

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

**APPLICATION NUMBER: 20-505/S-002
20-844/S-010**

STATISTICAL REVIEW

10000

RECEIVED JUN 12 1998

STATISTICAL REVIEW AND EVALUATION - 2
(For Study TL)

JUN 12 1998

NDA#: 20-505 SE1-002

Applicant: The R. W. Johnson Pharmaceutical Research Institute (PRI)

Name of Drug: Topamax (topiramate) oral tablets

Indication: 002 - Seizures associated with Lennox-Gastaut syndrome

Documents Reviewed: Vol.1.1, Vols 1.93-1.102 dated July 31, 1997
NDA amendment submission dated April 29, 1998
SAS Database (CANDA)

Medical Officer: Richard Tresley, M.D. (HFD-120)

This review has been discussed with the medical review team and the Biometrics Division-1 (HFD-710). A Divisional Review Round was given by this reviewer on May 14, 1998. Extensive discussions and important points raised during and after the Review Round were incorporated in this review. The tables/figures from the sponsor are labeled Table/Figure xS and those from this reviewer's evaluation and analyses are labeled Table/Figure xR.

1 BACKGROUND

Topiramate was approved as an adjunctive therapy for treatment of adults with partial onset seizures in December, 1997. The RW Johnson Pharmaceutical Research Institute submitted four well-controlled clinical studies, including YP, YL, YTC, and YTCE in support of three new indications: (1) pediatric partial onset seizures (Trial YP), (2) seizures associated with Lennox-Gastaut syndrome (Trial YL), and (3) generalized tonic-clonic seizures (Trials YTC and YTCE). The Lennox-Gastaut syndrome is characterized by mixed seizure types which include atypical absence and drop attacks (tonic-atonic seizures or other nomenclature defining these identical seizures) and may include tonic, tonic-clonic, myoclonic, and minor-motor seizures.

Nine months after the NDA submission, the sponsor further submitted NDA amendment (clinical) dated April 29, 1998 which included a supplementary analysis addressing the overall interpretation of the p-values, which were not performed according to the protocol plan.

This review pertains to indication 002. For indications 001 and 003, please see "Statistical Review and Evaluation - 1" and "Statistical Review and Evaluation - 3" dated May 12, 1998.

INDICATION 2: LENNOX GASTAUT SYNDROME

2 PIVOTAL TRIAL

PROTOCOL YL "A double-blind trial of topiramate in subjects w/ Lennox-Gastaut syndrome"

STUDY DESCRIPTION

STUDY DESIGN

This was a US multicenter (12 centers), randomized, double-blind, placebo-controlled study. The study design is summarized in Figure 2.15. Subjects were 12 months of age or older and had Lennox-Gastaut syndrome characterized by EEG recordings showing slow spike-and-wave patterns. Atypical absence seizures and drop attacks (i.e., tonic-atonic seizures) were required among other seizure types that could include tonic-clonic, myoclonic, and minor-motor seizures. Subjects were required to have at least 60 seizures during the month before baseline phase while being maintained on one or two standard antiepileptic drugs (AEDs). The trial includes a baseline phase (4-week) and a double-blind treatment phase (11-week) consisting of 3-week titration and 8-week maintenance periods. Eligible patients from baseline evaluation were randomized at each center to receive either topiramate (n=50) or placebo (n=48) while continuing on their background AED regimen. All subjects who completed the maintenance period of the trial were permitted to enter the open-extension phase of the study at the discretion of the investigator and the sponsor medical monitor. The trial initiated on July 27, 1993 and ended on April 11, 1996.

STUDY OBJECTIVE

The objective of this trial was to evaluate the safety and efficacy of topiramate as adjunctive therapy in subjects with Lennox-Gastaut syndrome. Protocol amendments were primarily modification of the inclusion/exclusion criteria. Seizure data were collected as follows. Subjects, parent or guardian recorded the number of seizures that occurred and a description of seizure types in their seizure diaries. Video EEGs were performed during baseline and used as a training tool to assist parents in monitoring seizures and seizure types. The investigator classified each seizure type described in the subject's diary.

The primary evaluation of efficacy (to be discussed in Section 3 of Reviewer's evaluations and comments) was based on a two-sided statistically significant between-group difference with respect to either

- A: % reduction in seizure rate (all seizures) OR
 - B: % reduction in drop attack (tonic-atonic seizure) rate, AND
 - C: parental global evaluation of seizure severity.
- each tested at the 5% significance level.

STATISTICAL PLAN

The primary analysis method was a two-way (with treatment and center as factors) ANOVA on ranks. The parental global evaluation of improvement in seizure severity was to be analyzed using Mantel-Haenszel methodology. Specifically, the statistical methods described in Appendix 2.2 of the study report were the Wilcoxon rank-sum tests with and without stratification by investigator (to be commented in Section 3 of Reviewer Evaluation and Comments). All statistical tests were two-sided.

The sponsor was interested in detecting a 30% between-group difference in % reduction in seizure rate. Assuming a population standard deviation of about 70% with type I error rate of 5%, it was estimated that 40 subjects per group would provide an 80% chance of declaring the groups statistically significant difference.

OVERVIEW OF THE SPONSOR RESULTS

Demographic and baseline characteristics for all randomized subjects were comparable between the topiramate and the placebo treatment groups (Table 2.1S). A subject (Subject 143) was considered prematurely discontinued from the study due to difficult family circumstances. Results of the intent-to-treat (ITT) analysis for primary and secondary efficacy variables are summarized in Table 2.2S.

Primary efficacy variable

A). % reduction in seizure rate for all seizures

Median %s reduction from baseline in the average monthly seizure rate for all seizures were 20.6% for topiramate and 8.8% for placebo group. The difference was not statistically significant ($p=0.43$, 2-way ANOVA on ranks). There was no statistically significant treatment by center interaction ($p>0.10$). The sponsor stated that this result is not unexpected in a population having a high frequency of occurrence of atypical absence seizure. There was no difference between placebo and topiramate in the % reduction in average monthly seizure rate for atypical absence seizures. When atypical absence seizures were excluded, median % reduction for all seizures was 23.9% in topiramate and 2.0% in placebo ($p=0.063$).

Median %s reduction in seizure rates for all seizures varied by center, sex, age, race, number of concomitant AEDs, and baseline seizure rate; no consistent trends by subgroup were identified.

B). % reduction in drop attack (tonic-atonic seizure) rate

Median %s reduction from baseline in the average monthly seizure rate for drop attacks were 14.8% in topiramate and -5.1% for placebo. The results showed that topiramate was superior to placebo ($p=0.041$, 2-way ANOVA on ranks). There was no statistically significant treatment by

center interaction ($p=0.247$). Median %s reduction in seizure rates for drop attacks were directionally consistent, i.e., favored topiramate over placebo, by sex, age, race, or by number of concomitant AEDs.

C). parental global evaluation of seizure severity

Fifty-two percent of subjects in topiramate experienced an improvement (minimally, much, or very much improved) in the severity of their seizures compared with 28% of subjects in placebo. The between-group difference was statistically significant with unstratified analysis ($p=0.037$, Wilcoxon rank sum test) and approached significance with stratified (by center) analysis ($p=0.059$).

Based on the above two components (B and C), the sponsor stated that this trial demonstrates that topiramate is effective as treatment of Lennox-Gastaut syndrome.

• **NDA amendment of a supplementary analysis regarding overall type I error rate**

In this amendment, the sponsor presented a one-sided ($\alpha=0.025$) superiority analysis. The sponsor performed a Bonferroni adjustment with use of 0.0125 for % reduction in seizure rate for all seizures and use of 0.0125 for the compound variable consisting of “% reduction in drop attack rate” component and “parental global evaluation of seizure severity” component. For % reduction in seizure rate for all seizures, the sponsor stated that an improvement was observed in patients treated with topiramate compared to placebo, although the difference was not statistically significant. For the compound endpoint, the sponsor performed an analysis by sampling from the data with re-randomization (Westfall and Young, 1993, pp.113-121; Liu, Li and Boyett, 1997) to obtain the joint randomization distribution of the p-values under the null hypothesis and taking into account the correlation (0.3036) between the p-values of the two individual components. The sponsor stated that “the one-sided significance level for each individual component is 0.0721 such that the false positive rate that both components are significant at level 0.0721 is 0.0125. Thus, the trial has succeeded in the compound variable for the % in drop attacks (one-sided p-value = 0.0204 < 0.0721) and parental global evaluation of seizure severity (one-sided p-value = 0.0298 < 0.0721).”

The sponsor further stated that “to assess the strength of evidence for the efficacy of topiramate that the trial has demonstrated, different overall significance levels were used. The significance levels for the individual components of the compound variable were 0.0640, 0.0512, and 0.040 for the overall significance level of 0.020, 0.015, and 0.010, respectively. Thus, the above findings that hold for the overall significance level of 0.025 also hold for significance levels of 0.020, 0.015, and 0.010. The smallest overall significance level for which the above findings will still hold is .0065 where the corresponding significance level for the individual component of the compound variable is .0307.”

The sponsor now claimed that the trial was successful at the overall one-sided significance level of 0.0065 for superiority. The contribution to the overall significance was from the compound variable, consisting of % reduction in drop attacks and parental evaluation of seizure severity.

Secondary efficacy variables - Percent treatment responders

A treatment responder was defined as a subject with a 50% or greater reduction from baseline in seizure rate during the double-blind phase. Across all seizures, %s of treatment responders were similar for topiramate- (17%) and placebo- (16%) treated subjects ($p=0.930$, CMH test stratified by center). Of those subjects who had drop attacks during the baseline phase, a greater number of subjects in topiramate (28%) than in placebo (14%) were treatment responders based on their reduction in drop attacks although the difference was not statistically significant ($p=0.071$, CMH stratified by center).

3 REVIEWER'S EVALUATIONS AND COMMENTS

The primary efficacy endpoints were labeled as A, B, and C as follows.

- A: % reduction in seizure rate (all seizures),
- B: % reduction in drop attack (tonic-atonic seizure) rate,
- C: parental global evaluation of seizure severity.

There were no orphan centers. The distribution of % reduction from baseline was not symmetric ($p<0.0001$, Shapiro-Wilk test for normality). The primary efficacy analysis defined by the sponsor was the 2-way ANOVA on ranks. This reviewer confirmed the sponsor's results (Table 2.2S). It is noted that there were 3 patients (2 in topiramate and 1 in placebo) without drop attacks at baseline.

For the compound primary efficacy variable, component 'B' showed a nominal p-value of 0.041 (2-way ANOVA on ranks) and component 'C' showed a nominal p-value of 0.037 (unstratified) or $p=0.059$ (stratified by center, Wilcoxon rank sum test). Should this result be considered statistical significance at 0.05 when each component is tested at 0.05 level? Both stratified and unstratified analyses for parental global evaluation of seizure severity were the specified analyses. If the stratified analysis is used, this result on the compound variable does not reach nominal significance. Both stratified and unstratified analyses gave valid nominal p-values. The choice between the two tests will depend on the power performance of these two tests. Even if the decision is to take the smaller p-value, such a p-value will need to be adjusted slightly upward because of high correlation between the two tests, and consequently the nominal p-value for endpoint 'C' after selection of either analysis will be between 0.037 and 0.059. Thus, the nominal p-value for the parental global evaluation of seizure severity is around 0.05.

The question is 'does the decision rule of either A or (B and C) control the overall type I error rate when each of the three variables is tested at two-sided 0.05 level of significance?' From

the protocol, the review round and the discussion with the medical team (Drs. Hung, Cui, Hoberman, Jin, Chi, Katz, and this reviewer), the null hypothesis of interest for endpoints B and C is the complete null hypothesis, which is the complement of the alternative hypothesis. In addition to the usual two-sided testing procedure, Drs. Hung, Jin and this reviewer pointed out that one might consider a one-sided test for endpoints B and C since the interest for the compound variable is that both B and C demonstrating statistical significance as in combination drug setting. Thus, for the compound variable (B and C), the null (H_{02}) and alternative (H_{A2}) hypotheses are

H_{02} : there is no difference between topiramate and placebo in component B or in component C ($\Delta_B = 0$ or $\Delta_C = 0$),

vs.

H_{A2} : topiramate differs from placebo in both B and C components ($\Delta_B \neq 0$ and $\Delta_C \neq 0$)

under two-sided test, or, the null (H_{01}) and alternative (H_{A1}) hypotheses are

H_{01} : topiramate is no better than placebo in component B or in component C ($\Delta_B \leq 0$ or $\Delta_C \leq 0$)

vs.

H_{A1} : topiramate is superior to placebo in both B and C components ($\Delta_B > 0$ and $\Delta_C > 0$)

under one-sided test. It is noted that the null hypothesis (H_{02}) consists of three subhypotheses: (i) $\Delta_B = 0$ and $\Delta_C = 0$, (ii) $\Delta_B = 0$ and $\Delta_C \neq 0$, and (iii) $\Delta_B \neq 0$ and $\Delta_C = 0$ for two-sided test and the null hypothesis (H_{01}) consists of three subhypotheses (i) $\Delta_B \leq 0$ and $\Delta_C \leq 0$, (ii) $\Delta_B \leq 0$ and $\Delta_C > 0$, (iii) $\Delta_B > 0$ and $\Delta_C \leq 0$ for one-sided test.

The grand null hypothesis and the grand alternative hypothesis for this decision rule are

$$\begin{aligned} H_0 &: \Delta_A = 0 \text{ and } (\Delta_B = 0 \text{ or } \Delta_C = 0), \\ H_A &: \Delta_A \neq 0 \text{ or } (\Delta_B \neq 0 \text{ and } \Delta_C \neq 0), \end{aligned} \quad (1)$$

under two-sided hypothesis, or

$$\begin{aligned} H_0 &: \Delta_A = 0 \text{ and } (\Delta_B \leq 0 \text{ or } \Delta_C \leq 0), \\ H_A &: \Delta_A \neq 0 \text{ or } (\Delta_B > 0 \text{ and } \Delta_C > 0), \end{aligned} \quad (2)$$

under two-sided hypothesis for endpoint A but one-sided hypothesis for endpoints B and C.

The overall type I error rate under the protocol specified complex decision rule is the maximum probability of this complex decision rule calculated under the grand null hypothesis H_0 of (1) and (2) above. The formulae for the overall type I error rate above have been derived by Dr. Jin motivated by comments and discussion from Dr. Hung regarding the applicability of Laska and Meisner's Min test [Biometrics 45, 1139-1151, 1989]. The formulae are given below:

Overall type I error rate under grand null hypothesis H_0 of (1)
 $=\max \{ \Pr (|Z_A| > 1.96 \text{ or } |Z_B| > 1.96 | \Delta_A = 0, \Delta_B = 0), \Pr (|Z_A| > 1.96 \text{ or } |Z_C| > 1.96 | \Delta_A = 0, \Delta_C = 0) \}$ (3)

Overall type I error rate under grand null hypothesis H_0 of (2)
 $=\max \{ \Pr (|Z_A| > 1.96 \text{ or } Z_B > 1.96 | \Delta_A = 0, \Delta_B = 0), \Pr (|Z_A| > 1.96 \text{ or } Z_C > 1.96 | \Delta_A = 0, \Delta_C = 0) \}$ (4)

The basic concept of the above derivation was use of set theory: $A \cup (B \cap C) = (A \cup B) \cap (A \cup C)$, the null hypothesis setting for the combination drug study (Snapinn SM, Statistics in Medicine, 1987, Laska EM and Meisner MJ, Biometrics, 1989), and the limiting probability theory. This reviewer calculated the overall type I error rate as displayed in Table 1R using the bivariate normal distribution.

When all three variables are in perfect correlation (correlation=1), the decision rule reduces to test for one primary variable, so the overall type I error rate is 0.05 (2-sided). In all other scenarios, the overall type I error rate calculated using the above formulae will be inflated and the amount of inflation depends on the correlation between A and B and the correlation between A and C. The true correlations were unknown. This reviewer calculated the overall type I error rate under grand null hypotheses (1) and (2) for correlations between 0.0 to 1.0. The amount of inflation can be seen in columns 2 and 3 of Table 1R, respectively.

Table 1R. The overall type I error rates for various correlations under the grand null hypothesis (1) and (2) above

Correlation*	Overall type I error rate when A,B,C each is tested at 2-sided 0.05 under Ho (1)	Overall type I error rate when A is tested at 2-sided 0.05, B and C each is tested at 1-sided 0.025 under Ho (2)
0.0	0.0975	0.0737
0.1	0.0972	0.0736
0.2	0.0964	0.0732
0.3	0.0951	0.0726
0.4	0.0932	0.0716
0.5	0.0907	0.0703
0.6	0.0875	0.0688
0.7	0.0834	0.0667
0.8	0.0781	0.0640
0.9	0.0703	0.0601

* correlation is the smaller of the correlations between A and B and that between A and C.

Knowing that the overall type I error is inflated, how do we assess the significance of the sponsor's findings? Dr. Chi suggested that for each correlation configuration, we should find the maximum individual nominal significance level α_i , $i=1, 2, 3$ for endpoints A, B and C, respectively such that the overall type I error is maintained at 0.05. He further suggested that in adherence to the spirit of the protocol, we should take the $\alpha_1=\alpha_2=\alpha_3$ for all three endpoints. Once we calculated these individual nominal significance level α_i , then we simply compare the observed p-values against these nominal significance level α_i . The results of this reviewer's calculations are displayed in column 2 of Table 2R for the two-sided grand null hypothesis. Similar results for the one-sided grand null hypothesis are given in columns 2 and 3 of Table 3R.

Table 2R. The individual nominal significance levels for various correlations under the grand null hypothesis (1)

Correlation*	Individual nominal significance level ($\alpha_1=\alpha_2=\alpha_3$) under Ho (1) in order to control the overall type I error rate at 0.05 level
0.0	0.0253
0.1	0.0254
0.2	0.0255
0.3	0.0258
0.4	0.0263
0.5	0.0270
0.6	0.0279
0.7	0.0293
0.8	0.0314
0.9	0.0350

* correlation is the smaller of the correlations between A and B and that between A and C.

To find the individual nominal significance level so that the overall type I error rate is 0.05 seen in Tables 2R [or 3R], this reviewer derived the following equation (5) and setting (3) [or (4)] to 0.05 for the grand null hypothesis (1) [or (2)]. Thus,

$$\begin{aligned}
 & \Pr ((|Z_A| \leq c \text{ and } |Z_B| \leq c) | \Delta_A=0, \Delta_B=0, \rho) \\
 & \quad Z_B = c \\
 & = \int_{Z_B = -c}^{Z_B = c} \{ \Phi((c - \rho Z_B)/\sqrt{1-\rho^2}) - \Phi((-c - \rho Z_B)/\sqrt{1-\rho^2}) \} \phi(Z_B) dZ_B, \quad (5)
 \end{aligned}$$

where Φ is the standard normal distribution function, ϕ is the standard normal density function

and ρ is the smaller correlation between $\rho_{AB} \geq 0$ and $\rho_{AC} \geq 0$.

We have (3) = 1 - (5).

This reviewer wrote a Fortran program to solve for 'c' by numerical method and obtained the individual nominal significance levels. Thus, the two-sided nominal significance level for testing each endpoint is $2*\Phi(-c)$ as shown in Table 2R. Similar calculations were performed as shown in Table 3R.

Table 3R. The individual nominal significance levels for various correlations under the grand null hypothesis (2)

Correlation*	Individual nominal significance levels under Ho (2) in order to control the overall type I error rate at 0.05 level	
	α_1 for endpoint A	$\alpha_2=\alpha_3$ for endpoints B and C
0.0	0.0337	0.0169
0.1	0.0338	0.0169
0.2	0.0339	0.0170
0.3	0.0342	0.0170
0.4	0.0346	0.0173
0.5	0.0352	0.0176
0.6	0.0360	0.0180
0.7	0.0372	0.0186
0.8	0.0388	0.0194
0.9	0.0414	0.0207

* correlation is the smaller of the correlations between A and B and that between A and C.

On the rank scale, the sample correlation estimates among the three endpoints were significantly different from zero, which were calculated based on the measurements used for the primary efficacy analysis in which larger values of an efficacy variable indicate better outcomes in terms of treatment effectiveness. The sample correlations showed that 'global evaluation of seizure severity' is slightly to moderately correlated with '% reduction of drop attack' ($\hat{\rho}_{BC}=0.269$ with 95% CI of 0.075 to 0.477) or with '% reduction of all seizures' ($\hat{\rho}_{AC}=0.325$ with 95% CI of 0.135 to 0.492). The % reduction of seizures between drop attack and all seizures are moderately to highly correlated ($\hat{\rho}_{AB}=0.703$ with 95% CI of 0.586 to 0.791). If the sample estimates of the correlations were used as a rough idea of the true correlations, it appears that the overall type I error rate of the decision rule for the primary efficacy grand null hypothesis (1) is in the range of

0.091 to 0.097 under two-sided test (i.e., each of the three variables is tested at 0.05 level two-sided) and in the range of 0.070 to 0.074 under the grand null hypothesis (2) (i.e., endpoint A is tested at 0.05 two-sided but endpoints B and C each is tested at 0.025 one-sided level).

Given that the decision rule leads to 40% to almost 100% inflation for various correlations under the grand null hypothesis (1) relative to 5% significance level, the individual observed p-values need to compare against a level much lower than 0.05 in order to protect the overall type I error rate at 5% level. This reviewer calculated the common individual nominal significance level under grand null hypotheses (1) and (2) such that the overall type I error rate is controlled at 5% level, see column (4) and column (5) of Table 1R, respectively. Recall that the individual 2-sided p-values under grand null hypothesis (1) were 0.430, 0.041, and ~0.05 for endpoints A, B, and C, respectively, and the individual p-values under grand null hypothesis (2) were 0.430, 0.0205, and ~0.025, respectively. When endpoints A and B (or endpoints A and C) are not extremely highly correlated, all these p-values are larger than the corresponding nominal significance levels required to control the overall type I error rate at 5% level. Thus, under the usual rule that the overall type I error rate should not exceed two-sided 5% level, the study did not provide sufficient evidence to show a significant topiramate effect.

Response to sponsor's NDA amendment

In the NDA amendment submitted April 29, 1998, instead of following the protocol plan of testing each of the three endpoints at 2-sided 0.05 level, **the sponsor used a different rule for distribution of α level**, i.e., one-sided 0.0125 for the % reduction of seizure rate for all seizures [A] and one-sided 0.0125 for the compound variable (% reduction of drop attack [B] and global evaluation of seizure severity improvement [C]). **Such a post hoc change after data is analyzed is problematic with interpretation of statistical data and inference.**

The sponsor's reanalysis is based on the presumption that only type I error rate for ($\Delta_B = 0$ and $\Delta_C = 0$, i.e., the restricted null hypothesis) needs to be controlled, which is a subset of H_{01} or H_{02} (see page 6). According to HFD-120, the proper null hypothesis should be the complete null hypothesis, and furthermore, the complete null hypothesis should include the endpoint A as well as formulated in H_{01} or H_{02} .

OVERALL SUMMARY AND CONCLUSION

Demographic and baseline characteristics were reasonably matched between topiramate and placebo. Early discontinuation rate was 1%.

For indication 002 "adult and children seizures associated with Lennox-Gastaut syndrome", the study failed to show a significant higher % reduction in seizure rate for all seizures ($p=0.430$) with topiramate compared to placebo. However, the topiramate treated patients appeared to have a significantly higher % reduction in average monthly seizure rates for drop attacks ($p=0.041$) and a marginally significant to significant improvement ($p=0.059$, from

stratified by center analysis, $p=0.037$, from unstratified analysis) on the parental global evaluation of seizure severity. Both stratified and unstratified analyses gave valid nominal p-values. The choice between the two tests will depend on the power performance of these two tests. Even if the decision is to take the smaller p-value, such a p-value will need to be adjusted slightly upward because of high correlation between the two tests, and consequently the nominal p-value after selection of either analysis will be around 0.05. The observed median % reduction was 14.8% in topiramate and -5.1% in placebo, and the observed improvement rate on global seizure severity was 52% in topiramate vs. 28% in placebo.

The question is whether the topiramate group conclusively showed a statistically significant treatment effect under the decision rule of A or (B and C) each tested at two-sided 0.05 level or A tested at two-sided 0.05 and B and C each tested at one-sided 0.025. Given that the nature of the problem was to reject the complete null hypothesis for endpoints B and C, the setup of the grand null hypothesis can be either (1) or (2) (see page 6), and true correlation between endpoints are not known. Based on this Reviewer's evaluation (see Section 3), it appears that the overall type I error rate under grand null hypothesis (1) is in the range of 0.091 to 0.097 (i.e., each of the three variables is tested at two-sided 0.05 level) and in the range of 0.070 to 0.074 under grand null hypothesis (2) (i.e., endpoint A is tested at two-sided 0.05 but endpoints B and C each is tested at one-sided 0.025 level).

Since the decision rule leads to 40% to almost 100% inflation under grand null hypothesis (1) relative to 5% significance level, the individual observed p-values need to compare against a level much lower than 0.05 in order to protect the overall type I error rate at 5% level. The individual 2-sided p-values under grand null hypothesis (1) were 0.430, 0.041, and ~0.05 for endpoints A, B, and C, respectively, and the individual p-values under grand null hypothesis (2) were 0.430, 0.0205, and ~0.025, respectively. When endpoints A and B (or endpoints A and C) are not extremely highly correlated, all these p-values are larger than the corresponding nominal significance levels required to control the overall type I error rate at 5% level. Thus, under the usual rule that the overall type I error rate should not exceed two-sided 5% level, the study did not provide sufficient evidence to show a significant topiramate effect.

151

Sue-Jane Wang, Ph.D. ✓
Mathematical Statistician

Concur:

Dr. Jin

151

6/12/98

Dr. Chu

151

6/12/98

cc:

NDA 20-505 SE1-002
HFD-120/Dr. Leber
HFD-120/Dr. Katz
HFD-120/Dr. Tresley
HFD-120/Mr. Purvis
HFD-120/Ms Ware
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Dr. Wang
HFD-710/Chron

SWANG/827-1517/First Draft: April 3, 1998; Final Draft: June 12, 1998/Topamax2.nda

This document consists of 12 pages of text, 3 appendices including 2 sponsor tables and 1 sponsor figure, 1 reviewer tables, with a total of 16 pages.

Reference: Laska EM and Meisner MJ, Biometrics, 1989.
Snapinn SM, Statistics in Medicine, 1987.

Appendix:

1. Figure 2.1S
2. Table 2.1S
3. Table 2.2S