

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 20505, S003**

**CHEMISTRY REVIEW(S)**

NOV 5 1997

**CHEMIST'S REVIEW  
OF SUPPLEMENT**

ORGANIZATION: HFD-120

NDA NUMBER: 20-505

SUPPLEMENT NUMBERS: S-001 [ ]  
S-003

LETTER DATE: 31-JUL-97

STAMP DATE: 01-AUG-97

**AMENDMENTS:**

LETTER DATE: 29-OCT-97

STAMP DATE: 30-OCT-97

**APPLICANT NAME & ADDRESS:**

**R.W. JOHNSON PHARMACEUTICAL  
RESEARCH INSTITUTE**  
Welsh & McKean Roads  
Spring House, PA 19477

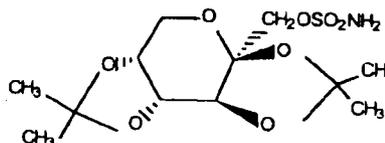
**NAME OF DRUG:**

TOPAMAX™

**NONPROPRIETARY NAME:**

**CHEMICAL NAME / STRUCTURE:**

2,3:4,5-Bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate



**DOSAGE FORM(S):**

Tablets

**POTENCY(IES):**

25, 50, 100, 200, and 300, 400-mg

**PHARMACOLOGICAL CATEGORY:**

Epilepsy

**HOW DISPENSED:**

XX (Rx)      (OTC)

**RECORDS / REPORTS CURRENT:**

XX (YES)      (NO)

**RELATED IND / NDA / DMF(S):**

**SUPPLEMENTS PROVIDE FOR:** additional indications: pediatric, partial onset seizures [ ]

**COMMENTS:** In the October 29, 1997 amendment the firm withdraws their environmental assessment submission and files an application for categorical exclusion under the 21 CFR 314.60 new revised requirements (effective August 28, 1997). The firm provides statements to certify that the estimated concentration of topiramate at the point of entry into the aquatic environment remains [ ]

**CONCLUSIONS AND RECOMMENDATIONS:** NDA 20-505 / S-001 [ ] S-003 include the adequate documentation for categorical exclusion from filing an environmental assessment.

**REVIEWER NAME**

**SIGNATURE**

**DATE COMPLETED**

Mona R. Zarifa, Ph.D.

[Signature]

November 4, 1997

cc: Orig.; NDA

HFD-120/Div. File

HFD-120/JWare

HFD-120/MGuzewska/MZarifa

INIT: MG [Signature] 537

Filename: 20505001.000

MAR - 1 1999

**CHEMIST'S REVIEW  
OF SUPPLEMENT**

**ORGANIZATION:** HFD-120  
**NDA NUMBER:** 20-505  
**SUPPLEMENT NUMBERS:** S-001

**LETTER DATE:** 31-JUL-97  
**STAMP DATE:** 01-AUG-97

**AMENDMENTS:**

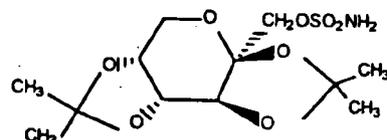
**LETTER DATE:** 29-JAN-99  
**STAMP DATE:** 01-FEB-99

**APPLICANT NAME & ADDRESS:**

**R.W. JOHNSON PHARMACEUTICAL  
RESEARCH INSTITUTE  
Welsh & McKean Roads  
Spring House, PA**

19477

**NAME OF DRUG:** TOPAMAX®  
**NONPROPRIETARY NAME:**  
**CHEMICAL NAME / STRUCTURE:**  
2,3:4,5-Di-O-isopropylidene- β-D-fructopyranose sulfamate



**DOSAGE FORM(S):** Tablets  
**POTENCY(IES):** 25, 50, 100, 200, and 300, 400-mg  
**PHARMACOLOGICAL CATEGORY:** Partial onset seizures in pediatric population.

**HOW DISPENSED:** XX (Rx)      (OTC)  
**RECORDS / REPORTS CURRENT:** XX (YES)      (NO)  
**RELATED IND / NDA / DMF(S):**

**SUPPLEMENT PROVIDES FOR:** Pediatric indication for partial onset seizures.

**COMMENTS:** The supplement is subject to approvable letter dated July 28, 1998. In this amendment the sponsor provides a combined draft labeling and proposed package insert to incorporate topiramate sprinkle dosage form subject to approved NDA 20-844.

**CONCLUSIONS AND RECOMMENDATIONS:** The Description and How Supplied sections of the proposed draft labeling and package insert are adequate from a CMC perspective.

REVIEWER NAME	SIGNATURE	DATE COMPLETED
Mona R. Zarifa, Ph.D.		February 25, 1999

cc: Orig.; NDA  
HFD-120/Div. File  
HFD-120/JWare  
HFD-120/MGuzewska/MZarifa

INIT: MGJ/S/3.1.99

Filename: 20505001.001

**CHEMIST'S REVIEW  
OF SUPPLEMENT**

APR 22 1999

ORGANIZATION: HFD-120  
NDA NUMBER: 20-505  
SUPPLEMENT NUMBERS: S-003

LETTER DATE: 31-JUL-97  
STAMP DATE: 01-AUG-97

**AMENDMENTS:**

LETTER DATE: 01-APR-99  
STAMP DATE: 02-APR-99

**APPLICANT NAME & ADDRESS:**

R.W. JOHNSON PHARMACEUTICAL  
RESEARCH INSTITUTE  
920 Route 202 South  
Raritan, NJ 08869-0602  
TOPAMAX®

**NAME OF DRUG:**

**NONPROPRIETARY NAME:**

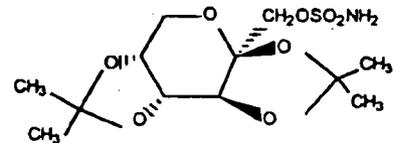
**CHEMICAL NAME / STRUCTURE:**

2,3:4,5-Di-O-isopropylidene- β-D-fructopyranose sulfamate

**DOSAGE FORM(S):**

**POTENCY(IES):**

Tablets  
25,100,200 mg



**PHARMACOLOGICAL CATEGORY:**

Adjunctive therapy for the treatment of  
generalized tonic-clonic seizures.

**HOW DISPENSED:**

**RECORDS / REPORTS CURRENT:**

**RELATED IND / NDA / DMF(S):**

XX (Rx)      (OTC)

XX (YES)      (NO)

**SUPPLEMENT PROVIDES FOR:** A new indication, adjunctive therapy in the treatment of  
generalized tonic-clonic seizures.

**COMMENTS:** In this amendment the sponsor responds to the non-approvable letter dated July 28,  
1998 and provides a combined draft labeling/proposed package insert to incorporate the sprinkles  
dosage form (NDA 20-844 S-004).

**CONCLUSIONS AND RECOMMENDATIONS:** The Description and How Supplied sections of the  
proposed draft labeling and package insert are adequate from a CMC perspective. These sections  
incorporate the two dosage forms and all relevant indications.

REVIEWER NAME

SIGNATURE

DATE COMPLETED

Mona R. Zarifa, Ph.D.

*[Handwritten Signature]*

April 21, 1999

cc: Orig.; NDA

HFD-120/Div. File

HFD-120/JWare

HFD-120/MGuzewska/MZarifa

INIT: MG/S/4.22.99

Filename: 20505003.000

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 20505, S003**

**STATISTICAL REVIEW(S)**

RECEIVED MAY 13 1998

STATISTICAL REVIEW AND EVALUATION - 1

NDA#: 20-505 SE1-001 MAY 12 1998  
Applicant: The R.W. Johnson Pharmaceutical Research Institute (PRI)  
Name of Drug: Topamax (topiramate) oral tablets  
Indication: 001 - Pediatric partial onset seizures  
Documents Reviewed: Vol.1.1, Vols 1.84-92 dated July 31, 1997  
SAS Database (CANDA)  
Medical Officer: Richard Tresley, M.D. (HFD-120)

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The following review has been discussed with medical review team and Biometrics Division Director. 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[ ]TC, and YTCE in support of three new indications: (1) pediatric partial onset seizures (Trial YP)[ ]  
[ ] (3) generalized tonic-clonic seizures (Trials YTC and YTCE).

This review pertains to indication 001. For indications 002 and 003, please see Statistical Review and Evaluation - 2 and Statistical Review and Evaluation - 3.

## 2 PIVOTAL TRIAL

### PROTOCOL YP "Topiramate clinical trial in children with partial onset seizures"

#### STUDY DESCRIPTION

##### TRIAL DESIGN

This was a randomized, double-blind, parallel design, placebo-controlled, multicenter (17 centers) trial. The study design is summarized in Figure 1.1S. Subjects were required to have at least 6 partial onset seizures during the 56-day (8-week) baseline phase, with at least one partial onset seizure occurring during each 28-day period, while being maintained on a stable regimen of one or two standard AEDs. Eligible patients were then randomized at each center to receive either topiramate (n=41) or placebo (n=45) while continuing on their background AED regimen. The double-blind treatment phase consists of a 56-day titration period and a 56-day stabilization period. During titration, study drug was titrated to the subject's assigned (target) dosage or maximum tolerated dosage, whichever was less. All subjects who completed the stabilization period of the trial were permitted to enter the open-label extension phase of the study at the discretion of the investigator and the sponsor medical monitor. The trial initiated on June 2, 1994 and completed on May 29, 1996.

##### STUDY OBJECTIVE

The study objective was to investigate the safety and efficacy of topiramate as adjunctive therapy in pediatric subjects with uncontrolled partial onset seizures with or without secondary generalized seizures. There were three amendments to the original protocol to increase enrollment and to further ensure the safety of study subjects. In the third amendment (approximately 56% of the subjects had been enrolled), the minimum age for trial eligibility was modified from four years to one year and the maximum age was modified from 14 years to 16 years. The sample size was decreased from 90 to 72. In addition, a change in the trial conduct was implemented to increase enrollment when fewer than 10 subjects were enrolled, i.e., subjects who had been participating in the baseline phase could reduce the duration of the baseline phase if they were able to provide seizure information retrospectively that totaled 56-day of seizure information when added to their prospective baseline experience.

The primary efficacy endpoint was **% change in partial onset seizure rate during the double-blind phase as compared to the baseline phase**. Other efficacy assessments were treatment responders defined as subjects with a 50% or greater reduction from their baseline seizure rate, parental global evaluations of seizure severity, etc.

## STATISTICAL PLAN

The primary analysis method was a two-way (with treatment and investigator as factors) analysis of variance. Responder rate was analyzed using logistic regression methodology. Treatment by investigator interactions was assessed at  $p\text{-value} \leq .10$ . Parental/guardian global evaluation was analyzed using Mantel-Haenszel methodology.

The sponsor was interested in detecting a 40% difference in % change from baseline in partial seizure rate between the two treatments. Assuming population standard deviation of about 60% with type I error rate of 5%, it was estimated that 36 subjects per group would provide an 80% chance of declaring the groups statistically significantly different based on a two-sided test.

## OVERVIEW OF THE SPONSOR RESULTS

Demographic and baseline characteristics for all randomized subjects were generally comparable between the topiramate and the placebo treatment groups (Table 1.1S). Subject 45 (1,133 seizures per month) and subject 522 (568 seizures per month) had unusually high baseline seizure rates and subject 47 (273 secondarily generalized seizure per month) and subject 564 (271 secondarily generalized seizure per month) had very high secondarily generalized seizure rates. These four subjects were from the placebo group.

Three subjects out of 86 randomized patients, two placebo-treated and one topiramate-treated, prematurely discontinued study medication during the trial. Seizure data for these subjects were averaged for that portion of the double-blind phase completed up to the time of study drug discontinuation, i.e., the sponsor assumes random dropouts. Results of the intent-to-treat (ITT) analysis of primary and secondary efficacy variables are summarized in Table 1.2S.

### Primary efficacy variable

#### Partial onset seizure

Median % reduction from baseline in the average monthly rate for partial onset seizures was 33.1% for topiramate-treated subjects and 10.5% for placebo-treated subjects. This difference was statistically significant ( $p=.034$ ) with 2-factor (treatment and center) ANOVA on ranks (to be discussed in the Reviewer's evaluations and comments). No statistically significant treatment-by-center interaction was detected ( $p=.159$ ). The median % reduction in seizure rates were directionally consistent, i.e., favored topiramate over placebo, regardless of age, sex, race, number of concomitant AEDs and baseline seizure rate.

## **Other efficacy variables**

### **All seizures**

Median % reduction from baseline in average monthly seizure rate based on all seizures was 31.9% for topiramate compared to 10.5% for placebo ( $p=.077$ , 2-way ANOVA on ranks). No statistically significant treatment-by-center interaction was detected ( $p=.252$ ).

### **Secondarily generalized seizures**

The most severe type of partial onset seizure, i.e., those evolving to generalized, did not increase in frequency. Topiramate-treated subjects with secondarily generalized seizures ( $n=20$ ) had a median % generalized seizure rate reduction of 31.6% while placebo-treated subjects ( $n=20$ ) had an increase of 10.6%. Among those who reported no generalized seizures during the baseline phase, % of subjects who remained free of generalized seizures during double-blind phase was 88% (21/24) for topiramate and 89% (25/28) for placebo.

### **Treatment responders**

Treatment responders were defined as subjects with a 50% or greater reduction from baseline in seizure rate during the double-blind phase. For partial onset seizures, 39% of topiramate-treated subjects compared with 20% of placebo-treated subjects were treatment responders ( $p=.08$ , CMH test). These rates were 39% (topiramate) vs. 22% (placebo) for all seizures ( $p=.127$ , CMH test). Among subjects with secondarily generalized seizures, 45% in topiramate and 30% in placebo were treatment responders. No statistically significant treatment-by-center interaction was detected for the analysis of treatment responder for partial onset seizure ( $p=.120$ ) or for all seizures ( $p=.206$ ).

### **Parental global evaluation of improvement in seizure severity**

Five scales (worse, no change, minimal, moderate, marked) were used for parental global evaluation of seizure severity. An improvement (minimal, moderate, marked) with 59% in topiramate was statistically significantly different from an improvement with 33% in placebo ( $p=.025$ , Wilcoxon-rank sum test stratified by center;  $p=.019$ , Wilcoxon-rank test unstratified).

### **Plasma concentrations of concomitant AEDs**

Except for lamotrigine, the mean changes in plasma concentration of each concomitant AED from the baseline phase to the double-blind phase were small and not statistically significant between topiramate and placebo subjects. There was a small increase in plasma lamotrigine concentration (0.7  $\mu\text{g/mL}$ ) in the placebo group and a corresponding decrease in the topiramate group (-0.8  $\mu\text{g/mL}$ ); the direction of the changes would not be expected to favor topiramate in treatment comparisons. The sponsor stated that the topiramate effects observed were not

mediated through changes in plasma concentrations of concomitant AEDs.

### 3 REVIEWER'S EVALUATIONS AND COMMENTS

Among 17 centers, there was one orphan center having one topiramate treated patient and no placebo treated patient.

- **Primary efficacy endpoint - % reduction from baseline in average monthly seizure rate for partial onset seizure rate**

This reviewer investigated whether the rank ANOVA is a reasonable analysis. A permutation test by sampling without replacement from the trial data assuming there is no difference between the topiramate and the placebo groups, viz., under the null hypothesis, was performed which resulted in  $p=.734$ . This is different from  $p=.640$  when % reduction from baseline in average monthly seizure rate for partial onset seizure rate was assumed to be normally distributed. Thus, the distribution of % reduction from baseline might not be symmetric. The empirical distribution appears to be heavily skewed ( $p<.0001$ , Shapiro-Wilk test for normality). It seems reasonable to perform the analysis based on ranks.

For the primary endpoint, PROC ANOVA on ranks performed by the sponsor is not quite appropriate ( $p=.034$ ) because the sample sizes of topiramate ( $n=41$ ) and placebo ( $n=45$ ) are unequal and unequal numbers of observations for the different combinations of treatment and center constitutes unbalanced design. When the design is unbalanced, results from PROC ANOVA can be misleading in that "the algorithm treated each arm with equal sample size". This reviewer performed PROC GLM ( $p=.056$ ). The trial showed a marginal statistical significance.

Table 1R. Efficacy results of Reviewer Analysis for Trial YP

Trial YP	placebo (n=45)	Topiramate (n=41)	p-value*
Primary efficacy endpoint: % reduction - partial seizure	10.5	33.1	.056
Secondary efficacy endpoints: % reduction - all seizures	10.5	31.9	.113
% reduction - generalized seizures	-10.6 (n=20)	31.6 (n=20)	.442**

\* 2-way ANOVA on ranks with treatment and center as the factors (contrast to sponsor Table 1S)

\*\* This is a subset comparison. Less than 50% of patients had baseline generalized seizures

### SUMMARY AND CONCLUSION

Demographic and baseline characteristics were reasonably matched between topiramate and placebo. Early discontinuation rates were 3%.

For "pediatric partial onset seizure" indication, a marginally significantly higher %

reduction from baseline in average monthly seizure rate for partial onset seizures was demonstrated in the topiramate treated patients ( $p=.056$ , 2-way ANOVA on ranks) compared to the placebo treated patients. The observed median % reduction were 33.1% in topiramate and 10.5% in placebo.

For secondary efficacy variables, there were about 50% of the patients with secondarily generalized seizures. The topiramate-treated subjects with secondarily generalized seizures ( $n=20$ ) had a median % generalized seizure rate reduction of 31.6% while placebo-treated subjects ( $n=20$ ) had an increase of 10.6%. Among those who reported no generalized seizures during the baseline phase, % of subjects who remained free of generalized seizures during double-blind phase was 88% (21/24) for topiramate and 89% (25/28) for placebo. The topiramate treated patients (59%) showed a larger improvement (minimal, moderate, marked) in parental global evaluation of seizure severity as compared to the placebo treated patients (33%). However, treatment responders of the partial onset seizures (39% in topiramate vs. 20% in placebo) and of all seizures (39% in topiramate vs. 22% in placebo) did not reach the statistical significance.

APPEARS THIS WAY  
ON ORIGINAL

/S/

Sue-Jane Wang, Ph.D.  
Mathematical Statistician

Concur:

Dr. Chi  
Division Director

/S/  
5/12/98

cc:

NDA 20-505 SE1-001  
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. Wang  
HFD-710/Chron

APPEARS THIS WAY  
ON ORIGINAL

SWANG/827-1517/Draft: April 3, 1998/Topamax1.nda

This document consists of 6 pages of text, 3 appendices including 2 sponsor tables and 1 sponsor figures, 1 reviewer table, with a total of 10 pages.

Appendix:

1. Figure 1.1S
2. Table 1.1S
3. Table 1.2S

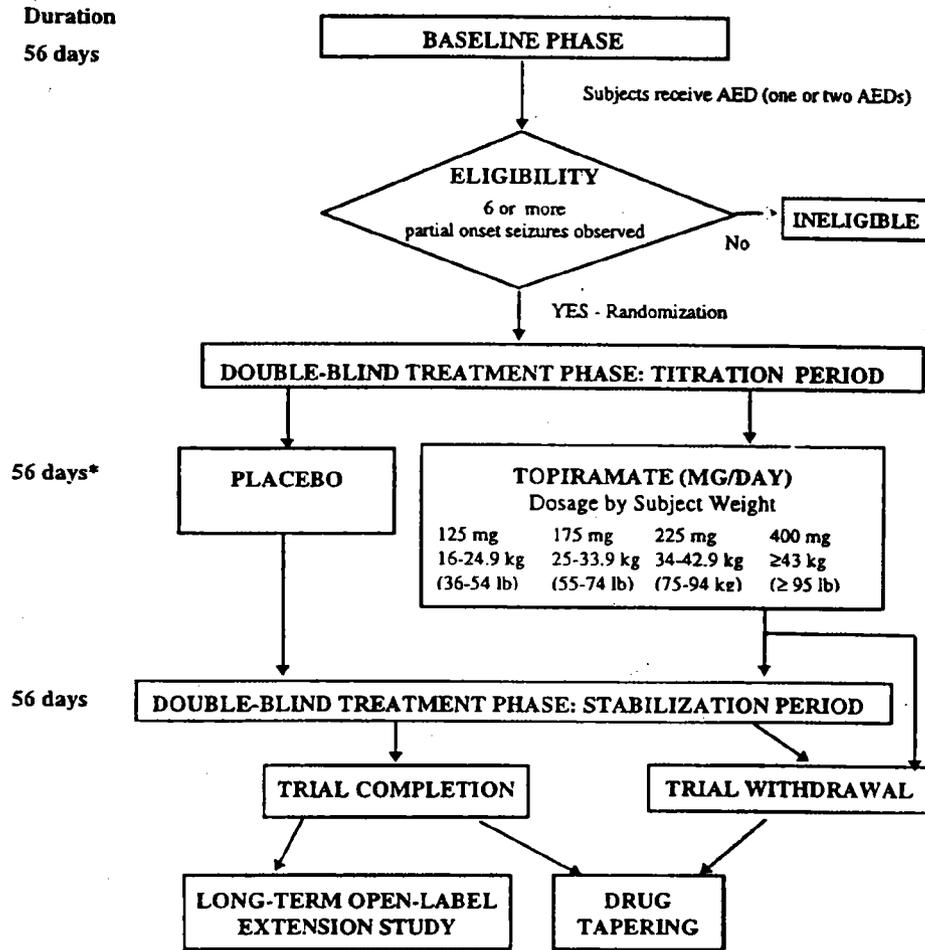
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ON ORIGINAL

Figure 1.1S

Topiramate: Clinical Study Report YP

A diagrammatic representation of the study design is presented in Figure 1.

Figure 1: Study Design for Protocol YP



\* If a subject was unable to tolerate the study medication, the investigator was permitted to reduce the subject's dosage or to maintain it at the level the subject was receiving at the time the dose-limiting adverse event occurred.

Cross-reference: Appendix 1.1

During the first visit of the 56-day baseline phase, subjects were evaluated for entry based on the inclusion and exclusion criteria (described in Section III.B.2 and III.B.3) which included a history of partial onset seizures with or without secondarily generalized seizures. As part of the inclusion criteria, subjects were required to have at least six partial onset seizures during the baseline phase, with at least one partial onset seizure occurring during each

Table 1.1S

## Topiramate: Clinical Study Report YP

**Table 6a: Demographic and Baseline Characteristics: Age, Weight, Height,  
and Average Monthly Seizure Rate  
(All Randomized Subjects; Protocol YP)**

	Placebo (N=45)	Topiramate (N=41)	Total (N=86)
<b>Age (yr)</b>			
1-7; No. (%)	15 (33)	17 (41)	32 (37)
8-11; No. (%)	20 (44)	13 (32)	33 (38)
≥12; No. (%)	10 (22)	11 (27)	21 (24)
Mean	9.0	8.8	8.9
SD	3.35	3.64	3.47
Median	10.0	9.0	9.0
Range	2-16	2-16	2-16
<b>Weight (kg)</b>			
15-24.9 kg	13 (29)	15 (37)	28 (33)
25-33.9 kg	13 (29)	7 (17)	20 (23)
34-42.9 kg	9 (20)	10 (10)	19 (22)
≥43 kg	10 (22)	9 (22)	19 (22)
Mean	35.1	34.7	34.9
SD	16.32	15.79	15.98
Median	32.0	30.0	31.5
Range	15.0-90.0	15.0-76.0	15.0-90.0
<b>Height (cm)</b>			
N	45	38	83
Mean	132.6	131.8	132.2
SD	19.05	23.90	21.27
Median	134.0	133.0	134.0
Range	94.0-178.0	90.0-178.0	90.0-178.0
<b>Baseline Average Monthly Seizure Rate:<sup>a</sup></b>			
<b>Partial Onset Seizures</b>			
Mean	84.5	45.6	65.9
SD	190.1	56.18	143.5
Median	19.0	21.5	21.3
Range	2.0-1132.6	1.8-231.5	1.8-1132.6
<b>Secondarily Generalized Seizures</b>			
N	17	17	34
Mean	41.1	16.4	28.8
SD	87.95	25.32	64.95
Median	5.0	6.3	5.6
Range	0.5-272.8	0.9-89.1	0.5-272.8
<b>All Seizures</b>			
Mean	86.2	46.0	67.0
SD	189.82	57.20	143.52
Median	23.0	21.5	22.2
Range	2.0-1132.6	1.8-244.0	1.8-1132.6

<sup>a</sup> Rate per 28 days.

Cross-reference: Attachment 1.1.1  
Appendix 3.1.1  
Appendix 3.7.1.1  
Appendix 3.7.1.2  
Appendix 3.7.1.3

Table 1.1S

## Topiramate: Clinical Study Report YP

**Table 6b: Demographic and Baseline Characteristics: Sex, Race, Background AED, and Seizure Type**  
(All Randomized Subjects; Protocol YP)

	Placebo (N=45)		Topiramate (N=41)		Total (N=86)	
	N	%	N	%	N	%
<b>Sex</b>						
Male	25	56	23	56	48	56
Female	20	44	18	44	38	44
<b>Race</b>						
White	43	96	36	88	79	92
Black	0	0	4	10	4	5
Oriental	2	4	1	2	3	4
<b>Background AED<sup>a</sup></b>						
Carbamazepine	26	58	25	61	51	59
Valproic Acid	10	22	10	24	20	23
Phenytoin	9	20	6	15	15	17
Gabapentin	4	9	10	24	14	16
Lamotrigine	5	11	5	12	10	12
Diazepam	5	11	3	7	8	9
Clonazepam	4	9	3	7	7	8
Lorazepam	1	2	6	15	7	8
Primidone	5	11	2	5	7	8
Clorazepate dipotassium	2	4	3	7	5	6
Phenobarbital	4	9	1	2	5	6
Ethosuximide	0	0	2	5	2	2
Felbamate	1	2	1	2	2	2
Methsuximide	0	0	2	5	2	2
Acetazolamide	0	0	1	2	1	1
Ethoin	1	2	0	0	1	1
One Background AED	19	42	13	32	32	37
Two Background AEDs	20	44	17	41	37	43
More than Two Background AEDs	6	13	11	27	17	20
<b>Baseline Seizure Type<sup>b</sup></b>						
Complex Partial	37	82	31	76	68	79
Secondarily Generalized	17	38	17	42	34	40
Simple Partial	12	27	11	27	23	27
All Other Types	3	7	3	7	6	7

<sup>a</sup> Individual subjects may have received one or more AEDs.

<sup>b</sup> Individual subjects may have had more than one seizure type during the baseline phase.

<sup>c</sup> Includes both valproic acid and divalproex sodium.

Cross-reference: Attachment 1.1.2  
Appendix 3.1.1  
Appendix 3.4.1  
Appendix 3.7.2

## B. STUDY COMPLETION/WITHDRAWAL INFORMATION

Eighty-three of the 86 subjects randomized to treatment completed double-blind therapy. Three subjects, two placebo-treated and one topiramate-treated, prematurely discontinued study medication during the trial (Table 7). The one topiramate-treated subject (Subject 110) was a 6

Table 1.2S

## Topiramate: Clinical Study Report YP

Table 14: Summary of the Efficacy Results for the Double-Blind Phase  
(All Randomized Subjects; Protocol YP)

Efficacy Assessment	Placebo	Topiramate	p-value
<b>Primary Variable</b>			
Percent reduction from baseline in average monthly seizure rate for partial onset seizures	10.5	33.1	0.034 <sup>b</sup>
<b>Secondary Variables</b>			
Percent reduction from baseline in average monthly seizure rate for:			
All seizures	10.5	31.9	0.077 <sup>b</sup>
Generalized seizures	-10.6	31.6	
Percent treatment responders <sup>a</sup> :			
Partial onset seizures	20.0	39.0	0.080 <sup>c</sup>
All seizures	22.0	39.0	0.127 <sup>c</sup>
Parental global evaluation of improvement in seizure severity <sup>d</sup>	33	59	0.025 <sup>e</sup> 0.019 <sup>f</sup>

<sup>a</sup> A treatment responder is defined as subject whose seizure rate was reduced 50% or more during the double-blind phase.

<sup>b</sup> TPM vs. placebo; two factor (treatment and center) ANOVA on ranks.

<sup>c</sup> TPM vs. placebo; Cochran-Mantel-Haenszel test.

<sup>d</sup> Percent of subjects who had minimal, moderate, or marked improvement in seizure severity.

<sup>e</sup> TPM vs. placebo; Wilcoxon rank-sum test stratified by center.

<sup>f</sup> TPM vs. placebo; Wilcoxon rank-sum test unstratified.

Cross-reference: Table 8  
Table 9  
Table 10  
Table 11

The efficacy of topiramate was based on a statistically significant between-group difference (topiramate vs. placebo) in percent reduction in the average monthly seizure rate for partial onset seizures. Topiramate-treated subjects had a median percent reduction in partial onset seizure rate of 33.1% while placebo-treated subjects had a median percent reduction in partial onset seizures of 10.5% ( $p=0.034$ ). While the sample size used in this trial was inadequate to demonstrate the statistical superiority of topiramate over placebo in reducing the most severe type of partial onset seizure, i.e., those evolving to generalized, the effect of topiramate on secondarily generalized seizures was examined to ensure that while topiramate was effective in reducing the overall rate of partial onset seizures it did not increase the rate of secondarily generalized seizures. In this trial, secondarily generalized seizures did not increase in frequency. Topiramate-treated subjects with secondarily

RECEIVED MAY 13 1998

**STATISTICAL REVIEW AND EVALUATION - 3**

NDA#: 20-505 SE1-003 MAY 12 1998  
Applicant: The R.W. Johnson Pharmaceutical Research Institute (PRI)  
Name of Drug: Topamax (topiramate) oral tablets  
Indication: 003 - Generalized tonic-clonic seizures  
Documents Reviewed: Vol.1.1, Vols 1.101-155 dated July 31, 1997  
NDA amendment submission dated April 29, 1998  
SAS Database (CANDA)  
Medical Officer: Richard Tresley, M.D. (HFD-120)

The following review has been discussed with medical review team and Biometrics Division Director. 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 [redacted] YTC, and YTCE in support of three new indications: (1) pediatric partial onset seizures (Trial YP), [redacted] (3) generalized tonic-clonic seizures (Trials YTC and YTCE).

This review pertains to indication 003. For indications 001 and 002, please see "Statistical Review and Evaluation - 1" and "Statistical Review and Evaluation - 2."

**INDICATION 3: PRIMARILY GENERALIZED TONIC-CLONIC SEIZURES (PGTC)**

**2 PIVOTAL TRIALS**

## 2.1 PROTOCOL YTC "Topiramate clinical trial in PGTC"

### STUDY DESCRIPTION

#### STUDY DESIGN

This was a randomized, double-blind, parallel-group, placebo-controlled, multicenter (17 US centers and 1 Costa Rica center) trial. The study design is summarized in Figure 3.1S. Subjects were required to have 3 or more primary generalized tonic-clonic (PGTC) seizures during the 56-day baseline phase (with at least one during each 28-day period) while on a stable regimen of one or two AEDs. Eligible patients were randomized at each center to receive either topiramate (n=39) or placebo (n=41) while continuing on their background AED regimen. The double-blind treatment phase consisted of a 56-day titration period and a 84-day stabilization period. All subjects who completed the stabilization period of the trial were permitted to enter the open-label extension phase of the study at the discretion of the investigator and the sponsor medical monitor. The trial initiated on May 5, 1994 and ended on July 5, 1996.

#### STUDY OBJECTIVE

The study objective was to evaluate the safety and efficacy of oral topiramate as adjunctive therapy to subjects with uncontrolled primary generalized tonic-clonic (PGTC) seizures, i.e., tonic-clonic seizures considered to be generalized from the onset, with or without other generalized seizure subtypes. No formal protocol amendments were made affecting the double-blind portion of the trial. A change to the trial conduct was implemented to increase enrollment whereby subjects who had been participating in the baseline phase could reduce the duration of the baseline phase if they were able to provide seizure information retrospectively (e.g., based on their own records) that totaled 56 days of seizure information when added to their prospective baseline experience. This change in trial conduct affected 20 subjects (10 subjects in each treatment groups) approximately 25% of the sample.

The primary efficacy parameter was % reduction from baseline to double-blind phase in average monthly PGTC seizure rate. Percent reduction from baseline in all seizures, treatment responders based on PGTC seizures and all seizures, and global evaluation of seizure severity were considered as secondary efficacy variables. Efficacy data were recorded by subjects (or their parents or guardians) in their seizure diaries including the number of seizures that occurred and a description of seizure types. The investigators classified each seizure type (according to the International Classification of Epileptic Seizures) described in the subject's diary before the data were recorded on the subject's case report form.

#### STATISTICAL PLAN

The primary efficacy analysis was a two-way ANOVA. Responder rate was analyzed using logistic regression methodology. Treatment by center interactions were assessed at  $p \leq .10$ .

Global evaluations were analyzed using Mantel-Haenszel methodology.

The sponsor was interested in detecting a 30% difference in % change from baseline in PGTC between the two treatments. Assuming a population standard deviation of about 45% with type I error rate of 5%, it was estimated that 36 subjects per group would provide an 80% chance of declaring the groups statistically significantly different based on a two-sided test.

## **OVERVIEW OF THE SPONSOR RESULTS**

Demographic and baseline characteristics for all randomized subjects were generally comparable between the topiramate and the placebo treatment groups except a 10 kg difference in body weight (62 kg in placebo and 72 kg in topiramate), see Table 3.1S. Subject 68 (299.9 PGTC seizure/month) in placebo and subject 52 (297.7 PGTC seizures/month) in topiramate experienced a large number of PGTC seizures during the baseline phase.

Eight subjects out of 80 randomized patients, 3 from placebo and 5 from topiramate, prematurely discontinued study medication during the trial. Every attempt was made to follow those subjects until all clinical visits were completed. One from placebo and 2 from topiramate groups completed all clinical visits and were considered by the sponsor to have completed the trial per protocol. The results of the ITT analysis of primary and secondary efficacy variables are summarized in Table 3.2S.

### **Primary efficacy variable**

#### **Primary Generalized Tonic-Clonic seizure (PGTC)**

Median %s reduction from baseline in the average monthly rate for PGTC were 56.7% for topiramate-treated subjects and 9.0% for placebo-treated subjects. This difference was statistically significant ( $p=.019$ , 2-way ANOVA on ranks). No statistically significant treatment-by-center interaction was detected ( $p=.796$ ).

### **Secondary efficacy variables**

#### **All seizures**

Median %s reduction from baseline in the average monthly seizure rate for all seizures were 42.1% in topiramate and 0.9% in placebo. This difference was statistically significant ( $p=.003$ , 2-way ANOVA on ranks). There was no statistically significant treatment by center interaction ( $p=.584$ ).

#### **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. Topiramate-treated subjects had a responder rate of 56% compared with placebo-treated subjects of 20% for PGTC ( $p=.001$ , CMH stratified by center). For all seizures, topiramate-treated subjects had a responder rate of 46% compared with placebo-treated subjects of 17% ( $p=.003$ , CMH stratified by center). No statistically significant treatment-by-center interaction was found ( $p>.677$ ) for either PGTC or all seizures.

### Global evaluation of improvement in seizure severity

Sixty-two percent of subjects in topiramate showed an improvement (minimal, moderate or marked) compared with 56% in placebo. This between-group difference was not statistically significant ( $p=.49$  stratified by center;  $p=.388$  unstratified analysis).

### REVIEWER'S EVALUATIONS AND COMMENTS

There were 7 orphan centers: 6 of them each had a placebo patient only and one center had a topiramate patient only. The sponsor defined an algorithm for pooling centers at the time of analysis. The algorithm ranked all centers in order of their sample size and then alphabetically within sample size. Centers with 8 or more subjects remained as independent centers; centers with fewer than 8 subjects were pooled into groups no larger than 16 and no fewer than 8 subjects each. These analysis centers were not optimal in that all orphan centers were pooled into one analysis center. The number of patients between treatment and placebo for this analysis center may not be reasonably balanced. However, the algorithm did not subjectively influence either treatment or placebo. Thus, it is acceptable.

The protocol defined analysis was a 2-way ANOVA. The empirical distribution appeared to be heavily skewed ( $p<.0001$ , Shapiro-Wilk test for normality). It seems reasonable to perform the analysis based on ranks. This reviewer performed a one-way ANOVA on ranks without center adjustment excluding one patient in the placebo arm who did not have PGTC seizure at baseline. The unadjusted analyses on these efficacy related outcome were consistent with the sponsor's adjusted analyses ( $p=.018$  for PGTC and  $p=.004$  for all seizures, Table 1R) in that the statistical evidence of a treatment effect still holds.

Table 1R. The results of efficacy related outcome for Trial YTC

Trial YTC	placebo	Topiramate	p-value*	p-value**
Primary efficacy endpoint: % reduction - PGTC	9.0% (n=40)	56.7%(n=39)	.019	.018
Secondary efficacy endpoints: % reduction - all seizures	0.9% (n=41)	42.1%(n=39)	.003	.004

\* 2-way (treatment and center) ANOVA on ranks of %s redcution (the sponsor Table 3.1S)

\*\* two group comparisons on %s reduction on ranks unstratified by center

## 2.2 PROTOCOL YTCE "clinical trial in primarily generalized tonic-clonic seizures"

### STUDY DESCRIPTION

#### STUDY DESIGN

This was a randomized, double-blind, parallel-group, placebo-controlled, multicenter (16 centers, 6 in US and 10 in Europe) trial. The study design is identical to Protocol YTC. Eligible patients were randomized at each center to receive either topiramate (n=40) or placebo (n=40) while continuing on their background AED regimen. The trial initiated on Sept. 15, 1994 and ended on Nov. 12, 1996.

#### STUDY OBJECTIVE

The study objective was to evaluate the safety and efficacy of oral topiramate as adjunctive therapy to subjects with uncontrolled PGTC seizures, i.e., tonic-clonic seizures considered to be generalized from the onset, with or without other generalized seizure subtypes. No formal protocol amendments were made affecting the double-blind portion of the trial. A change to the trial conduct was implemented to increase enrollment whereby subjects who had been participating in the baseline phase could reduce the duration of the baseline phase if they were able to provide seizure information retrospectively (e.g., based on their own records) that totaled 56 days of seizure information when added to their prospective baseline experience. This change in trial conduct affected 26 subjects (15 subjects in placebo and 11 subjects in treatment).

#### STATISTICAL PLAN

The primary efficacy analysis for the primary efficacy endpoint, % reduction from baseline seizure rate based on PGTC, was a two-way (with treatment and center as factors) ANOVA. The sponsor was interested in detecting a 30% difference in % change from baseline in PGTC between the two treatments. Assuming a population standard deviation of about 45% with type I error rate of 5%, it was estimated that 36 subjects per group would provide an 80% chance of declaring the groups statistically significantly different based on a two-sided test.

#### OVERVIEW OF THE SPONSOR RESULTS

Demographic and baseline characteristics for all randomized subjects were generally comparable between the topiramate and placebo treatment groups on age, weight, height, sex, and race (see Table 4.1S). Baseline PGTC seizures appeared to be imbalanced between placebo (median 3.0 sz per 28 days) and topiramate (median 5.0 sz per 28 days).

Twenty subjects out of 80 randomized patients, 11 from placebo and 9 from topiramate groups, prematurely discontinued study medication during the trial. Reasons of discontinuation were limiting adverse event (18% in placebo vs. 13% in topiramate), investigator's discretion

(3% in placebo vs. 0% in topiramate), subject choice (0% in placebo vs. 5% in topiramate), and others (8% in placebo vs. 5% in topiramate). The results of the ITT analysis of primary and secondary efficacy variables are summarized in Table 4.2S.

### **Primary efficacy variable**

#### **Primary Generalized Tonic-Clonic seizure (PGTC)**

Median %s reduction from baseline in the average monthly rate for PGTC were 57.1% for topiramate-treated subjects and 33.2% for placebo-treated subjects. This difference was not statistically significant ( $p=.124$ , 2-way ANOVA on ranks;  $p=.078$  2-way ANCOVA on ranks with baseline PGTC as covariate). No statistically significant treatment-by-center interaction was detected ( $p=.250$ ).

### **Secondary efficacy variables**

#### **All seizures**

Median %s reduction from baseline in the average monthly seizure rate for all seizures were 26.0% for topiramate and 12.1% for placebo. This difference was not statistically significant ( $p=.212$ , 2-way ANOVA on ranks). There was no statistically significant treatment by center interaction ( $p=.781$ ).

#### **Treatment responders**

A responder was defined as a subject with a 50% or greater reduction from baseline in seizure rate during the double-blind phase. Topiramate-treated subjects had a responder rate of 54% compared with placebo-treated subjects of 35% for PGTC ( $p=.102$ , CMH stratified by center). In all seizures, the topiramate-treated subjects had a responder rate of 40% compared with the placebo-treated subjects of 20% ( $p=.061$ , CMH test). No statistically significant treatment-by-center interaction was found for either PGTC ( $p=.285$ ) or all seizures ( $p=.671$ ).

#### **Global evaluation of improvement in seizure severity**

Forty-eight percent of subjects in topiramate showed an improvement (minimal, moderate or marked) compared with 33% in placebo. This between-group difference was nominally statistically significant ( $p=.026$  stratified by center;  $p=.024$  unstratified Wilcoxon rank sum test).

### **REVIEWER'S EVALUATIONS AND COMMENTS**

From the electronic database, there were 3 orphan centers with 2 centers having a placebo patient only and 1 center having a topiramate patient only. The sponsor defined an algorithm for pooling centers, similar to Trial YTCE, at the time of analysis. This reviewer performed a two-

sample treatment comparison on the % reduction in PGTC seizures without center adjustment. The result ( $p=.107$ , Wilcoxon rank sum test) is consistent with the 2-way ANOVA on ranks ( $p=.124$ ).

### Results differ between Trial YTC and Trial YTCE

Median %s reduction of PGTC in topiramate were similar (57%) in both trials. But this % reduction in placebo was much higher for Trial YTCE (33.2%) than for Trial YTC (9.0%).

Medical team is concerned with the inconsistent results between the two trials having identical design. This reviewer explored the baseline characteristics between these two trials. From the description of baseline characteristics seen in Table 2R below, although it

Table 2R. Baseline Characteristics Comparison between Trials YTC and YTCE

	YTC	YTCE
Age ( $\leq 16$ vs. $> 16$ )	26% vs. 74%	14% vs. 86%
Age (median, range)	25.5 (3-59)	29.5 (7-60)
Weight (kg) (median, range)	64.0(17-143)	74.4(25-146)
Height (cm) (median, range)	166 (101-196)	169(119-200)
Baseline average monthly seizure rate - PGTC	5.0(.7-299.9)	3.7(.5-159.5)
Baseline average monthly seizure rate - all sz	16.0(1.0-79109)	20.8(1 to 18232)
sex (M:F)	56% vs. 44%	48%:52%
Race (White: black: others)	85%: 14%: 1%	99%: 1%: 0%
Background AEDs (1 : 2: $>2$ )	23%:51%:26%	25%:56%:19%
Tonic-Clonic seizures only	33%	23%
Tonic-Clonic & $\geq 1$ other generalized sz type	66%	76%

appeared that patients in Trial YTCE tended to be older (median age: 29.5 yrs vs. 25.5 yrs), heavier (median weight: 74.4kg vs. 64 kg), having less severe baseline PGTC seizure (median: 3.7 sz/28day vs. 5.0 sz/28day), almost all Caucasian (99% vs. 85%), fewer patients with only tonic-clonic seizures (23% vs. 33%), more patients with tonic-clonic and more than one other generalized type (76% vs. 66%) at baseline, none of these numerical differences reach a statistical significance.

This reviewer further explored if there were any administration differences between the US and the European countries. Trial YTC consisted of 17 US centers + 1 Costa Rica center, all coded as USA. In Trial YTCE, 39% of the patients were from USA and 61% were from Europe.

Table 3R. Summary of baseline PGTC seizure per 28days & its % reduction by country

Trial YTC	Placebo (n=41)#		Topiramate (n=39)		p-value
baseline PGTC (median, range)	4.5 (.7, 299.9)		5.0 (1.0, 297.7)		.502!
% reduction of PGTC from baseline (median,range)	9.0% (-1100%,100%)		56.7% (-226.2%, 100%)		.019*
Trial YTCE	Placebo (n=40)		Topiramate (n=40)#		
baseline PGTC (median, range)	3.0 (.5, 34.1)		5.0 (.5, 159.5)		.019!
% reduction of PGTC from baseline (median,range)	33.2% (-134%, 100%)		57.1% (-188.2%, 100%)		.124*
Country	USA(n=15)	Europe(n=25)	USA(n=16)	Europe(n=23)	
baseline PGTC (median, range)	2.5(.5, 24.9)	3.2(1.0, 34.1)	8.8(.8, 74.9)	3.5(.5, 159.5)	.007 (US)!
% reduction of PGTC from baseline (median,range)	37.9% -134%100%	31.4% -60.6%,100%	48.5% -188.2%100%	60% 35.2%,100%	.502 (EU)!
%reduction PGTC-ANOVA*	p=.611 (USA)		p=.114 (Europe)		
%reduction PGTC-unadj.~	p=.614 (USA)		p=.099 (Europe)		

# patient 161 does not have baseline PGTC seizures in Trial YTC

# patient 39 at Blankenhorn site does not have baseline PGTC seizures in Trial YTCE

\* 2-way (treatment and pooled centers) ANOVA on ranks

~ two group comparisons of % reduction PGTC seizures on ranks within each country

! Wilcoxon rank sum test

Table 3R summarizes the baseline PGTC seizure and its % reduction from baseline by country. Baseline PGTC seizures were comparable in Trial YTC (median: 4.5 sz per 28 days in placebo and 5.0 sz per 28 days in topiramate), but appeared to be imbalanced ( $p=.0185$ , Wilcoxon rank sum test) between placebo (median: 3.0 sz per 28 days with 95% CI of .5 to 34.1 sz per 28 days) and topiramate (median: 5.0 sz per 28 days with 95% CI of .5 to 159.5 sz per 28 days) in Trial YTCE. In Trial YTCE, baseline PGTC seizures were similar between the topiramate treated patients and the placebo treated patients in each of the age groups ( $\leq 16$  vs.  $> 16$  yrs) and each sex. They were also comparable in European centers (medians: 3.2 sz per 28 days in placebo and 3.5 sz per 28 days in Topiramate;  $p=.502$ , Wilcoxon rank sum test) but appeared to be imbalanced in US centers ( $p=.007$ , Wilcoxon rank sum test). The topiramate treated patients had 3.5 times as high in median baseline PGTC seizures (8.8 sz per 28 days vs. 2.5 sz per 28 days) than the placebo treated patients in US centers.

When the primary efficacy analyses (2-way ANOVA on ranks or 2-group comparison on ranks) were performed within the country subgroup, the % reduction of PGTC seizure from baseline did not show a statistically significant ( $p>.09$ ) topiramate treatment effect from either the US or Europe centers. Numerically, the European sites appeared to show twice as high in % reduction for topiramate (60%) than for placebo (31.4%), but such rates were not very different in the US sites (48.5% in topiramate vs. 37.9% in placebo).

Patient discontinuation patterns were somewhat different between these two Trials. The discontinuation rate was half-time as high in placebo (7%=3/41) as in topiramate (13%=5/39) for Trial YTC and was higher in placebo (28%=11/40) than in topiramate (22%=9/40) for Trial YTCE. This reviewer explored a potential differential treatment effect between patients completed versus those discontinued the trial. From Table 4R, patients' baseline PGTC were comparable in incompleters but were twice as high in topiramate (6.2 sz per 28 days) than in placebo (3.0 sz per 28 days) within completers. The % reduction of PGTC seizure from baseline did not show a topiramate effect from a simple comparison between topiramate vs placebo ( $p=.107$ ), a 2-way ANOVA adjusted for country ( $p=.109$ ), such analyses within completed patients, and such analyses within discontinued patients. There was a numeric trend of topiramate effect in median % reduction of PGTC seizures (60% in topiramate vs. 33.8% in placebo) within those patients completed the trial. However, sample size was too small to compare within those patients discontinued the trial.

Table 4R. Summary of PGTC seizures per 28days & its % reduction by discontinuation status

Trial YTCE (n=80)*	Completers (n=60)		Incompleters (n=19)		p=.327
	baseline PGTC (median, range) % reduction of PGTC from baseline (median,range)	.13 (.5 - 74.9) 39.8% -134%, 100%		3.2 (.8 - 159.5) 50.9% -188.2%, 100%	
Treatment	PBO(n=29)	TOP(n=31)	PBO(n=11)	TOP(n=8)	
baseline PGTC (median, range)	3.0(.5-34.1)	6.2(.5-74.9)	2.5(1.5,28)	3.5(.8-159.5)	
Wilcoxon rank sum test	p=.020		p=.648		
% reduction of PGTC from baseline (median,range)	33.8% -134%100%	60% -45.9%100%	31.4% -48.2%100%	54% -188.2%100%	
%reduction PGTC-ANOVA** %reduction PGTC-unadj.-	p=.0927 p=.0907		p=.756 p=.796		p=.109 p=.107

\* patient 39 at Blankenhorn site does not have baseline PGTC seizures  
 \*\* 2-way ANOVA on ranks adjusted for country  
 ~ two-group comparisons on % reduction of PGTC on ranks without any adjustments

For both trials, the randomization was done within centers. However, the design factors such as the characteristics of the patient population on baseline PGTC seizures in Trial YTCE may lead to a reduced difference between topiramate vs. placebo. In addition, the study conduct such as efforts of prevention of study dropouts (discontinuation rates were 25% in YTCE vs. 10% in YTC) may influence a trial's ability to show a difference between topiramate vs. placebo.

## OVERALL SUMMARY AND CONCLUSION

In summary, demographic and baseline characteristics appeared to be comparable between Trials YTC (US centers) and YTCE (US and Europe centers) except baseline PGTC seizure in Trial YTCE. It appeared that baseline PGTC seizures in Trial YTCE were comparable in European centers but not in US centers. These baseline PGTC seizures were not comparable in those patients completed the trial.

For indication 003 "adults and children generalized tonic-clonic seizures", Trials YTC and YTCE were identical in design but one study showed a statistical significance of topiramate effect (YTC) and the other study did not (YTCE). The primary efficacy endpoint analysis showed a higher % reduction of PGTC seizures from baseline in topiramate than in placebo for Trial YTC ( $p=.019$ ) but not for YTCE ( $p=.124$ ).

The topiramate treated patients had 2 (Completers) or 3 (US sites) times higher baseline PGTC seizures compared to the placebo treated patients. The %s reduction of PGTC from baseline were similar among placebo treated patients either subsetting by country or by completer status, i.e., the median % reduction of PGTC from baseline were in the neighborhood of 31.4% to 37.9%. However, these medians were 48.5% (US topiramate treated patients) to 60% (Europe topiramate or completer topiramate treated patients) among topiramate treated patients. For both trials, the randomization was done within centers. However, the design factors such as the characteristics of the patient population on baseline PGTC seizures in Trial YTCE may lead to a reduced difference between topiramate vs. placebo. In addition, the study conduct such as efforts

of prevention of study dropouts (discontinuation rates were 25% in YTCE vs. 10% in YTC) may influence a trial's ability to show a difference between topiramate vs. placebo.

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This document consists of 11 pages of text, 5 appendices including 4 sponsor tables and 1 sponsor figure, 4 reviewer tables, with a total of 18 pages.

Appendix:

1. Figure 3.1S
2. Table 3.1S
3. Table 3.2S
4. Table 4.1S
5. Table 4.2S

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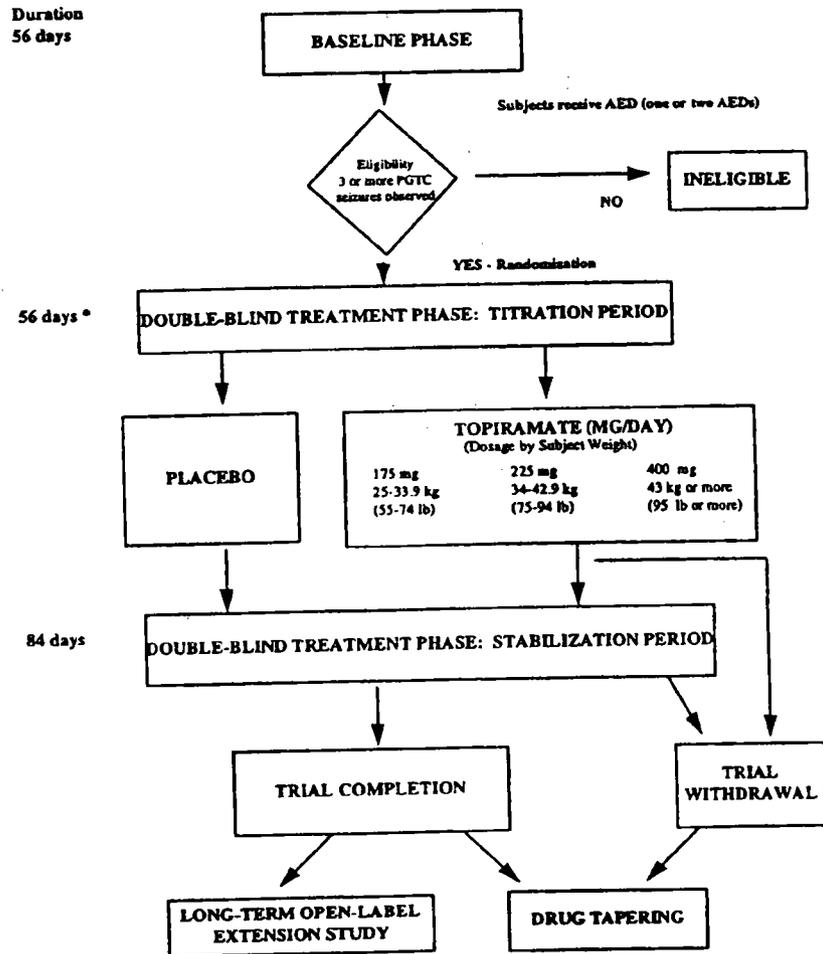
Figure 3.1s

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**Topiramate: Clinical Study Report YTC**

A diagrammatic representation of the study design is presented in Figure 1.

**Figure 1: Study Design for Protocol YTC**



\* If a subject was unable to tolerate the study medication, the investigator was permitted to reduce the subject's dosage or maintain it at the level the subject was receiving at the time the dose-limiting adverse event occurred.

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Cross-reference: Appendix 1.1

During the first clinical visit of the 56-day baseline phase, subjects were evaluated for entry based on the inclusion and exclusion criteria (described in Sections III.B.2 and III.B.3), which included a history of primary generalized epilepsy including primary generalized tonic-clonic seizures with or without other seizure types, and a recent history of maintenance on a fixed antiepileptic drug (AED) regimen of one or two standard AEDs.

Table 3.1S

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Topiramate: Clinical Study Report YTC



Medical histories for all randomized subjects are given in Appendix 3.1.2.

**Table 6a: Demographic and Baseline Characteristics: Age, Weight, Height, and Average Monthly Seizure Rate (All Randomized Subjects; Protocol YTC)**

	Placebo (N=41)	Topiramate (N=39)	Total (N=80)
<b>Age (yr)</b>			
≤16; No. (%)	13 (32)	8 (21)	21 (26)
>16; No. (%)	28 (68)	31 (79)	59 (74)
Mean	25.6	26.8	26.2
SD	13.38	12.82	13.04
Median	26.0	25.0	25.5
Range	3.0 to 50.0	5.0 to 59.0	3.0 to 59.0
<b>Weight (kg)</b>			
25-33.9; No. (%)	6 (15)	5 (13)	11 (14)
34-42.9; No. (%)	2 (5)	1 (3)	3 (4)
≥43; No. (%)	33 (80)	33 (85)	66 (83)
Mean	61.3	71.8	66.5
SD	25.06	28.52	27.14
Median	62.0	72.0	64.0
Range	17 to 129	22 to 143	17 to 143
<b>Height (cm)<sup>a</sup></b>			
N	38	35	73
Mean	159.1	166.1	162.4
SD	19.44	17.21	18.61
Median	161.0	168.0	166.0
Range	101 to 196	117 to 193	101 to 196
<b>Baseline Avg. Monthly Seizure Rate<sup>a</sup>:</b>			
<b>PGTC Seizures</b>			
N	40	39	79
Mean	15.8	20.3	18.0
SD	47.23	51.51	49.12
Median	4.5	5.0	5.0
Range	0.7 to 299.9	1.0 to 297.7	0.7 to 299.9
<b>All Seizures</b>			
Mean	2000.9	91.1	1069.9
SD	12347	214.7	8839
Median	17.5	15.3	16.0
Range	1.6 to 79109	1.0 to 1134.0	1.0 to 79109

<sup>a</sup> Rate per 28 days. Monthly rate based on prospective baseline data.

Cross-reference: Attachment 1.2.1  
Appendix 3.1.1

Table 3.15

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Topiramate: Clinical Study Report YTC

**Table 6b: Demographic and Baseline Characteristics:  
Sex, Race, Background AED, and Seizure Type  
(All Randomized Subjects; Protocol YTC)**

	Placebo (N=41)		Topiramate (N=39)		Total (N=80)	
	No.	%	No.	%	No.	%
<b>Sex</b>						
Male	21	51	24	62	45	56
Female	20	49	15	38	35	44
<b>Race</b>						
White	36	88	32	82	68	85
Black	5	12	6	15	11	14
Other	0	0	1 <sup>a</sup>	3	1	1
<b>Background AED<sup>b</sup></b>						
Valproic acid <sup>c</sup>	20	49	19	49	39	49
Phenytoin	13	32	12	31	25	31
Carbamazepine	9	22	11	28	20	25
Lamotrigine	10	24	6	15	16	20
Phenobarbital	3	7	8	21	11	14
Clonazepam	6	15	6	15	12	15
Gabapentin	3	7	5	13	8	10
Diazepam	4	10	3	8	7	9
Lorazepam	3	7	4	10	7	9
Primidone	6	15	0	0	6	8
Clorazepate dipotassium	1	2	3	8	4	5
Ethosuximide	3	7	1	3	4	5
Felbamate	2	5	2	5	4	5
Methylphenobarbital	2	5	0	0	2	3
Mephenytoin	0	0	1	3	1	1
Methsuximide	1	2	0	0	1	1
One Background AED	9	22	9	23	18	23
Two Background AEDs	22	54	19	49	41	51
More Than Two Background AEDs	10	24	11	28	21	26
<b>Baseline Seizure Type<sup>d</sup></b>						
Tonic-Clonic	40 <sup>e</sup>	98	39	100	79	99
Absence	16	39	16	41	32	40
Tonic	10	24	9	23	19	24
Myoclonic	8	20	8	21	16	20
Drop attack <sup>f</sup>	5	12	2	5	7	9
Atypical absence	4	10	2	5	6	8
Clonic	1	2	1	3	2	3
Other <sup>g</sup>	1	2	1	3	2	3
Tonic-Clonic Only	13	32	13	33	26	33
Tonic-Clonic and at least one other generalized seizure subtype	27	66	26	67	53	66

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ON ORIGINAL<sup>a</sup> Subject 146 was of Hispanic descent.<sup>b</sup> Individual subjects may have received more than one background AED.<sup>c</sup> Includes valproate disodium.<sup>d</sup> Individual subjects may have had more than one seizure type. Baseline seizure types are based on prospectively collected seizure data.<sup>e</sup> Subject 161 did not experience a PGTC seizure during either baseline or double-blind phase (see Section IV.E, Protocol Deviations).<sup>f</sup> Includes seizures described as violent myoclonic jerks, atonic seizures, or drops to the floor.<sup>g</sup> Subject 98 (placebo) experienced seizures of an unknown type that were categorized as "other".

Subject 71 (topiramate) experienced complex partial seizures that were categorized as "other".

Cross-reference: Attachment 1.2.2

Appendix 3.1.1

Appendix 3.4.1

Appendix 3.7.2

Table 3.2S

Topiramate: Clinical Study Report YTC

**Table 14: Summary of the Efficacy Results for the Double-Blind Phase  
(All Randomized Subjects; Protocol YTC)**

Efficacy Assessment	Placebo	Topiramate	p-value
<b>Primary Variable</b>			
Percent reduction from baseline in average monthly seizure rate for PGTC seizures	9.0	56.7	0.019 <sup>b</sup>
<b>Secondary Variables</b>			
Percent reduction from baseline in average monthly seizure rate for all seizures	0.9	42.1	0.003 <sup>b</sup>
Percent treatment responders <sup>a</sup> :			
PGTC seizures	20	56	0.001 <sup>c</sup>
All seizures	17	46	0.003 <sup>c</sup>
Subject's global evaluation of improvement in seizure severity <sup>d</sup>	56	62	0.490 <sup>e</sup> 0.388 <sup>f</sup>

<sup>a</sup> A treatment responder is defined as subject whose seizure rate was reduced 50% or more during the double-blind phase.

<sup>b</sup> Topiramate vs. placebo; two factor (treatment and center) ANOVA on ranks.

<sup>c</sup> Topiramate vs. placebo; Cochran-Mantel-Haenszel test.

<sup>d</sup> Percent of subjects who had minimal, moderate, or marked improvement in seizure severity.

<sup>e</sup> Topiramate vs. placebo; Wilcoxon-rank sum test stratified by center.

<sup>f</sup> Topiramate vs. placebo; Wilcoxon-rank sum test unstratified.

Cross-reference: Table 9  
Table 10a  
Table 11

Topiramate was statistically superior to placebo with respect to percent reduction in average monthly seizure rate for both PGTC seizures and all seizures combined. Median percent reduction from baseline in average monthly seizure rate was 56.7% for topiramate and 9.0% for placebo (p=0.019) based on PGTC seizures and 42.1% for topiramate and 0.9% for placebo (p=0.003) based on all seizures. The percent reduction from baseline in average monthly seizure rate numerically favored topiramate over placebo for absence (53% vs. 4%), myoclonic (52% vs. an increase of 401%), and tonic (16% vs. an increase of 1%) seizures.

A statistically greater number of topiramate-treated subjects responded to treatment with a 50% reduction in PGTC seizure rate (56%) than in the placebo group (20%) and a 50% reduction in seizure rate for all seizures (46%) compared to the placebo group (17%) (p≤0.003). When treatment responder was defined more broadly...

Topiramate:

Clinical Study Report YTCE **BEST POSSIBLE COPY**

Table 4.1S

Table 6a: Demographic and Baseline Characteristics: Age, Weight, Height, and Average Monthly Seizure Rate (All Randomized Subjects; Protocol YTC-E)

	Placebo (N=40)	Topiramate (N=40)	Total (N=80)
<b>Age (yr)</b>			
≤ 16; No. (%)	2 (5)	9 (23)	11 (14)
>16; No. (%)	38 (95)	31 (77)	69 (86)
Mean	29.1	29.2	29.1
SD	8.69	12.44	10.66
Median	29.0	30.0	29.5
Range	12 to 46	7 to 60	7 to 60
<b>Weight (kg)</b>			
25-33.9; No. (%)	1 (3)	4 (10)	5 (6)
34-42.9; No. (%)	0 (0)	2 (5)	2 (3)
≥43; No. (%)	39 (97)	34 (85)	73 (91)
Mean	78.7	71.3	75.0
SD	19.34	23.63	21.78
Median	77.9	73.6	74.4
Range	33 to 146	25 to 123	25 to 146
<b>Height (cm)</b>			
N	33	37	70
Mean	170.3	166.6	168.4
SD	8.83	17.15	13.90
Median	170.0	168.0	169.0
Range	155 to 188	119 to 200	119 to 200
<b>Baseline Average Monthly Seizure Rate:<sup>a</sup></b>			
<b>PGTC Seizures</b>			
N	40	39	79
Mean	6.5	15.5	10.9
SD	8.68	28.62	21.38
Median	3.0	5.0	3.7
Range	0.5 to 34.1	0.5 to 159.5	0.5 to 159.5
<b>All Seizures</b>			
Mean	422.3	604.5	513.4
SD	1799	2880	2388
Median	15.0	25.7	20.8
Range	1.0 to 10876	1.5 to 18232	1.0 to 18232

*p* = .018  
*Wilcoxon*

*p* = .338

<sup>a</sup> Rate per 28 days. Monthly rate based on prospective baseline data

Cross-reference: Attachment 1.2.1  
Appendix 3.1.1

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Table 4.1S

Table 6b: Demographic and Baseline Characteristics:  
Sex, Race, Background Antiepileptic Drug, and Baseline Seizure Type  
(All Randomized Subjects; Protocol YTC-E)

	Placebo (N = 40)		Topiramate (N=40)		Total (N=80)	
	N	%	N	%	N	%
<b>Sex</b>						
Male	21	52	17	43	38	48
Female	19	48	23	57	42	52
<b>Race</b>						
White	40	100	39	97	79	99
Black	0	0	1	3	1	1
<b>Background AED<sup>a</sup></b>						
Valproic acid <sup>b</sup>	23	58	22	55	45	56
Lamotrigine	16	40	13	33	29	36
Carbamazepine	14	35	11	28	25	31
Phenytoin	8	20	7	18	15	19
Gabapentin	4	10	4	10	8	10
Lorazepam	2	5	5	13	7	9
Phenobarbital	1	3	5	13	6	8
Clobazam	1	3	4	10	5	6
Ethosuximide	1	3	3	8	4	5
Clonazepam	2	5	1	3	3	4
Mephobarbital	0	0	2	5	2	3
Primidone	2	5	0	0	2	3
Vigabatrin	1	3	1	3	2	3
Methsuximide	1	3	0	0	1	1
Diazepam	0	0	1	3	1	1
One Background AED	11	27	9	23	20	25
Two Background AEDs	22	55	23	57	45	56
More than Two Background AEDs	7	18	8	20	15	19
<b>Baseline Seizure Type<sup>c</sup></b>						
Tonic-clonic	40	100	39 <sup>d</sup>	98	79 <sup>d</sup>	99
Absence	19	48	14	35	33	41
Myoclonic	10	25	13	38	23	29
Tonic	5	13	6	15	11	14
Atypical absence	2	5	7	18	9	11
Drop attack <sup>e</sup>	3	8	1	3	4	5
Clonic	0	0	1	3	1	1
Other <sup>f</sup>	2	5	2	5	4	5
Tonic-Clonic Seizures Only	9	23	9	23	18	23
Tonic-Clonic Seizures and at Least One Other Generalized Seizure Type	31	77	30	75	61	76

<sup>a</sup> Individual subjects may have received more than one background AED.  
<sup>b</sup> This category includes both valproic acid (31 subjects) and valproate semisodium (14 subjects).  
<sup>c</sup> Individual subjects may have had more than one seizure type.  
<sup>d</sup> Subject 39 did not have tonic-clonic seizures recorded during baseline or the double-blind phase.  
<sup>e</sup> Includes seizures described as atonic seizures and severe myoclonus.  
<sup>f</sup> Subject 235 (topiramate) experienced prolonged absence/uncertain seizures categorized as "other". Additional information for Subjects 60 and 225 (placebo), and Subject 235 (topiramate) was unavailable.

Cross-reference: Attachment 1.2.2  
 Appendix 3.1.1  
 Appendix 3.4.1  
 Appendix 3.7.2

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Table 4.2S

**Table 14: Summary of the Efficacy Results of the Double-Blind Phase  
(All Randomized Subjects; Protocol YTC-E)**

Efficacy Assessment	Treatment Group		p-value
	Placebo (N=40)	Topiramate (N=40)	
<b>PGTC Seizures</b>			
<b>Primary Variable</b>			
N	40	39	
Median percent reduction from baseline in average monthly seizure rate	33.2	57.1	0.124 <sup>a</sup> 0.078 <sup>b</sup>
<b>Secondary Variable</b>			
N	40	39	
Percent Treatment Responders <sup>c</sup>	35	54	0.102 <sup>d</sup> 0.016 <sup>e</sup>
<b>All Seizures</b>			
<b>Secondary Variables</b>			
Median percent reduction from baseline in average monthly seizure rate	12.1	26.0	0.212 <sup>a</sup>
Percent treatment responders <sup>c</sup>	20	40	0.061 <sup>d</sup>
Subjects' global evaluation of improvement in seizure severity <sup>f</sup>	33	48	0.026 <sup>g</sup> 0.024 <sup>h</sup>

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<sup>a</sup> Topiramate vs. placebo; two factor (treatment and center) ANOVA on ranks  
<sup>b</sup> Topiramate vs. placebo; two factor (treatment and center) ANCOVA on ranks with baseline PGTC seizure rate as covariate.  
<sup>c</sup> A treatment responder is defined as a subject whose seizure rate was reduced 50% or more during the double-blind phase.  
<sup>d</sup> Topiramate vs. placebo; Cochran-Mantel-Haenszel test  
<sup>e</sup> Topiramate vs. placebo; Logistic regression including treatment, center, and baseline PGTC seizure rate as terms in the model.  
<sup>f</sup> Percent of subjects who had minimal, moderate, or marked improvement in seizure severity.  
<sup>g</sup> Topiramate vs. placebo; Wilcoxon Rank Sum test stratified by center  
<sup>h</sup> Topiramate vs. placebo; Wilcoxon Rank Sum test unstratified

Cross-reference: Table 9  
 Table 10a  
 Table 11

Although the efficacy results of this trial consistently favored topiramate over placebo, the treatment comparisons generally did not achieve statistical significance using standard, unadjusted, intent-to-treat analyses. There are, however, indications that the standard analysis tended to underestimate topiramate efficacy in this particular study. One such indication is that intent-to-treat analyses adjusting for a substantial imbalance in baseline PGTC seizure rates favor topiramate more strongly, resulting in a p-value of 0.078 for the primary efficacy variable, percent reduction from baseline in PGTC seizure rate (57.1% vs. 33.2%), and a highly significant difference (p=0.016)