 48 hour rule (see Table 5). Twenty six (26) placebo, 29 TPM

50 mg, and 30 TPM 100 mg completed the study. An analysis of completers alone also yielded a nominally significant result for the 100 mg vs. placebo comparison of the percent reduction over the last 12 weeks based on the subject classification and the 48 hour rule(LSMean 71 vs. 40, p=0.005), but not for the 50 mg group vs. placebo comparison (p=0.994).

Table 5 Analyses of Percent Reduction in Migraine Attack Rate over Last 12 Weeks of Double Blind Phase

		Placebo		TPM 100		P-value*
Endpoint	Migraine Classification	Mean (STD)	Median (Min;Max)	Mean (STD)	Median (Min;Max)	
Percent Change	Subject	42.3 (43.2)	44.4 (-36.4;100)	70.1 (25.1)	72.2 (0.0;100.0)	0.0109
Percent Change	IHS	-15.4 (256.7)	55.6 (-999;100)	59.5 (37.9)	64.3 (-72.6;100.0)	0.2220

*p-value based on ANCOVA of ranked percent reductions with adjustments for age group, pooled sites, and baseline rate

The analysis of percent reduction over the last 12 weeks compared to baseline based on the IHS classification of migraines with the 48 hour rule was not significant for the 100 mg vs. placebo comparison (p=0.2220 unadjusted; p=0.4440 Hochberg adjusted). The median percent reductions were 64.3 and 55.6 for TPM 100 mg and placebo, respectively.
An exploratory analysis excluding those 10 patients with zero IHS migraines during baseline gave an unadjusted p-value of 0.2552 for the 100 mg vs. placebo percent reduction in IHS migraines using the 48 hour rule comparison over the last 12 weeks. For the subject's classification of migraines the corresponding unadjusted p-value was 0.1020.

In a further post hoc exploratory analysis to assess the impact of the subjects with no IHS qualified migraines this reviewer computed a modified percent change by adding 1 to both the numerator and denominator, i.e., both migraine counts and day counts. The analysis results for this modified percent change are shown in the following table.

Table 6 Exploratory Analysis using Modified Definition of Percent Reduction over Last 12 Weeks (IHS/48 hour)

Endpoint	Analysis	Dose Group	Mean Difference From Placebo	Std. Error	P-value
%CHANGE	ANCOVA	100	-19.84	10.41	0.0597
Ranked %CHANGE	ANCOVA	100	-12.04	7.09	0.0925
CHANGE	ANCOVA	100	-0.754	0.38	0.0485
Ranked CHANGE	ANCOVA	100	-11.78	5.50	0.0347

Also, the analysis of the ordinarily defined change from baseline over the last 12 weeks (not percent change or percent reduction) based on the IHS classification and the 48 hour rule was nominally significant (p=0.0386 based on ranks or -1.3 vs. -2.1 were the LSMeans, p=0.0300 based on non-ranked analysis) for the TPM 100 mg vs. placebo comparison (Table 7).

Table 7 Analyses of Change from Baseline in Migraine Attack Rate over Last 12 Weeks of Double Blind Phase

		Placebo		TPM 100		P-value
Endpoint	Migraine Classification	Mean (STD)	Median(Min;Max)	Mean (STD)	Median(Min;Max)	
Change	Subject	1.7 (1.8)	1.7 (-1.0;5.7)	3.0 (1.5)	2.9 (0.0;7.0)	0.0051
Change	IHS	1.4 (1.8)	1.7 (-2.3;6.0)	2.4 (1.7)	2.5 (-0.7;7.0)	0.0300

*p-value based on ANCOVA of changes with adjustments for age group, pooled sites, and baseline rate

Assuming that the reduction from baseline rate in the double blind period is normally distributed with constant variance across subjects (which is a common assumption for ANCOVA) implies that the percent reduction, which is 100* reduction/ baseline rate, would have variability changing across subjects as a function of the baseline rate. Therefore, an exploratory weighted least squares analysis of the percent reduction using the 48 hour rule and the IHS algorithm may be appropriate and was done by this reviewer as a sensitivity analysis. The weight was the square of the baseline rate which should tend to make the variance of percent reduction constant across

subjects if the reduction is normally distributed. A weighted ANOVA gave a p-value of -22.6, p= 0.0131 for the 100 mg vs. placebo comparison of the percent reduction over the last 12 weeks.

The preceding sensitivity analyses of the percent reduction over the last 12 weeks based on the IHS algorithm with the 48 hour rule, together with the significance of the apparently prespecified primary analysis using the subject classification, may alleviate concerns somewhat about the insignificance of TPM 100 mg compared to placebo in terms of the IHS based percent reduction over the last 12 weeks.

This reviewer did not find a significant difference between 100 mg and placebo in percent reduction in an analysis of Month 4 migraine data compared to baseline based on the subject classification of migraines with the 48 hour rule. The results may vary if the operational definition of Month 4 was slightly different. However, the reviewer's estimated difference in percent reduction over month 4 between 100 mg and placebo was 10.8, p=0.0987 based on those with >14 days in month 4 (defined here as day 85 through 112). Note that there was 1 TPM 50 mg subject with only 1 day in Month 4, 1 TPM 100 mg with 7 days, as well as 7 placebo, 3 TPM 50 mg and 4 TPM 100 mg subjects with zero days).

3.1.2 CAPSS-122 Study

This was a multicenter, outpatient, randomized, double-blind, placebo controlled, parallel study composed of 3 phases: pre-randomization, double blind and open-label extension. This study was to be conducted on approximately 150 subjects. Eligible subjects were 6 to 15 years of age who had headache symptoms that met the proposed IHS Classification of Pediatric Migraine with or without aura. The double-blind phase consisted of 2 periods: the titration period (56 days) and the maintenance period (84 days). A brief synopsis of the analysis plan follows.

Migraine episode: A headache with symptoms fulfilling the criteria for pediatric migraine according to the Proposed IHS Classification of Pediatric Migraine. The duration of the migraine episode was the period from onset of painful migraine symptoms to resolution of pain or 24 hours after onset of painful symptoms, whichever was shorter. Migraine episodes that persisted or recurred within 24 hours were considered the same episode. There was no minimum duration of a migraine episode. Aura symptoms that resolved without pain after administration of abortive medication (taken within 60 minutes of aura onset) were considered a migraine episode. Aura symptoms that occurred and resolved without the subject having taken 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 above definition.

Monthly rate of migraine episodes: The monthly rate of migraine episodes during the double-blind phase was the total number of migraine episodes during the double-blind phase, divided by the total duration of double-blind phase (in days) and then multiplied by 28. Monthly migraine episode rates were computed for the maintenance period and each visit window in a similar manner. The monthly migraine episode rate during the prospective baseline period was the total number of migraine episodes during the last 28 days prior to the date of the first dose.

Primary Analysis
The statistical significance of any reduction in monthly migraine-days over the whole treatment period between treatment groups **originally** was to be assessed by an analysis of covariance with treatment and center as qualitative factors and baseline monthly migraine-days as a covariate.

The analyses of rate of headache days per month and headache episodes per month was conducted using a Cochran-Mantel-Haenszel (CMH) test stratified by baseline rate instead of an analysis of covariance. The distribution of the rate of headache variables was not normal. The CMH can be a more sensitive test of treatment differences when the underlying distribution is not normal.
The statistical significance of a reduction in monthly migraine-days between treatment groups was assessed with a Cochran-Mantel-Haenszel test with modified ridit scores and stratified by baseline migraine days.

Sample Size Determination
According to the study design, subjects were to be randomized according to a 2:1 ratio of topiramate to placebo. The sample size of 150 subjects (100 topiramate and 50 placebo) was not based on statistical considerations. However, a minimum detectable difference was determined based on this non-statistically determined sample size under the following assumptions:
a) the null hypothesis was that the proportion of responders, where response was defined as 50% or more reduction in the monthly rate of migraine-days, was the same for both groups
b) the placebo response rate was 20%;
c) a 2-sided Fisher's exact test was conducted at the 5% significance
level; and
d) the power was at least 80% for detecting the alternative.
Under these assumptions, a response rate of 45% in the topiramate group was to be detectable (i.e., the minimum detectable difference is 25%).

The ITT population was defined as all subjects randomized to double-blind study medication who received at least 1 dose of study medication and for whom a post-baseline efficacy evaluation is available.
Evaluable for Efficacy population was defined as all subjects randomized who completed the study to Day 141 and had no major protocol violations.

3.1.2.1 Sponsor's Results

Of the 162 subjects randomized, 157 (96.9%) were included in the ITT population, 126 (77.8%) were included in the Evaluable-for-Efficacy population and 157 (96.9%) were included in the Evaluable-for-Safety population.

The average number of migraine days during the prospective baseline period (the last 28 days prior to randomization) ranged from 2 to 11 days with a mean of 5.4 days. The average number of migraine episodes during the prospective baseline period ranged from 2 to 10 with a mean of

5.0 migraine episodes. The average duration of migraine episodes during the prospective baseline period ranged from 0 to 18 hours with a mean of 6.7 hours.

Primary Efficacy Analysis

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 is presented in Table 8. The mean double blind migraine day rates were 2.8 for Topiramate and 3.5 for placebo in the ITT population. 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. According to the sponsor the between-group difference approached statistical significance (p=0.061).

Table 8 CAPSS-122 Summary and Analysis of Monthly (28-Day) Rate of Migraine Days

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.

Note: this table was copied from page 81 of the sponsor's study report

Decreases in the mean monthly (28-day) rate of migraine-days per month in the Evaluable-for-Efficacy population, were 2.8 days in the topiramate group and 2.2 days in the placebo group.

The between-group difference was statistically significant (p=0.033). Seventy six percent (n=85) of those randomized to Topiramate and 82 percent (n=41) of those randomized to placebo were qualified for inclusion in this dataset.

Secondary Analysis

Number of Monthly (28-day) Migraine Episodes

The mean monthly (28-day) rates of monthly migraine episodes are presented in Table 9 for the ITT population. The mean double blind migraine episode rates were 2.6 for Topiramate and 3.3 for placebo in the ITT population. The reduction in the mean monthly (28-day) rate of migraine episodes was numerically greater for subjects in the Topiramate group (2.3 episodes) than for subjects in the placebo group (1.8 episodes) in the ITT population; the between-group difference was not statistically significant (p=0.133).

A post hoc analysis of subjects, 24 hour rule based percent reduction in monthly migraine episode rate gave median (ranges) of 40.43 (-138.5;96.0) for Topiramate and 52.41 (-112.1;100.0) for Placebo, p= 0.1731.

Table 9 CAPSS-122 Summary and Analysis of Monthly (28-Day) Rate of Migraine Episodes

Monthly Rate of Migraine Episodes[a]	Topiramate (N=108)	Placebo (N=49)	p-value[c]
Prospective Baseline[b]			
n	108	49	
Mean	5.0	5.1	
Median	5.0	5.0	
SD	1.69	1.75	
(Min,Max)	(2.0, 9.0)	(3.0, 10.0)	
Double-Blind			
n	108	49	
Mean	2.6	3.3	0.133
Median	2.2	2.6	
SD	2.29	3.04	
(Min,Max)	(0.0, 15.3)	(0.2, 19.6)	
Change from Baseline			
n	108	49	
Mean	-2.3	-1.8	
Median	-2.4	-2.1	
SD	2.45	2.90	
(Min,Max)	(-8.8, 8.3)	(-6.2, 12.6)	

[a] 28-Day Rate of Migraine Episodes = ((total number of migraine episodes during the double-blind phase / total duration (days) of double-blind phase) * 28).

[b] Prospective baseline = total number of migraine episodes in the last 28 days prior to randomization.

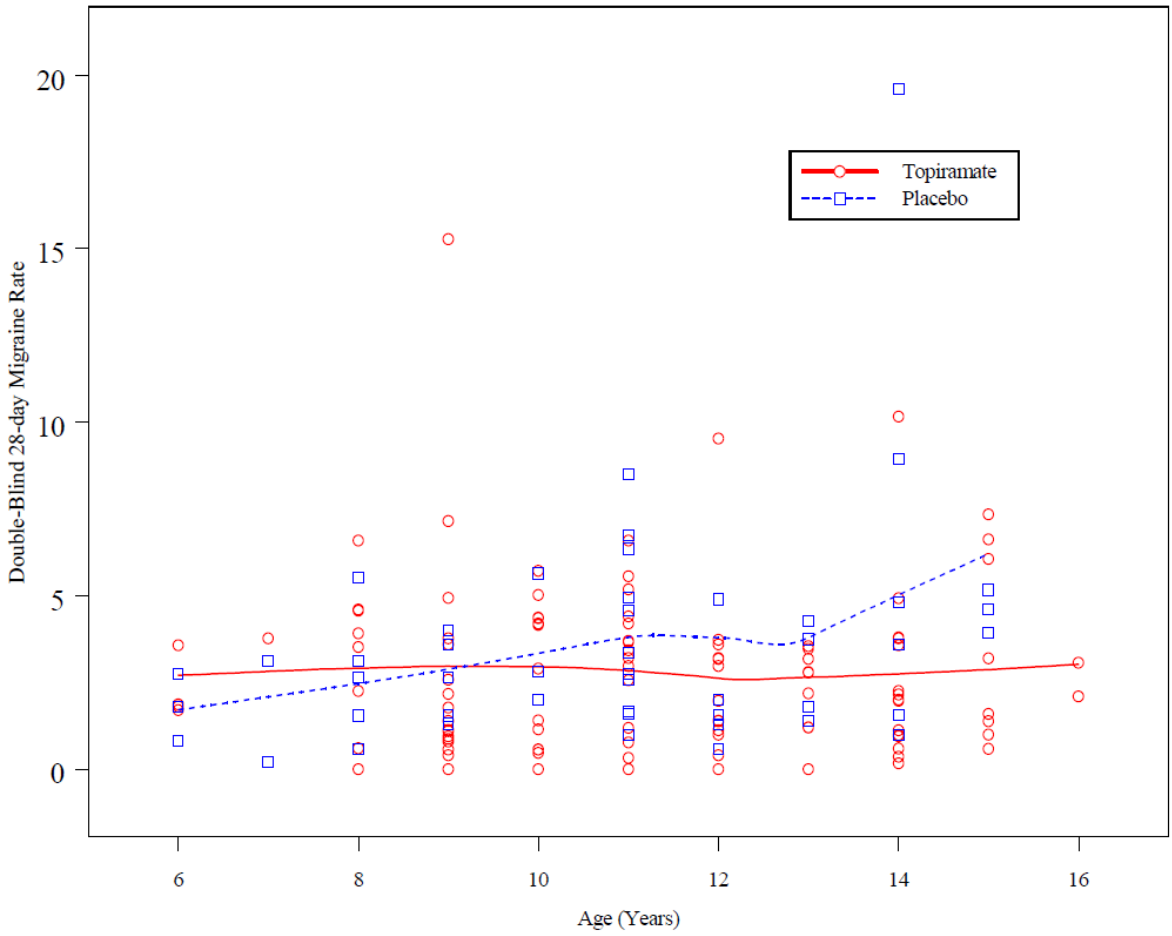
[c] p-value for the comparison of placebo versus topiramate is based on Cochran-Mantel-Haenszel Test, with scores=modridit, stratified by baseline headache rate.

NOTE: Subjects who did not have any migraine episodes during the Double-Blind Phase have a rate of migraine episodes set at 0.

Note: this table was copied from page 98 of the sponsor's study report

The relationship between age and rate of migraine days during the double blind phase for both the topiramate and placebo groups is depicted in Figure 4. For the topiramate group, the smoothed age by migraine day rate graph does not indicate any relationship between age and the rate of migraine days. However, for the placebo group, a slight trend toward the migraine day rate increasing as age increases is noted.

Figure 4 CAPSS-122 Relationship between Age and Rate of Migraine Days in the Double-Blind Phase



Note: This figure was copied from page 91 of the sponsor's CAPSS-122 study report

Exploratory P-values for analysis of Reduction in Monthly migraine day rate by Age subgroup were: P= 0.3752 for Age<=12 (N=114) and p=0.0487 for Age>12 (N=48).
The reduction from baseline in the monthly migraine episode rate during the double baseline period also was nominally significant in the adolescent subgroup, but this was not so in the 6-12 age group.

3.2 Evaluation of Safety

Safety is not reviewed in this document. Please see the medical officer's review for the evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Sixty one percent (61%) of randomized subjects in study 3006 were female. A test for a differential treatment effect by gender group was not significant, p=0.4625. Table 10 shows summary statistics for percent reduction in monthly migraine attack rate over the last 12 weeks (using the 48 hour rule and subject migraine classification) by gender subgroups.

Table 10 Percent Reduction over Last 12 Weeks by Gender

	Gender								All
	FEMALE				MALE				
	% Reduction in Monthly Migraine Attack Rate				% Reduction in Monthly Migraine Attack Rate				
	N	Mean	Median	StdErr	N	Mean	Median	StdErr	N
Treatment Group									
Placebo	21	34.4	39.6	9.4	12	56.2	61.7	11.9	33
TPM 100 mg/day	17	71.8	73.3	5.3	18	68.6	66.7	6.7	35
TPM 50 mg/day	25	34.5	44.6	8.8	10	33.0	61.1	25.2	35
All	63	44.5	51.7	5.3	40	55.9	66.7	7.9	103

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 11 shows summary statistics for percent reduction in monthly migraine attack rate over the last 12 weeks (using the 48 hour rule and subject migraine classification) by race subgroups.

Table 11 Percent Reduction over Last 12 Weeks by Race

	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

Proportions of randomized subjects in the following age categories were age 12-14: 54%, age 15-17: 43%, and age >17: 3%. A test for a differential treatment effect by Age group did not reveal a significant effect, p=0.3734; using 2 age groups: 12-14 and ≥15. An alternative analysis, assuming a linear effect of age within each treatment group also did not reveal a significant difference in treatment effects by age: a test for different slopes for age within treatment groups resulted in a p-value of .9495. Table 12 shows summary statistics for percent reduction in monthly migraine attack rate over the last 12 weeks (using the 48 hour rule and subject migraine classification) by Age subgroups.

Table 12 Percent Reduction over Last 12 Weeks by Age

	Age group (years)												All
	12-<15				15-17				>17				
	% 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	17	36.8	33.3	10.7	14	48.5	54.3	12.2	2	45.7	45.7	3.2	33
TPM 100 mg/day	19	70.3	72.2	6.3	15	71.8	73.3	5.7	1	41.7	41.7	.	35
TPM 50 mg/day	20	41.8	49.9	12.3	15	23.8	16.7	14.4	0	.	.	.	35
All	56	49.9	61.0	6.1	44	48.0	58.5	7.1	3	44.3	42.5	2.3	103

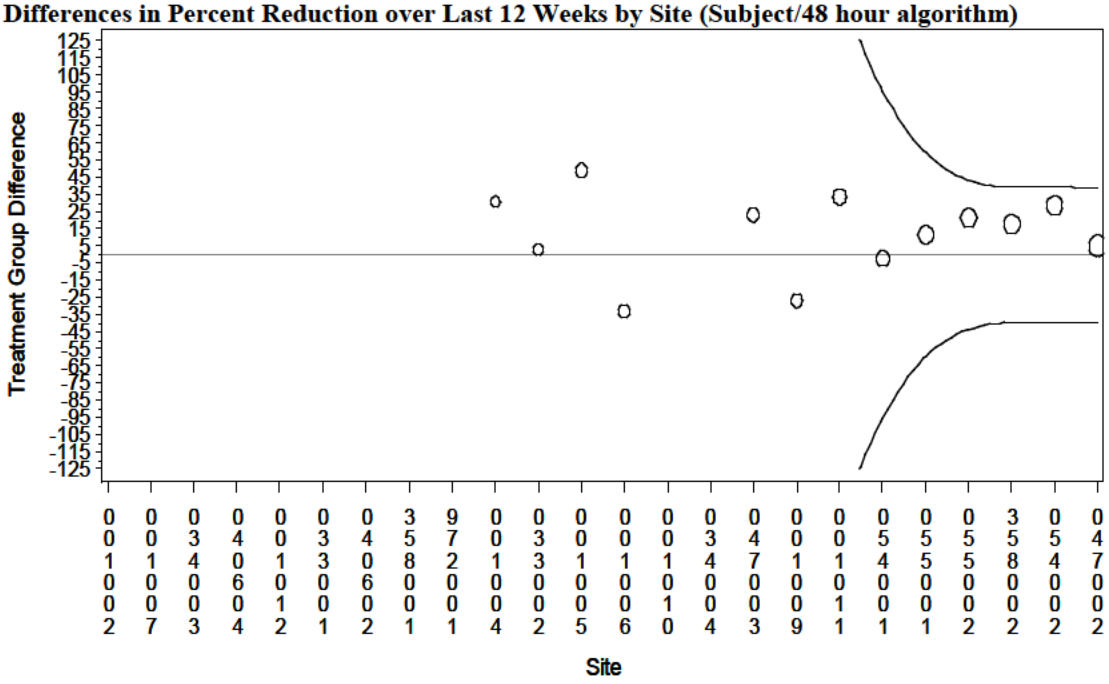
Geographic representation was as follows: 30%US, 41%Europe+Israel, and 29%Argen+Brazil; A test for a differential treatment effect by region did not reveal a significant differential effect (prespecified pooled centers: p=0.9801; regions: US vs. Other: p=0.8114). Table 13 shows summary statistics for percent reduction in monthly migraine attack rate over the last 12 weeks (using the 48 hour rule and subject migraine classification) by geographic subgroups.

Table 13 Percent Reduction over the last 12 weeks by Region

	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

Figure 5 shows observed mean treatment group differences in rank of percent reduction over the last 12 weeks of TPM 100 mg from placebo within individual study sites. There were 24 sites. The size of the plotting symbol is proportional to the number of patients randomized in the particular site. Positive differences favor the TPM 100 group. The upper and lower curves indicate roughly the sample size adjusted site specific levels for a significant difference.

Figure 5 Differences in Percent Reduction over Last 12 Weeks by Site (Subject/48 hour algorithm)



4.2 Other Special/Subgroup Populations

No other special/subgroup populations will be presented.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The vast majority of the evidence of efficacy in adolescent migraine prophylaxis comes from study 3006. The other non-adult studies were either not positive, in the case of CAPSS-122, or enrolled very few non-adult subjects.

The sponsor changed the primary headache classification criteria from the IHS to that of subject's diary just before unblinding. There were 10 randomized subjects that had zero baseline migraines according to IHS classification criteria, which presents a problem for the percent reduction primary endpoint, since dividing by zero results in an undefined percent reduction. This problem could be determined in a blinded data review as suggested by the sponsor. There were no subjects with zero migraines during baseline according to the subject's classification of migraines. 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.

5.2 Conclusions and Recommendations

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.

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/s/

TRISTAN S MASSIE
02/27/2014

KUN JIN
02/27/2014
I concur with the review.

KOOROS MAHJOOB
02/28/2014
I concur with the review.