

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 20 505

SPONSOR: THE R.W. JOHNSON PHARMACEUTICAL
RESEARCH INSTITUTE

BRAND NAME (GENERIC NAME) TOPIMAX (TOPIRAMATE)

INDICATION: PARTIAL ONSET EPILEPSY

NDA CLASSIFICATION IS

ORIGINAL RECEIPT DATE DECEMBER 29, 1994

REVIEW COMPLETION DATE: OCTOBER 11, 1995

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0.0 OVERVIEW

This NDA, and additional supplementary clinical materials received since the original submission December 29, 1994 contains six completed adequate and well-controlled trials for the short-term evaluation of topiramate in the treatment of partial epilepsy. Five of these studies evaluated topiramate against placebo as therapy adjunctive to marketed antiepileptic drugs.

15.

The safety evaluation consisted of short term exposure in normal individuals, short term controlled exposure, and longer duration open label, uncontrolled exposure. No foreign marketing of topiramate exists, and therefore the safety experience is derived solely from the NDA, largely US exposure. The spectrum of routine adverse events are those commonly seen with antiepileptic drug products and those which occur by virtue of its property as a carbonic anhydrase inhibitor. Serious adverse events have been identified by the sponsor include psychosis, depression and renal calculi.

1.0 MATERIAL UTILIZED IN REVIEW

1.1 NDA

The following table lists the specific volumes that were examined in reviewing this NDA. For the review of efficacy, the individual study reports rather than the Integrated Summary of Efficacy were relied upon. For the primary review of safety the Integrated Safety Summary was used only as a point of departure for the overall safety review. Tables of adverse events grouped by study type (open label vs. controlled epilepsy), case report forms identified through the CANDAs for specific adverse events, and case report forms by death, dropout and serious adverse events were relied upon heavily for this review.

Table of NDA Volumes Reviewed for Clinical Evaluation of Topiramate

CATEGORY	STUDY	Date rec'd	Volume(s)
Efficacy	Overview: N/A	12/29/1994	2.1-2.2
	YD	12/29/1994	2.89-2.99
	YD CRFs	5/9/1995	8.1-8.79
	YE	12/29/1994	2.99-2.110
	Y3	12/29/1994	2.111-2.115
	Y3 CRFs	3/13/1995	5.1-5.20
	Y1	3/20/1995	6.1-6.10
	Y2	3/20/1995	" "
	YI	6/21/1995	10.1-10.3
	YF/G	ns	—
	YK (LennoxGastaut)	ns	—
	ISE	12/29/1994	2.216
	Safety	ISS	12/29/1994
CRF (deaths)		12/29/1994	2.261-2.269
CRF (Serious AE)		12/29/1994	2.270-2.304
CRF (WDAE)		12/29/1994	2.305-2.411
7 month SU		7/14/1995	13.1-13.42
CRF (deaths)		" "	13.43-13.52
CRF (Serious AE)		8/18/1995	15.1-15.53
CRF (WDAE)		8/18/1995	" "

1.2 MATERIAL FROM IND

Data from safety reports received from 1991 to present (Retained in this reviewer's database) and the annual report for IND for the previous year 1994 were consulted during this review.

1.3 REVIEW OF PUBLISHED LITERATURE

The sponsor was asked to submit an analysis of the world's literature. A compilation of the world's literature regarding topiramate has not yet been received.

2.0 BACKGROUND

2.1 INDICATION

This medication was developed as a treatment primarily for patients with refractory partial seizures and was studied largely as adjunctive therapy,

This will be discussed in the Efficacy section. It has not been studied in comparison to existing therapies. The sponsor does not make the case that it has any particular qualities which would make it necessarily a preferred medication.

2.2 Related INDs and NDAs

There is only one marketed drug product (acetazolamide, Diamox) which closely resembles that of topiramate, an anticonvulsant and a carbonic anhydrase inhibitor. The existing labeling for diamox was reviewed and the profile of this drug was kept in mind during the review of topiramate. Known toxicity include anaphylaxis, Stevens Johnson Syndrome, TEN, bone marrow depression, renal calculi, hepatic necrosis, aggravation of acidosis, paraesthesia, and adverse interaction with high dose aspirin (anorexia, tachypnea, lethargy, coma and death), teratogenicity.

Certain adverse events were compared across recently marketed NDA's for antiepileptic drug products (gabapentin, felbamate and lamotrigine) and this one (topiramate).

2.3 Administrative History

June 19, 1986: The original IND for topiramate was submitted by McNeil Laboratories. The IND was allowed to proceed in humans.

May 28, 1988: Meeting held to discuss an amendment to allow women of childbearing potential to participate in clinical trials. Request denied because of failure of the firm to provide preliminary evidence of efficacy of the drug.

June 15, 1989: Topiramate IND transferred to R.W. Johnson Pharmaceutical Research Inc.

June 28, 1990: Sponsor given permission to enroll women of childbearing potential into clinical trials.

August 21, 1990: Meeting at the request of R.W. Johnson to discuss the summary of the clinical efficacy and proposed phase III trials. FDA suggested: 1) a minimum of 1000 patient exposure, several hundred of whom have been exposed for over 6 months 2) ADME in special populations 3) better characterization of interactions with antiepileptic drugs 3) Pediatric claim should be supported by trials in children.

May 28, 1993: Sponsor Requested a Pre-NDA meeting. Separate meeting was held with Division of Biopharmaceutics

August 29, 1995: NDA 20-505 was submitted to FDA.

September , 1995: FDA contacted R.W.Johnson that it had refused to file NDA 20-505.

December 29, 1995: NDA 20-505 was again resubmitted and filed.

2.4 DIRECTIONS FOR USE

The sponsor recommends that the minimum daily topiramate dose is 200 mg/day. The recommended usual dose is 200-600 mg/day. The sponsor asserts that some patients may require up to 1600 mg/day, although doses only to 1000 were studied in controlled trials. Tolerance for higher doses is limited by adverse events which are dose related (see section 8.0).

Sponsor recommends the following titration schedule: 100 mg per day. Subsequent increments of 100 mg/day may be introduced weekly. Sponsor recommends that dose titration should be guided by clinical outcome. (This is the regimen for titration used in clinical studies, YD, YE, Y1,Y2, and Y3).

Sponsor indicates that topiramate can be taken without regard to meals. (Please refer to Human Biopharmaceutics Review with regard to this advice).

Sponsor indicates that it is not necessary to monitor blood levels during titration to optimize therapy, but that on rare occasions the addition of topimax to phenytoin may require an adjustment in phenytoin dosing. Similarly the addition or withdrawal of phenytoin or carbamazepine during adjunctive therapy with topiramate may require adjustment in topiramate dosing.

Patients with renal impairment are advised to titrate based on clinical outcome (ie, seizure control, avoidance of side effects)¹ with the knowledge that subjects with known renal impairment may require a longer time to reach steady state at each dose.

Sponsor advises elderly patients that dosage adjustments of topiramate are not necessary in the absence of renal disease. No special directions are given to patients with moderate hepatic impairment, or based on the patient's age or gender.

2.5 FOREIGN MARKETING

Currently this drug is not marketed in any foreign countries. Topiramate has been under development since 1986 in North America (United States, Canada, Mexico), South America (Argentina and Brasil) Europe (Austria, Belgium, France, Germany, Italy, Netherlands, Portugal and Spain, Norway, Denmark, Sweden, and Finland, United Kingdom) and Africa (South Africa).

¹PLEASE REFER TO EFFICACY REVIEW P. FOR COMMENTS ABOUT THE FALLACY OF TITRATION BASED ON EFFECTIVENESS.

3.0 CHEMISTRY

Topiramate [2,3:4,5-bis-O-(1-mentylethylidene)- β -D-fructopyranose sulfamate] is a structurally novel compound. It has a molecular weight of 339.36. Some of the physical and chemical characteristics of topiramate are tabulated below:

Properties	Characteristics
Organoleptics	Solid, white, crystalline powder, with a bitter taste
Dissociation	A weak acid; the pK_a determined by potentiometric titration and regression modeling is 8.61 at 25 C and 8.53 at 37 C
Solubility	<p>The solubility of Topiramate is approximately 1:10 in acetone, chloroform, dimethylsulfoxide, ethanol, glacial acetic acid, methanol and methylene chloride. In water (without buffer and/or ionic strength adjustment), the solubility is 9.8 mg/ml. The pH of the saturated solution in water is 6.3.</p> <p>Topiramate is most soluble in alkaline solutions, pH @9 to 10; Solubility data from a variety of alkaline buffers and pH adjusting solutions containing sodium hydroxide or sodium phosphate suggests that topiramate forms sodium salts in-situ; in citric acid-phosphate buffers (pH 2.3 to 8.0) adjusted to constant ionic strength ($\mu=0.5$) the solubility is between 6.55 and 7.45 mg/ml</p>

The stability of topiramate for two years is expected at 25 C and ambient humidity. The sponsor suggests that the drug be stored below 30 C in polyurethane (protected from moisture) and reassayed annually.

There are four strengths manufactured: 100, 200, tablets.

Topiramate is structurally different from all other known anticonvulsants, but its sulfonamide moiety is similar to that sulfonamide found in some carbonic anhydrase inhibitors, such as acetazolamide.

The chemistry and manufacturing of Topiramate have been reviewed separately. However, there are no outstanding manufacturing and control problems with clinical implications.

4.0 Animal Pharmacology

The animal pharmacology has been reviewed separately, and only a very brief summary is presented here.

4.1 Pharmacology (Mechanism of Action)

Topiramate was shown to be highly effective in blocking the hindlimb tonic-extensor component of the maximal electroshock seizure (MES) in mice and rats. Topiramate was also found to effectively block seizures in mouse and rat models of hereditary epilepsy, in some animal models of kindled epilepsy, and in a rat model of stroke-induced epilepsy. It was either weak or inactive in blocking seizures induced by the chemical convulsants, pentylenetetrazol, bicuculline, picrotoxin, and strychnine. Compared with phenytoin, phenobarbital, carbamazepine, acetazolamide, ethosuximide, and valproic acid, topiramate exhibits the greatest separation between maximum anticonvulsant activity (MES test) and significant neurotoxicity in rodents.

Pharmacologic effects that are thought to possibly contribute to anticonvulsant activity include a state-dependent blockade of voltage-activated Na⁺ channels, potentiation of γ -aminobutyrate (GABA)-induced Cl⁻ fluxes across neuronal cell membranes through a mechanism independent of benzodiazepine sites on GABAA receptors, and an antagonism of glutamate at the kainate/AMPA subtype but not the N-methyl-D-aspartate (NMDA) subtype of excitatory amino acid receptors.

Topiramate is an inhibitor of erythrocyte carbonic anhydrase in several species. It has minimal pharmacologic effects on the cardiovascular, gastrointestinal, endocrine, blood, renal and pulmonary tissues.

4.2 Preclinical ADME

Eight metabolites of topiramate have been identified in animals and humans. Two metabolites, which retained most of the structure of topiramate, were tested and found to have little or no anticonvulsant activity.

4.3 Preclinical Toxicology

Although carbonic anhydrase inhibition by topiramate may not be a major component of its antiepileptic activity, some toxicologic effects of topiramate in animal models (teratogenic effects, gastric hyperplasia associated with increased serum gastrin levels and hyperplasia of the renal pelvis and urinary bladder associated with urinary tract calculi are consistent with CA inhibition. Hyperplasia of the gastric and renal epithelial cells seen in shorter term studies did not progress to neoplasia after lifetime exposure in rats or mice and has not been reported during clinical studies.^{41,42} Smooth muscle tumors of the urinary bladder in mice appear to be unique to the species.⁴¹ There is no known clinical counterpart; therefore, these tumors were not considered to be of relevance to man.

Topiramate is teratogenic in mice, rats, and rabbits. The teratologic effects of topiramate seen in rats and rabbits appear to be related to carbonic anhydrase inhibition.(refer to Dr. Ed Fisher's review). Reductions in weight of progeny were also indicated by reproductive studies in these species, but no effect on fertility was observed for male or female rats. Based on results of in vitro and in vivo mutagenicity assays, topiramate does not show genotoxic potential.

5.0 DESCRIPTION OF CLINICAL DATA SOURCES

The following are the key documents that contain safety data showing the cutoff dates for collection of that data, as well as the dates received by the FDA:

Document	Date Received	Cutoff date for data
NDA/ISS	12/29/94	12/31/1992
Routine AE	12/29/94	12/31/1992
Deaths, serious AE	12/29/94	12/21/1992
Safety Update	7/14/95	3/ 31/ 1994
Routine AE	7/14/95	3/31/ 1994
Deaths	7/14/95	3/31/1995
Serious AE	8/15/95	3/31/1995

5.1 PRIMARY CLINICAL DEVELOPMENT PROGRAM

Summary: The topiramate clinical development program has consisted of a total of 44 studies: 13 clinical pharmacology studies in nonepileptic patients, 31 clinical epilepsy studies (of which 5 were placebo controlled trials and 1 double blind dose-controlled monotherapy trial, 7 were pharmacokinetics studies in epileptic patients, 15 uncontrolled studies in Epilepsy including two pediatric studies).

Type of study	Number of studies	US	nonUS
Clinical Pharmacology (nonepileptic)	13	13	0
Clinical Pharmacology (epileptic)	7	7	0
Clinical Efficacy:			
Placebo Controlled	7	4	3
Dose controlled	2		0
Clinical Safety-open label long range Epilepsy	15	11	4

The clinical program for topiramate was developed to evaluate topiramate as adjunctive therapy in the treatment of refractory adult partial onset seizures (POS). The NDA along with its numerous additional submissions includes seven completed adequate and well controlled trials (YD, YE, YF, YG¹, Y1, Y2, Y3, YI) and fifteen open label safety studies to evaluate topiramate in the treatment of partial onset epilepsy in adults, one study in children (YP) and 20 clinical pharmacology studies.

Protocols YD, YE, and YF and YG were completed in the United States and evaluated three oral (target) topiramate doses (200, 400, and 600 mg/day; 600, 800, and 1,000 mg/day; and 1,000 mg/day, respectively), while Protocols Y1, Y2, and Y3 were conducted in Europe using daily (target) dosages of 400, 600, or 800 mg, respectively. An additional seven open label safety studies

Subjects completing Studies YD, YE, Y1, Y2, and Y3 were able to enter long-term, open-label therapy under Study YKP/YKT² (for Protocols YD and YE) and YEP/YET (for Protocols Y1, Y2, and Y3). Further extension was provided in Protocols YLT and YLTE. Similarly, subjects from Protocol YF and YG could enter long-term, open-label therapy under Protocol YF/YG extension. Data from YLTE, YKT and YKP are included in the four-month safety update. Protocols YEP, YET, YLT, YLTE, and YF/YG extension were ongoing as of the March 31, 1994 cutoff date for the four-month update but do contribute some new data up to that date.

The 44 topiramate studies that were either completed or ongoing as of March 31, 1994, and that contribute data to the four-month safety update, are listed below in "Summary of All Studies with Topiramate". In addition to the 44 clinical studies that contribute safety data for comprehensive analysis in this four-month safety update, 11 new studies are presented which contribute topiramate exposure data and serious adverse event information, only. These studies include two double-blind trials of topiramate in children or adults with generalized seizures, two double-blind trials evaluating topiramate adjunctive therapy in children with Lennox-Gastaut syndrome and POS, respectively, an open-label

¹Study YF and YG were initially designed as two separate studies, but the sponsor has combined their data for analysis. The data was not actually submitted as the report is not yet complete.

²The nomenclature YKP indicates patients who had been randomized to placebo in the double blind controlled trials, where YKT indicates patients who had been randomized to topiramate.

safety, efficacy, and pharmacokinetics study in children with POS, one completed probenecid interaction study and five open-label studies in Japan (two safety and efficacy studies in epileptics and three clinical pharmacology studies in healthy subjects).

SUMMARY OF CLINICAL STUDIES WITH TOPIRAMATE

Study Type/Number	Design	Country	N
PHARMACOKINETICS (ADME)			
Bioequivalence			
MS-212	Open label two period crossover comparative bioavailability : fasted	USA	18
MS-213	Open label two-period crossover comparative bioavailability:fasted	USA	18
Relative Bioavailability			
MS-174	Open label three-period crossover comparative bioavailability:fasted/fed	USA	21
Food Effect			
MS-211	Open label two-period crossover: fasted v. fed	USA	19
MS-214	Open label two-period crossover: fasted v. fed	USA	18
Multiple Dosing			
YB	Double blind, placebo controlled ascending multiple dosing (normals)	USA	42
Dose Proportionality			
MS-210	Open label three-period crossover: fasted adults (100, 200, 400 mg)	USA	27
YA	DB, placebo controlled in normal adults (100,200,400,800,1200,1600, Pbo)	USA	31
Absorption, Excretion, Biotransformation			
MS-177	Open label C14 Topiramate 100mg normal adults: fasted	USA	6
Effect of Renal Insufficiency			
MS-191A	Open label parallel study in pts with mild to severe renal impairment	USA	32
MS-221	Open label study in pts with ESRD requiring dialysis	USA	8
Effect of Hepatic Insufficiency			
MS-209	Open label parallel study in pts with hepatic insufficiency	USA	11

Drug Interactions--Subjects with Epilepsy				
MS-215	Open label dose titration phenytoin-tpm interaction study (normals)	USA	12	
MS-216	Open label dose titration carbamazepine-tpm interaction study (normals)	USA	12	
MS-218	Open label dose titration valproate-tpm interaction study (normals)	USA	12	
YZL	Open label dose titration study assessing interaction with phenytoin or valproate (patients with partial sz)	USA	13	
YZT	Open label dose titration study assessing interaction with carbamazepine (patients with partial seizures)	USA	8	
YZW	Open label dose titration study assessing interaction with phenobarbital or primidone (patients with partial seizures)	USA	6	
Oral Contraceptive Drugs--Definitive Study				
MS-220	Open label dose titration study assessing interaction with norethindrone/estradiol (female patients)	USA	12	
Drug Interactions--Healthy Males				
MS-219	Open label sequential two-period crossover assessing potential interaction with digoxin: fasted healthy males	USA	12	
EFFICACY STUDIES:				
Adult Double-Blind /Placebo Control/ Add-on:				
YD	DB, placebo controlled adjunctive, doses 200, 400, 600, Pbo.	USA	181	
YE	DB, placebo controlled adjunctive, doses 600, 800, 1000, Pbo.	USA	190	
YF	DB, placebo controlled adjunctive, doses 1000 mg/Pbo.	USA	207	
YG	Combined with YF	USA	-	
Y1	DB, placebo controlled adjunctive, doses 400 mg/Pbo.	non US	47	
Y2	DB, placebo controlled adjunctive, doses 600 mg/ Pbo.	nonUS	60	
Y3	DB, placebo controlled adjunctive, doses 800 mg/ Pbo.	nonUS	54	

SAFETY STUDIES

Study ID	Description	Country	Number of Patients
Open Label YC/YCO/YCO2	Open label safety as adjunctive therapy in refractory PCS (up to 2 years) Doses 200-1600 mg.	USA	23
YKP	Open label in adults with refractory PCS. Doses 200-1600 mg. Patients randomized to PLACEBO in studies YD, YE, YZT and YZW.	USA	70
YKT	Open label in adults with refractory PCS. Patients randomized to TOPIRAMATE in studies YD, YE, YZT and YZW.	USA	224
IP	Open label in adults with PCS. Dose 100 mg x 7 days.	Italy	10
YF/YG extension	Open label extension of studies YF and YG in adults with PCS. Doses 200-1600.	USA	148
YLT	Open label in adults with PCS. Adjunctive therapy allowed. Doses 200- 1600 mg. Long term extension for YKP, YKT, YCO2, and MS-215, MS-216, MS-218.	USA	181
YOLYH	Open label in subjects 14 yrs and older with any seizure type. Adjunctive medications were allowed. Doses 200-1600 mg.	USA	277 YOL 275 YH2
YEP	Open label in adults with PCS. Extension from Y1, Y2, Y3. Patients randomized to PLACEBO. Doses 200-1600 mg.	NonUS	69
YET	Open label in adults with PCS. Extension from Y1, Y2, Y3. Patients randomized to TOPIRAMATE. Doses 200-1600 mg.	NonUS	53
YLTE	Open label in adults with PCS. Long term extension from protocols YEP and YET. Doses 200-1600 mg.	NonUS	31
YOLE	Open label in patients 14 years and older with any seizure type. Long term study. Doses 200-1600 mg	NonUS	224
OL	Extension of studies YI and YJ	USA	16

or assumed to have received even a single dose of topiramate.

SUMMARY OF ALL STUDIES

Pools by Study Design	Number of Subjects by Treatment Group	
	Topiramate	Placebo
Phase 1 (Clinical Pharmacology) Studies in Nonepileptic Subjects		
Studies in Healthy Volunteers		
Single Dose	155	28
Multiple Dose	42	12
SUBTOTAL	197	38
Studies in Special Populations		
Renally Impaired Subjects, Single dose	25	0
Hepatically Impaired Subjects, Single dose	5	0
Matched Healthy Volunteers, Single dose	24	0
SUBTOTAL	54	0
TOTAL No. of NONEPILEPTIC SUBJECTS	251	38
Studies in Subjects With Epilepsy		
Phase 1 (Clinical Pharmacology) Studies		
Single Dose	0	0
Multiple Dose	75	0
SUBTOTAL	75	0
Phase 2-3 Efficacy and Safety Studies		
Placebo-Controlled Trials	527	216
Dose-Controlled Trials	36*	0
Uncontrolled Studies		
Short-term	10	0
Long-term	798** (468)***	0
SUBTOTAL	1,371	0
TOTAL No. of SUBJECTS WITH EPILEPSY	1,446	216
SINGLE DOSE TOTAL	209	26
MULTIPLE DOSE TOTAL	1,488	228
GRAND TOTAL	1,697	254

*Study Y1 had not completed its recruitment of 48 patients by the cutoff date of the 7 month Safety Update

**Includes only epileptic subjects whose initial exposure to topiramate was in an open-label study.

Topiramate-treated subjects who were initially enrolled in a placebo-controlled trial or in a clinical pharmacology study before participating in an open-label extension study are not included.

***The number in parentheses represents subjects participating in open-label extension studies but already

counted under a previous heading.

In general, throughout this review the following subgroups will be used:
Epilepsy, placebo controlled add-on trials (N=527 topiramate, N=216
placebo); Epilepsy; and All epilepsy (n=1446).

Note that the cutoff date for the majority of data in the safety update was March 31, 1994. From that date to the cutoff for the reporting of Deaths and Serious Adverse Events, March 31, 1995 there were additional patients exposed to topiramate for a total denominator of 2086 for deaths and Serious Adverse events.

5.1.2 DEMOGRAPHICS

The three tables on the following pages provide basic demographic information for the following groups : Placebo controlled Epilepsy studies, Open label and All Epilepsy Studies Combined.

The first table includes the demographic data from the double blind placebo controlled trials in epilepsy:

Demographic Profile for Double Blind Epilepsy Studies

	Placebo (N=216)	Topiramate (N=527)
AGE (YR)		
Mean	34.4	35.8
Range	15-68	17-67
Groups		
13-18	5 (2%)	7 (1%)
19-29	79 (37%)	156 (30%)
30-39	62 (29%)	190 (36%)
40-49	48 (22%)	108 (20%)
50-59	16 (7%)	50 (9%)
≥60	6 (3%)	16 (3%)
SEX		
Male	157 (73%)	375 (71%)
Female	59 (27%)	152 (29%)
RACE		
White	196 (91%)	469 (89%)
Black	13 (6%)	42 (8%)
Other	7 (3%)	16 (3%)
WGT (LB)		
MEAN	165.5	172.9

Similarly, the demographics in the only completed topiramate monotherapy study, open label, dose controlled, is shown below, similar to the placebo controlled group. While there were two studies designed only one study, YI has been completed and has data available. Study YJ was discontinued for administrative reasons, and the data are not reflected in the table on the following page.

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**Demographic Profile for All Topiramate
Subjects with Epilepsy (Double blind and
Open label studies)**

**Topiramate
(N=1446)**

AGE**Groups :****Pediatric**

4-12	20 (1%)
13-18	68 (5%)
Mean (yrs)	14.6
Range (yrs)	4-18

Adult

19-29 yrs	457 (32%)
30-39 yrs	464 (32%)
40-49 yrs	285 (20%)
50-59 yrs	116 (8%)
>60	36 (2%)
Mean (yrs)	35.4
Range (yrs)	19-74

SEX

Female	503 (35%)
Male	943 (65%)

RACE

White	1265 (87%)
Black	88 (6%)
Other	83 (6%)
Unknown	10 (1%)

WEIGHT

Mean (lbs)	165.2 (40.8%)
Range	33.7-343.0 lbs

Baseline characteristics with regard to background AEDs for all topiramate-treated subjects with epilepsy are shown in the table below taken from Sponsor's Table 7 (SU vol 13.1 p.67).

**Baseline Characteristics
(All Topiramate-Treated Subjects with Epilepsy)**

	Topiramate (N=1,446)	
	No.	%
Background AED(s)*		
Carbamazepine	474	33
Phenobarbital	18	1
Phenytoin	173	12
Primidone	30	2
Valproic Acid	75	5
Carbamazepine/Valproic Acid	163	11
Phenobarbital/Carbamazepine	68	5
Phenobarbital/Carbamazepine/Valproic Acid	12	1
Phenobarbital/Phenytoin	38	2
Phenobarbital/Phenytoin/Carbamazepine	14	1
Phenobarbital/Phenytoin/Carbamazepine/Valproate	3	<1
Phenobarbital/Phenytoin/Primidone	5	<1
Phenobarbital/Phenytoin/Valproic Acid	4	<1
Phenytoin/Primidone/Carbamazepine	4	<1
Phenobarbital/Primidone/Carbamazepine	4	<1
Phenobarbital/Valproic Acid	19	1
Phenytoin/Carbamazepine	138	10
Phenytoin/Carbamazepine/Valproic Acid	27	2
Phenytoin/Primidone	21	2
Phenytoin/Primidone/Valproic Acid	3	<1
Phenytoin/Valproic Acid	61	4
Primidone/Carbamazepine	43	3
Primidone/Carbamazepine/Valproic Acid	5	<1
Primidone/Valproic Acid	5	<1
Primidone/Phenobarbital/Phenytoin/Carbamazepine	1	<1
Primidone/Phenobarbital/Carbamazepine/Valproate	1	<1
Other AEDs	39	3

5.1.3 EXTENT OF EXPOSURE (DOSE/DURATION)

At the pre-NDA meeting August 1994, the sponsor was advised by FDA of the minimal requirements for filing its NDA for a chronic drug in epilepsy. Generally stated the firm was advised to obtain exposures of 1000 patients in general and ~500 patients for over 6 months exposure within the dose range of interest. The sponsor has succeeded in generating this degree of exposure data as will be described below.

The following is the sponsor's table showing duration of exposure to topiramate, reflecting the total data base (both epilepsy and nonepilepsy

subjects) as of March 31, 1995, the cutoff date for the SU serious adverse events and deaths.

Sponsor's Table 12: Duration of Subject Exposure to Topiramate (N=1697)

Exposure	Number of Subjects Treated	Exposure	Number of Subjects Treated
0 - 6 months	956	4 - 5 years	32
6 months - 1 year	294	5 - 6 years	61
1 - 2 years	411	6 - 7 years	49
2 - 3 years	225	>7 years	3
3 - 4 years	55		

The following table is extracted from Sponsor's tabulation of exposure to topiramate by mean dose (attachment 3d, safety update p. 09 00246, volume 13.1)):

EXPOSURE TO TOPIRAMATE BY MEAN DOSE: ALL EPILEPSY PATIENTS

MEAN DOSE	NUMBER OF SUBJECTS
<200 MG	218
200-499	474
500-799	256
>800	498
TOTAL	1446

(A similar table showing all patients exposed to topiramate by mean dose has been requested of the sponsor and is outstanding.

The following page shows the Sponsor's Table 11a which tabulates the distribution of subjects receiving topiramate for various time periods until March 31, 1994, the cutoff for the NDA safety update. The table displays the duration of exposure by most frequent groups of doses received in the group of all epilepsy patients (N=1446).

**Sponsor's Table 11a: Distribution of Subjects by Duration of Therapy and Most Frequent Dosage
(All Topiramate-Treated Subjects with Epilepsy as of March 31, 1994)**

Duration of Therapy	No. of Subjects (N=1,446)	Topiramate Dosage (mg/day)			
		Most Frequent Dosage			
		<200	200-499	500-799	≥800
0-3 months	1,446	249	716	215	266
3-6 months	1,083	49	327	305	402
6 months - 1 year	845	26	191	207	421
1-2 years	616	11	126	142	337
2-3 years	244	4	43	61	136
3-4 years	176	2	32	44	98
4-5 years	119	2	20	28	69
>5 years	56	1	6	15	34

It can be seen that there were over 600 patients who received topiramate for 6 months to one year in the relevant dose range, and indeed, nearly 500 who received topiramate from 1-2 years in the range of interest.

5.2 SECONDARY SOURCES

No secondary source data is described.

5.2.1 Non-IND Studies

Besides the NDA, no other primary data were found.

5.2.2 POST-MARKETING EXPERIENCE

No postmarketing data are available since the drug has not been approved in any other countries as yet.

5.2.3 Literature

The sponsor was requested to submit to the NDA a literature section based on a thorough search of the world literature pertinent to topiramate. This is currently outstanding.

6.0 SUMMARY OF HUMAN PHARMACOKINETICS

The following is a very brief summary of topiramate pharmacokinetics data, which were reviewed and analyzed independently.

Summary

The sponsor submitted 19 studies of human pharmacokinetics and pharmacodynamics, and obtained population pharmacokinetics data from three of the controlled trials. In addition to the human studies, in vitro studies in human microsomes were conducted to identify cytochrome P450 isoforms involved in topiramate metabolism and to predict potential drug interactions.

ADME:

Topiramate has been found to be rapidly and well-absorbed after oral administration and not extensively metabolized. Six trace (<5% of the sample) metabolites have been identified, isolated and characterized. (Study MS-177). The metabolites are formed through glucuronidation, hydroxylation, hydrolysis and have been identified in plasma and urine.

Following 400 mg. multiple oral dose administration every 12 hours, peak plasma concentration of 27 µg/mL is reached in about 2 hours. There appears to be no effect of food on the bioavailability of topiramate.

Topiramate is poorly bound to human plasma proteins. Over the clinically relevant plasma concentration range of up to 33 µg/ml topiramate is generally about 17% plasma protein bound.

The mean elimination half-life of topiramate is approximately 21 hours.

Topiramate plasma C_{max} and AUC increase proportionally with dose over the 100-400 mg dose range. Oral plasma clearance is independent of dose. (Study MS210)

Renal excretion: The major route of elimination of topiramate is the kidney, with 80% excretion unchanged in 24 hours. Renal and total clearance of topiramate is reduced in renally-impaired patients (ClCr <60 mL/min) resulting in an increase in plasma elimination half-life. Topiramate is removed by hemodialysis. (Studies MS-A and MS-221) Clearance of topiramate is not affected by gender, age or race.

Moderate increases in plasma concentration of topiramate are seen in patients with hepatic insufficiency due to a decrease in clearance. (Study MS-209)

Drug Interactions:

Topiramate C/F increased 106.4% to 144.5% during combination therapy with phenytoin relative to monotherapy resulting in decreased steady plasma topiramate concentrations. A small decrease in phenytoin concentration occurs in some patients due to the addition of topiramate. (Study MS-215)

Topiramate oral plasma clearance and nonrenal clearance were higher (~2 to 3-fold) during concomitant carbamazepine therapy; topiramate renal clearance was unaffected. No significant effect of topiramate on total and unbound carbamazepine and carbamazepine epoxide were observed. (Study MS-216). Concomitant administration of topiramate to patients treated with phenytoin and/or carbamazepine appeared to have no significant effect on phenytoin or carbamazepine trough plasma concentrations. (Study YC)

When given as adjunctive therapy to phenobarbital or primidone, topiramate pharmacokinetics appeared to increase proportionately with dose. (Study YZW)

Topiramate pharmacokinetics are linear over 100-300mg q12h dose range when administered concomitantly with phenytoin or valproic acid. (Study MS YZL) Topiramate pharmacokinetics are linear over 100-600 mg q12h when given concomitantly with carbamazepine. (Study YZT)

Slight decreases in AUC of digoxin with concomitant topiramate are seen. (Study MS-219)

PK/PD and Population PK analyses

Topiramate clearance and volume of distribution were not affected by age and race. Gender had no effect on topiramate clearance, but volume of distribution was 50% lower in females. The effect of concomitant antiepileptic drugs on clearance was not significant. There was no correlation between the percent change in seizure rate with adjunctive therapy and trough topiramate concentration. Average plasma topiramate concentrations were higher in patients reporting CNS adverse experiences. (address this in the safety review) (Studies YD, YE and Y3)

7.0 EFFICACY FINDINGS

This section (7.0-7.6) is a joint Clinical-Statistical review of the Efficacy data presented by R.W. Johnson Pharmaceutical Research Institute.

The sponsor has submitted reports of the following six completed controlled trials designed to determine the efficacy of topiramate as an anti-epileptic drug in patients with partial onset epilepsy:

ADJUNCTIVE THERAPY:	STUDY # YD	(PBO/200 MG/400 MG/600 MG)
	STUDY # YE	(PBO/600 MG/800 MG/1000 MG)
	STUDY # Y1	(400 MG)
	STUDY # Y2	(600 MG)
	STUDY # Y3	(800 MG)

Out of these 6 studies, all were designed to evaluate topiramate for the treatment of refractory partial onset seizures. The first five listed were designed to evaluate topiramate as adjunctive therapy against a background of one or more antiepileptic medications. The sixth was an

The five adjunctive therapy trials were performed under a nearly identical protocol, with only slight variations in duration of the treatment period, and exploring different doses of topiramate. These will be discussed in individual detail.

7.1 STUDY YD

TITLE: A double-blind parallel comparison of three doses of topiramate (low to mid range) and placebo in refractory partial epilepsy

OBJECTIVE: To evaluate the comparative efficacy and safety of topiramate, 200 mg/ day, 400 mg/day and 600 mg/day and placebo as adjunctive therapy for patients with refractory partial epilepsy on a maximum of two concomitant anticonvulsants.

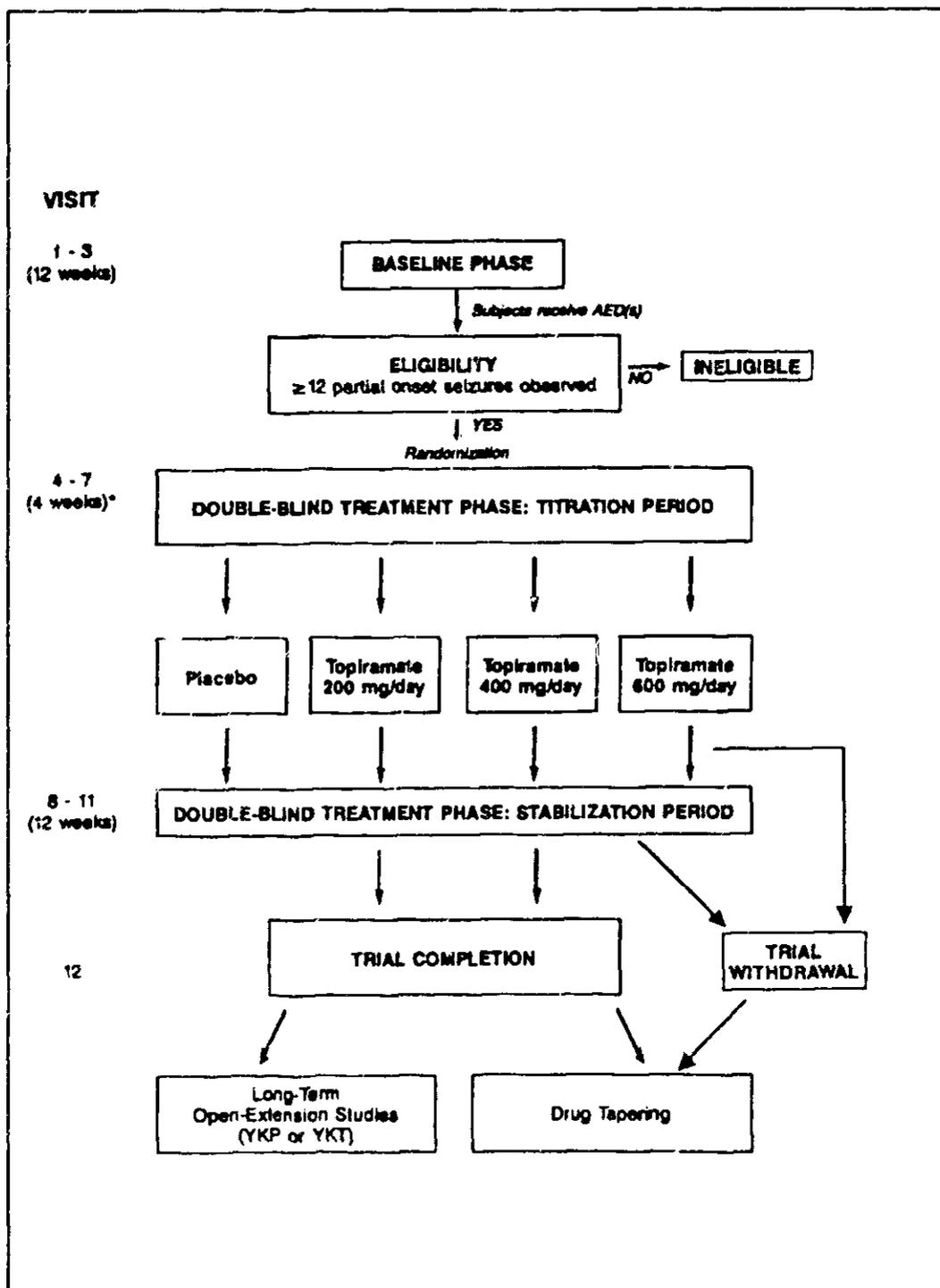
PROTOCOL:

STUDY DESIGN: a multicenter, outpatient, parallel, double-blind, placebo-controlled study, shown in the schematic on the following page.

Study Schedule:The study consists of three parts: Baseline, Double-blind Titration and Double-blind Stabilization (maintenance).

- The Baseline phase lasts approximately 12 weeks.
- Following the completion of the baseline phase, patients entered the Double-blind Phase, titration period. The titration schedule was planned to consist of four one-week intervals with protocol-specified adjustments to this schedule that allowed for subjects unable to tolerate the titration schedule as planned to titrate at a slower pace if necessary.¹ If a subject was unable to tolerate the titration schedule, the investigator would be able to invoke any of the following measures: increase the dosage of study medication by only one tablet (100 mg) of topiramate or one tablet of placebo weekly, increase the length of each scheduled titration interval from one to two weeks, or discontinue the titration period and begin the stabilization period after two weeks of a given dosing regimen.
- During the stabilization period, the subjects were to be followed on their established regimen for approximately 12 weeks.

¹The initial dose administered to subjects during the first titration interval was either 100 mg topiramate or one tablet of placebo every morning. During the second titration interval, subjects were administered either 100 mg topiramate b.i.d. or one tablet of placebo b.i.d. Subsequently, the dose increment for each remaining titration interval was either 100 mg topiramate b.i.d. or one tablet of placebo b.i.d. until the subject reached the assigned maximum dosage (or the maximum tolerated dosage, if less) and the titration period was completed.



Enrollment

- Approximately 180 patients with refractory partial epilepsy, maintained on a maximum of two of the following anticonvulsants: carbamazepine, phenytoin, valproic acid, phenobarbital and/or primidone.

Inclusion Criteria

- Eighteen to 65 years old, inclusive, and, if female, postmenopausal or surgically rendered incapable of having children.
- Unequivocal history of partial seizures with or without secondary generalized seizures with either clinical or electroencephalographic (EEG) evidence of localized cerebral discharge. An EEG tracing demonstrating a lateralized epileptiform pattern consistent with a diagnosis of partial epilepsy was required within five years before study entry. For entry into the double-blind phase, subjects were required to have at least 12 partial seizures during the 12-week baseline phase while maintained at therapeutic AED plasma concentrations. During the 12-week baseline phase of the study, the longest allowable seizure-free interval was three weeks and only one such seizure-free interval was permitted.
- Steady state trough plasma concentrations of one or two of the following AED(s) within a restricted range:

Concomitant AED	Trough Plasma Concentration Range ($\mu\text{g}/\text{mL}$)
Carbamazepine	4-14
Phenytoin	8-25
Phenobarbital	15-40
Primidone	5-15
Valproic Acid	40-120

- Good physical health. Note: mild to moderate hypertension was allowed if well-controlled with a stabilized regimen of a β -adrenergic blocking agent (β -blocker) or angiotensin converting enzyme inhibitor.
 - CAT scan or MRI within the preceding two years to exclude potentially progressive neurologic diseases.
-

Exclusion Criteria

- Treatable cause of seizures or progressive neurologic disorder
 - Documented history of status epilepticus while complying with appropriate therapy
 - Significant acute or chronic confounding physical disease (e.g., malignancy with metastatic potential, or a history or other serious medical diseases, including cardiovascular, hepatic, renal, gastrointestinal, metabolic, or endocrine diseases)
 - History of alcohol or drug abuse within one year before admission
 - History of a serious psychiatric disorder, symptoms of schizophrenia, any psychotic symptomatology, or history of suicide attempt
 - History of poor compliance with therapy
 - Known allergy or hypersensitivity to carbonic anhydrase inhibitors or sulfonamides, or those in whom carbonic anhydrase inhibitors were contraindicated
 - Treatment with an experimental drug or use of an experimental device within 60 days before admission
 - Abnormal baseline laboratory parameters except for the following: liver function tests of serum glutamate-oxaloacetate transaminase (SGOT), serum glutamate-pyruvate transaminase (SGPT), and alkaline phosphatase which could be elevated to a level of twice the upper limit of normal; and hematologic parameters including WBC count >3000 cells/mm³, neutrophil count $>1,500$ cells/mm³, hematocrit $>37\%$, and platelet count $>150,000$ cells/mm³
 - History of nephrolithiasis
 - Inability to take medication or maintain a seizure calendar, independently or with assistance
-

No anti-anxiety agents, antidepressants, neuroleptics or sedatives (other than chloral hydrate) are permitted. No centrally acting drugs (including antihistamines) were to be permitted.

Efficacy

The main measure of efficacy is seizure frequency. "Each patient will have a weekly seizure frequency computed for baseline and for dosing periods. Computations will assess whether at least 50% of patients will have achieved a 50% reduction in seizure rates. Comparisons among the 4 treatment groups will be done by computing change from baseline seizure rates and employing appropriate statistical tests.

Efficacy will also be assessed by analyzing the severity of seizures, duration of seizure-free intervals, and physician and patient rating scales."

STATISTICAL METHODS

Analyses Planned

Protocol amendment (January 4, 1988 (before the trial began)), provides statistical information regarding planned analyses and the basis for sample size estimates. Pairwise comparisons of the changes in seizure rate from baseline were to be made between each treatment group and placebo using two-way analysis of variance. Additionally, analyses of the severity of seizures and physician and subject global ratings of efficacy were planned, as was analysis of responders (subjects with a 50% or greater reduction from baseline in seizure rate). The analysis of the duration of the seizure-free intervals was also planned.

A sample size of 45 subjects per treatment group was estimated to provide 90% power to detect a between-group difference in seizure rate change of about six seizures per month, assuming a standard deviation of 10 seizures per month for the seizure rate change in each treatment group.

Before initiation of the study, an administrative interim analysis was scheduled to be performed when data were available from one-third of the planned sample size. The interim analysis was not to be used to make decisions concerning the design or conduct of this study, but was to be used as an aid for decisions concerning future studies.

STUDY CONDUCT

ENROLLMENT

A total of 181 subjects from 17 centers qualified for randomized assignment to a treatment group and then received study medication. One hundred thirty-six subjects received topiramate and 45 subjects received placebo. Of the 136 topiramate-treated subjects, 45 received 200 mg/day, 45 received 400 mg/day, and 46 received 600 mg/day.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Of the 181 randomized subjects, 143 (79%) were men and 38 (21%) were women. One hundred fifty-nine (88%) subjects were white, 21 (12%) subjects were black, and one (1%) subject was hispanic. The mean age was 36.9 years, the mean weight was 173.9 pounds, and the mean height was 68.4 inches. All subjects were required to have documented refractory partial epilepsy. Most of the subjects (75%) were receiving carbamazepine either alone or in combination with valproic acid, phenytoin, primidone, or phenobarbital. The median seizure rate at baseline ranged from 10.0 to 11.5 across the treatment groups. The demographic and baseline characteristics for all randomized subjects by treatment group are summarized in the table below and were comparable among the treatment groups.

**Table adapted from Sponsor's Table 6a/6b:
Demographic and Baseline Characteristics:
Age, Gender, Race, Baseline Average Monthly Seizure Rate,
Background AEDs, and Seizure Type
(All Randomized Subjects; Protocol YD)**

Attribute	Placebo (N=45)	Topiramate			Total (N=181)
		200 mg/day (N=45)	400 mg/day (N=45)	600 mg/day (N=46)	
Gender					
Male	36	80	29	64	39
Female	9	20	16	36	6
Race					
White	41	91	37	82	41
Black	4	9	7	16	4

Background AED(s)					
Carbamazepine	13	28	9	20	11
Phenytoin	2	4	6	13	1
Primidone	1	2	0	0	3
Phenobarbital	0	0	0	0	1
Carbamazepine/valproic acid	11	24	10	22	7
Carbamazepine/phenytoin	9	20	5	11	8
Carbamazepine/primidone	1	2	5	11	2
	2	4	4	9	2
Carbamazepine/phenobarbital	1	2	3	7	4
Phenytoin/valproic acid	2	4	1	2	2
Phenytoin/primidone	2	4	1	2	2
Phenytoin/phenobarbital	1	2	1	2	2
Valproic acid/phenobarbital	0	0	0	0	0
Valproic acid/primidone	45	100	45	100	45
Total					
Seizure Type					
Simple Partial	20	44	16	40	21
Complex Partial	39	87	42	93	43
Secondarily Generalized	30	67	27	60	26
Generalized Tonic-Clonic	1	2	0	0	1
Total	45		45		45
Baseline Average Monthly Seizure Rate					

DISCONTINUATION/COMPLETION INFORMATION:

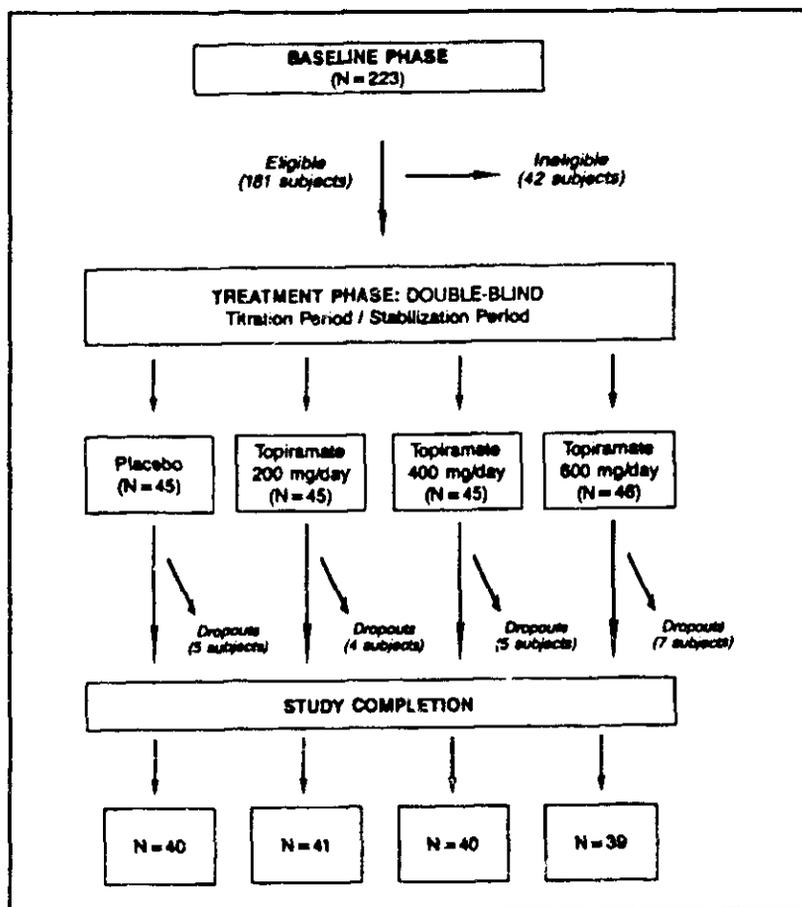
One-hundred sixty (88%) of 181 subjects completed the trial. Fifteen (8%) subjects discontinued from the trial because of adverse events. A summary of the reasons for discontinuation are seen in the Sponsor's Table 4.

Sponsor's Table 4: Summary of Discontinuation/Completion Information: Double-Blind Phase (All Randomized Subjects; Protocol YD)

Reason	Placebo (N=45)		Topiramate						Total (N=181)	
	N	%	200 mg/day (N=45)		400 mg/day (N=45)		600 mg/day (N=46)		N	%
Study completed	40	89	41	91	40	89	39	85	160	88
Study discontinued										
Limiting adverse events	3	7	2*	4	4	9	8	13	15	8
Subject's choice	1	2	1	2	0	0	0	0	2	1
Significant protocol violation	0	0	0	0	1	2	0	0	1	1
Administrative/other	1	2	1	2	0	0	1	2	3	2
Total discontinued	5	11	4	9	5	11	7	15	21	12

* One subject discontinued from the study after one 100-mg dose of topiramate because of increased seizures.

Information on completion and discontinuation for the double-blind phase of the trial is presented in Sponsor's Figure (below) and Sponsor's Table 4 on the previous page.



Forty-one (91%) subjects in the topiramate 200 mg/day group, 40 (89%) in the topiramate 400 mg/day group, 39 (85%) in the topiramate 600 mg/day group, and 40 (89%) in the placebo group completed the trial. Twenty-one (12%) of 181 subjects withdrew from the trial prematurely, including 15 (8%) because of limiting adverse events. Of the 15 subjects who withdrew prematurely because of one or more adverse events, three were in the placebo group, two were in the topiramate 200 mg/day group, four were in the topiramate 400 mg/day group, and six were in the topiramate 600 mg/day group.

TITRATION/DOSAGE

Dosage titration to the assigned dosage fell short of expected because of adverse events over the entire double-blind treatment phase (titration and stabilization periods) and resulted in median by-subject average dosages of 193.8 mg/day, 366.9 mg/day, and 518.6 mg/day in the topiramate 200 mg/day, 400 mg/day, and 600 mg/day groups, respectively. A summary of the mean and median dosages for the double-blind phase is presented by treatment group in Sponsor's Table 9 below.

**Table 9: Summary of the Average Dosage^a: Double-Blind Phase
(All Randomized Subjects; Protocol YD)**

Treatment	Mean	Standard Deviation	Median
Placebo ^b (N=45)	4.9	0.98	5.3
Topiramate			
200 mg/day (N=45)	187.6	23.11	193.8
400 mg/day (N=45)	334.4	76.38	366.9
600 mg/day (N=48)	454.7	122.54	518.6

^a Subject's average over the entire double-blind phase

^b Placebo dosages are given as number of tablets.

The summary of the average dosage for the stabilization period only is presented by treatment group in Sponsor's Table 10. The median average dosages during the stabilization period coincided with the target daily dosages (200 mg/day, 400 mg/day, and 600 mg/day) for the three topiramate treatment groups.

**Table 10: Summary of the Average Dosage^a: Stabilization Period
(All Randomized Subjects Who Entered the Stabilization Period; Protocol YD)**

Treatment	Mean	Standard Deviation	Median
Placebo ^b (N=42)	5.9	0.41	5.0
Topiramate			
200 mg/day (N=42)	200.2	1.23	200.0
400 mg/day (N=40)	390.6	40.15	400.0
600 mg/day (N=41)	556.0	99.53	600.0

^a Subject's average over the stabilization period.

^b Placebo dosages are given as number of tablets; the target was 6 tablets/day.

Clearly the 600 mg/day group had the most difficulty in achieving their targeted dosages. If one were to look at patients who failed to

approximate their targeted dose during the stabilization (maintenance) phase one would find that of the 46 subjects randomized to 600 mg, a total of 34 (74%) were treated with mean doses approximating 600 mg for the last half or all of the stabilization period. (7 patients received maintenance doses ranging from 100 to 500 mg) and 5 dropped out prior to stabilization). Only two patients in the 400 mg group were treated with considerably less than the targeted dose, and all patients in the placebo and 200 mg group were treated as randomized.

**TABLE: MEAN STABILIZATION DOSE BY INVESTIGATOR AND PATIENT
FOR PATIENTS NOT ACHIEVING TARGETED DOSE (STUDY YD)**

CENTER	PT #	STUDY DRUG (TARGET DOSE)	AVERAGE DOSE	MAINTENANCE DOSE*
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The duration of the double-blind phase as stated in the protocol was 112 days. The median duration of double-blind therapy was 119 days for the topiramate 200 mg/day group, 114 days for the topiramate 400 mg/day group, and 113 days for the topiramate 600 mg/day group. Subjects in the placebo group received a median of 113 days of double-blind therapy.

Protocol Violations

One subject (24/21) was withdrawn from the trial because of a significant protocol violation. That subject was in the topiramate 400 mg/day group and was withdrawn prematurely because of excessive alcohol consumption during the trial. No other significant protocol variations were identified.

The use of medications with anticonvulsant properties in addition to those allowed and on a prn basis during this trial were reviewed and found to be negligible.

Plasma Levels

Mean plasma concentrations of topiramate for the entire double-blind phase in subjects randomized to target dosages of 200 mg/day, 400 mg/day, and 600 mg/day were obtained per protocol and were 1.4 ± 0.63 $\mu\text{g/mL}$, 2.4 ± 1.31 $\mu\text{g/mL}$, and 3.0 ± 1.35 $\mu\text{g/mL}$, respectively. Sponsor admits that the relationship between dosage and plasma concentration is impossible to interpret given the variability in the duration of the titration period and the fact that many subjects did not achieve (or maintain) the target assigned dosage level.

Efficacy Data Collection:

Counting seizures

Patients (or caretakers) recorded the date, time, and description of seizures in their diaries. The protocol stated that the duration of each seizure should be recorded in the subject's diary; however, because of the difficulty associated with subjects' timing the duration of their seizures, these data were not collected consistently and were not analyzed.

The investigator classified each seizure type as simple partial (SP), complex partial (CP) or partial evolving to secondarily generalized (PE) based on the description obtained.

As in most epilepsy clinical trials some clusters or flurries of seizures can often defy the observer's ability to count seizures accurately. There are often artificial paradigms developed in advance of the study so that a consistent approach is used throughout the study. In this study patients were told that clusters should be counted either as one (1) seizure or as a group of seizures (with the best estimate given). In any case, these groups would be identified as "CL" for clusters. Whatever was chosen by the patient was to be used consistently throughout the study.

In general the convention of counting individual seizures was used more than the alternative, however, in a few patients, it appears that a consistent approach was not, indeed, used. However, the number of patients who violated this provision was small and therefore did not likely create a significant inaccuracy. While the use of the convention of listing of a cluster as 1 seizure (when only one seizure was reported on a given day as 1 CL) was used by only 5 patients, it was only used during the baseline period. This occurred in 2 placebo patients and 3

patients in the 200 mg group. Therefore, there did not appear to be a systematic bias in favor of the drug.

Global Evaluations and Assessments

Global evaluations and assessments were performed by the investigators and patients at the last visit of the double-blind phase. The investigators global evaluation of improvement relative to baseline for each patient was recorded as worse (1), none (2), minimal (3), moderate (4), or marked (5). Similarly, the patient's overall impression of medication was recorded as poor (1), fair (2), good (3), or excellent (4).

Efficacy Criteria: Analysis

Primary

Percent Reduction In Seizure Rate

The primary efficacy variable was the percent reduction in the average seizure rate from baseline (average during the last 12 pretreatment weeks for a given subject) to the double-blind phase (average during the double-blind phase for a given subject). It was defined as $100(B-D)/B$, where B represents the baseline seizure rate and D represents the double-blind phase seizure rate.

The average monthly (28-day) seizure rates were computed for the baseline phase and the double-blind phase. The average monthly seizure rate for a time period was calculated as (the total number of seizures reported during the period divided by the number of days in the period) multiplied by 28 days. The baseline seizure rate was calculated as the average monthly seizure count for the last 12 pretreatment weeks. Thus, for a subject whose baseline was restarted or extended, usually due to a change in background AED dosage, only data from the final 12 weeks were used. The double-blind phase seizure rate was defined for each subject as the average monthly seizure rate over the portion of the double-blind phase completed by that subject.

Secondary

Treatment Responders

Subjects with a 50% or greater reduction from their baseline seizure rates were considered to be "treatment responders."

Global Evaluations and Assessments

The global evaluations and assessments performed by investigators and subjects at the end of double-blind therapy relative to baseline are tabulated in this report as part of the efficacy evaluations.

Generalized Seizures

This secondary efficacy variable was analyzed in a manner analogous to partial seizures by percent seizure reduction from baseline based only on generalized seizures. The analyses of generalized seizures included subjects who had generalized seizures during the baseline phase or double-blind phase.

Trial YD: Sponsor's Results

Efficacy analyses were conducted (i) using all double-blind phase data (both titration period and stabilization period); and (ii) using only stabilization period data. These analyses employed identical methods; therefore, the following description will refer to the double-blind phase.

Primary Variable: Percent reduction in Seizure Rate

To assess efficacy of the three topiramate dosages, pairwise comparisons to placebo were made using three separate two-factor (treatment, center, and treatment-by-center interaction) analyses of variance on ranks. All randomized patients were used in the efficacy analyses.

The sponsor performed an interim analysis of efficacy data from 71 patients. The interim analysis was not used to make decisions concerning the design or conduct of the trial, but as an aid to decisions concerning future trials.

Medians and ranges for the primary efficacy variable as well as statistical results for pairwise treatment comparisons with placebo are shown below. For the 21 patients who were discontinued early, seizure rates were calculated based on the actual time in the trial.

Topiramate 400 mg and topiramate 600 mg were statistically superior ($p < 0.05$) to placebo in reducing the average monthly seizure rate compared to baseline. The topiramate 200 mg vs placebo comparison approached statistical significance ($p = 0.051$) in favor of topiramate. Additionally, the topiramate 200 mg and 400 mg comparisons with placebo yielded statistically significant treatment-by-center interactions ($p < 0.10$).

Results of the Primary Efficacy Evaluation: Percent Reduction in Average Monthly Seizure Rate for the Double-Blind Phase (All Randomized Subjects; Protocol YD)

Treatment	Percent Reduction		P-value ^a
	Median	Range ^a	

Placebo (N=45)	13.1	(-87.7, 97.9)	
Topiramate			
200 mg/day (N=45)	29.6	(-186.5, 86.7)	0.051*
400 mg/day (N=45)	47.8	(-107.5, 100.0)	0.007*
600 mg/day (N=46)	44.7	(-58.7, 100.0)	<0.001

* Negative numbers denote an increase in seizure rate.

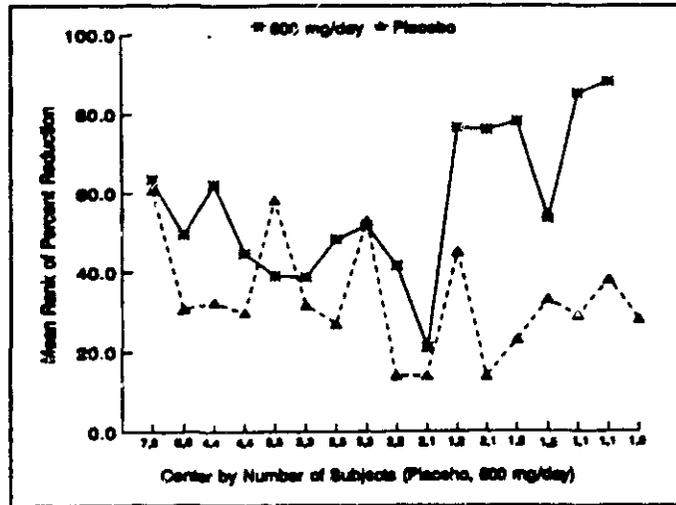
* Topiramate vs. placebo; two-factor ANOVA on ranks with type III sums of squares.

* Statistically significant treatment-by-center interaction ($p \leq 0.10$).

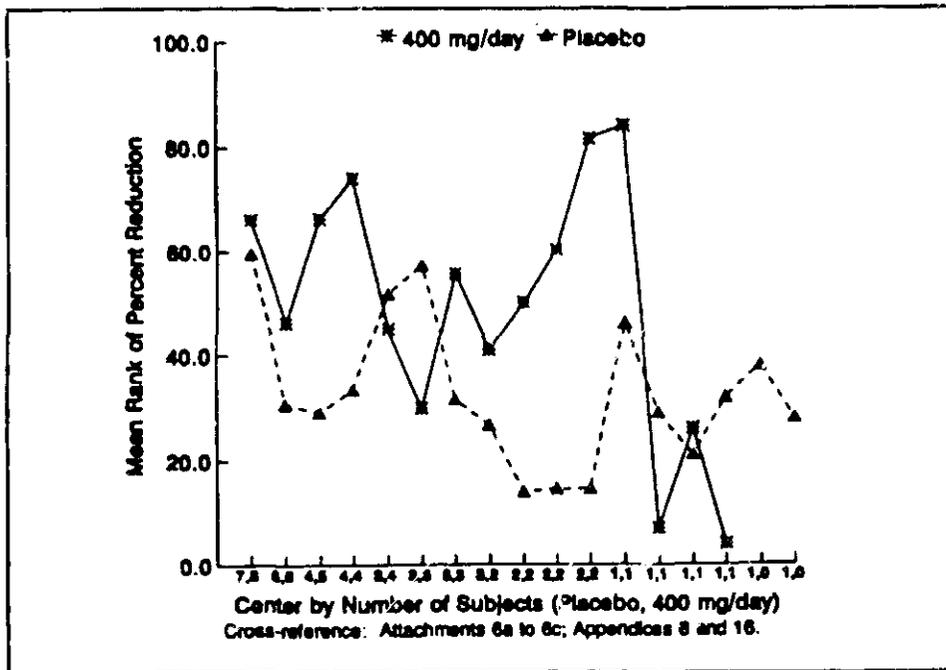
The sponsor investigated the consistency of results for the primary efficacy variable across centers. For a given comparison between topiramate and placebo, patients were ranked and the mean ranks calculated for each center and treatment group. The results are plotted in Figure 1 (topiramate 600 mg vs placebo), Figure 2 (topiramate 400 mg vs placebo) and Figure 3 (topiramate 200 mg vs placebo).

Figure 1 shows that the mean rank of the percent seizure rate reduction was larger for topiramate 600 mg compared with placebo for 14 of 16 centers (87.5%). (At one center, no patients received topiramate 600 mg/day; no treatment comparison was feasible.)

**FIGURE 1: MEAN RANK OF PERCENT SEIZURE RATE REDUCTION BY CENTER
TOPIRAMATE 600 MG/DAY COMPARED WITH PLACEBO**



From Figure 2, results favored topiramate 400 mg/day over placebo for 11 of 15 centers (73.3%). (At two centers, no patients received topiramate 400 mg/day.)



**FIGURE 2: MEAN RANK OF PERCENT SEIZURE RATE REDUCTION BY CENTER
TOPIRAMATE 400 MG/DAY COMPARED WITH PLACEBO**

From Figure 3, results favored topiramate 200 mg/day over placebo for 9 of 16 centers (56.3%). (At one center, no patients received topiramate 200 mg/day.)

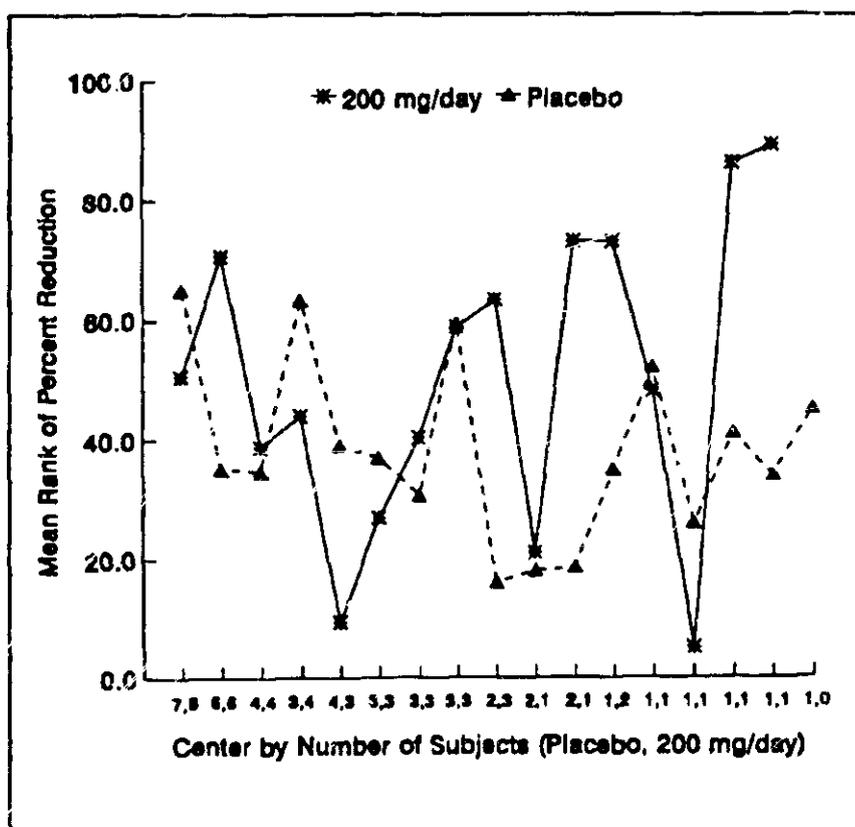


FIGURE 3: MEAN RANK OF THE PERCENT SEIZURE RATE REDUCTION BY CENTER (TOPIRAMATE 200 MG/DAY COMPARED WITH PLACEBO)

Dose-response analyses of seizure percent reduction were performed using the Jonckheere-Terpstra test, with and without the placebo treatment group. There was a statistically significant dose-response relationship: $p < 0.001$ with placebo, $p = 0.023$ without placebo.

Secondary variables

Responder Rate

A patient was defined as a treatment responder if the percent seizure rate reduction during the double-blind phase from baseline was greater than or equal to 50%. The percentage of responders in each topiramate treatment group were compared in a pairwise fashion with placebo using the Cochran-Mantel-Haenszel method stratified by center. A statistically greater percentage of patients in the topiramate 400 mg (47%) and topiramate 600 mg (46%) treatment groups were treatment responders compared with the placebo group (18%).

P-values were 0.013 and 0.027, respectively. The result for the topiramate 200 mg (27% response rate) vs placebo comparison was not statistically significant ($p=0.620$).

TREATMENT RESPONDERS FOR THE DOUBLE-BLIND PHASE
(ALL RANDOMIZED SUBJECTS; PROTOCOL YD)

Treatment	Treatment Responders ^a		P-value ^b
	N	%	
Placebo (N=45)	8	18	
Topiramate			
200 mg/day (N=45)	12	27	0.620
400 mg/day (N=45)	21	47	0.013
600 mg/day (N=46)	21	46	0.027

^a Subjects with 50% or greater seizure rate reduction from baseline.

^b Topiramate vs. placebo; Cochran-Mantel-Haenszel test stratified by investigator.

Dose-response analyses of percent responders were performed using the Cochran-Armitage test. There was a statistically significant relationship between topiramate dose and response: $p=0.001$ with the placebo treatment group and $p=0.042$ without placebo.

Investigator's Global Evaluation

The investigator's global evaluation of improvement at the end of the double-blind phase compared with baseline (5-point scale: 1=worse, 2=none, 3=minimal, 4=moderate, 5=marked) were analyzed by Wilcoxon rank-sum tests stratified by center. All dosages of topiramate were statistically superior to placebo. P-values for the topiramate 200 mg (mean score 3.3), 400 mg (3.8) and 600 mg (3.6) vs placebo (2.7)

comparisons were 0.004, <0.001 and <0.001, respectively.

Refer to table below.

**INVESTIGATOR'S GLOBAL EVALUATION OF IMPROVEMENT AT THE END
OF THE DOUBLE-BLIND PHASE COMPARED WITH BASELINE
(ALL RANDOMIZED SUBJECTS; PROTOCOL YD)**

Rating	Topiramate							
	Placebo (N=45)		200 mg/day (N=45)		400 mg/day (N=44) ^a		600 mg/day (N=46)	
	N	%	N	%	N	%	N	%
Worse (1)	0	0	1	2	1	2	1	2
None (2)	26	58	8	18	8	18	7	15
Minimal (3)	8	18	16	36	4	9	10	22
Moderate (4)	10	22	15	33	19	43	21	46
Marked (5)	1	2	5	11	12	27	7	15
Mean	2.7		3.3		3.8		3.6	
P-value ^b			0.004		<0.001		<0.001	

^a One subject was not assessed for this efficacy variable at the final visit.

^b Topiramate vs. placebo; Wilcoxon rank sum test stratified by investigator.

Patient's Overall Assessment

The patient's overall assessment of medication at the end of the double-blind phase compared with baseline (4-point scale: 1=poor, 2=fair, 3=good, 4=excellent) were analyzed by Wilcoxon rank-sum tests stratified by center. The patient's overall assessment of medication was statistically superior for topimax 200 mg vs placebo (p=0.030) and topimax 400 mg vs placebo (p=0.007). The 600 vs placebo comparison was marginally significant at p=0.053. Mean scores were 2.6 for the topiramate 200 mg treatment group, 2.8 for the topiramate 400 mg treatment group, 2.6 for the topiramate 600 mg treatment group and 2.2 for the placebo group.

**SUBJECT'S OVERALL ASSESSMENT OF MEDICATION
AT THE END OF THE DOUBLE-BLIND PHASE COMPARED WITH BASELINE
(ALL RANDOMIZED SUBJECTS; PROTOCOL YD)**

Rating	Topiramate							
	Placebo (N=45)		200 mg/day (N=44) ^a		400 mg/day (N=43) ^a		600 mg/day (N=45) ^a	
	N	%	N	%	N	%	N	%
Poor (1)	13	29	4	9	5	12	6	13
Fair (2)	15	33	12	27	10	23	14	31
Good (3)	13	29	24	55	18	37	17	38
Excellent (4)	4	9	4	9	12	28	8	18
Mean	2.2		2.5		2.8		2.8	
P-value ^b			0.030		0.007		0.053 ^c	

- ^a One subject in the 200 mg/day group, two subjects in the 400 mg/day group, and one subject in the 600 mg/day group did not assess this efficacy variable at the final visit.
- ^b Topiramate vs. placebo; Wilcoxon rank sum test stratified by investigator.
- ^c When analysis was performed using only data from subjects who entered the stabilization period, p=0.022.

Plasma concentrations of concomitant antiepileptic drugs

The sponsor investigated changes in plasma concentrations of concomitant antiepileptic drugs from the baseline phase to the double-blind phase. The analysis used a one-way ANOVA to compare topiramate (all dosages combined) with placebo with respect to the mean change from baseline.

Plasma concentrations of carbamazepine, phenytoin, valproic acid, phenobarbital and primidone were comparable ($p \geq 0.268$) between topiramate- and placebo-treated patients. Thus the statistically significant reduction in seizure rate observed with topiramate could not be attributed to higher concentrations of any of the concomitant antiepileptic drugs compared to concentrations in the placebo group.

Trial YD: FDA Statistical Reviewer's Analysis

The sponsor submitted efficacy data on diskette to the Agency in the form of three datasets: (1) patient demographics, (2) daily seizure

counts for each patient by seizure type, and (3) efficacy variables (including seizure counts and rates) derived from the raw seizure data in dataset 2. The derived variables in dataset 3 formed the basis of the NDA submission.

This reviewer attempted to verify the seizure counts and rates in dataset 3. Using the raw seizure data in dataset 2, this reviewer calculated "revised" seizure counts (rates). In Trial YD, eight of 181 randomized patients had revised seizure counts during the baseline or double-blind phases (but not both) that disagreed with sponsor-derived counts (dataset 3). According to the sponsor, the start and end dates for the different trial phases for some patients were misspecified. These errors resulted in the improper inclusion or exclusion of seizures during certain trial phases. Seven of the discrepancies were associated with the baseline phase, prior to randomization. (Twenty-three (23) of 190 randomized patients in Trial YE had revised seizure counts that disagreed with sponsor-derived counts during the baseline and/or double-blind phases. These discrepancies are described in greater detail in the discussion of YE.)

The sponsor also scrutinized the raw seizure data (dataset 2) in the two trials. No errors were discovered in Trial YD. (Four patients in YE had incorrect raw seizure data. Zero counts were erroneously assigned for certain seizure types. These discrepancies are described in greater detail in the discussion of YE.)

Use of the revised data resulted in small changes in the sponsor's percent seizure rate reduction for some patients. These changes sometimes produced small changes in the summary measures.

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**Trial YD: Seizure Percent Reduction From Baseline
Revised Rates**

	Seizure Percent Reduction from Baseline	
	Median	Range
Placebo (n=45)	11.6	(-90.0, 97.9)
Topiramate		
200 mg/day (n=45)	27.2	(-180.0, 88.7)
400 mg/day (n=45)	47.5	(-107.5, 100.0)
600 mg/day (n=46)	44.7	(-90.0, 97.9)

(Changes in treatment means were more pronounced than changes in medians using the revised data. However, the mean is less relevant than the median as a summary measure because the data were not normally distributed.)

This reviewer used the sponsor's statistical model -- two-factor (treatment, center and treatment-by-center interaction) Analysis of Variance (ANOVA), for the analysis of the primary efficacy variable using the ranks of the revised data. (Nonparametric analyses were indicated because the distributions of the response variable were highly skewed towards negative values for the topiramate 200 mg and 400 mg treatment groups ($p < 0.01$ for both), and slightly skewed towards negative values for topiramate 600 mg ($p = 0.06$.) Initially, an F-test comparing all four treatment groups was conducted. Because the F-test was statistically significant ($p < 0.01$), three pairwise comparisons between each active treatment group and placebo were conducted using a family-wise type I error rate $\alpha = 0.05$ and a Bonferroni adjustment for each comparison with placebo at $\alpha = 0.05/3 = 0.0167$. The topiramate 400 mg and 600 mg treatment groups were statistically superior to placebo ($p = 0.009$ and $p = 0.0003$). The topiramate 200 mg treatment group was not statistically superior to placebo ($p = 0.080$). This last result was less favorable for topiramate 200 mg compared to the sponsor's result ($p = 0.051$).

Two patients did not have 12 seizures during the baseline as required by protocol: Patient 1404 had 3 seizures during baseline, and patient 2405 had 10 seizures during baseline. Both patients received topiramate 200

mg, and experienced -75.0 and -12.5 (revised) percent seizure rate reductions.

TRIAL YD: P-VALUES FOR VARIOUS TREATMENT COMPARISONS

Treatment comparison	P-value ^a	
	Revised Data	Sponsor's data
All treatment groups	0.0004	0.0002
topiramate 200 mg vs placebo	0.0796	0.0502
topiramate 400 mg vs placebo	0.0092	0.0066
topiramate 600 mg vs placebo	0.0003	0.0004

^aTopiramate vs placebo; two-factor ANOVA on ranks with type III sums of squares

Use of the revised data did not change the number of centers favoring topiramate over placebo for any pairwise comparison of active treatment groups with placebo. However, use of the revised data did remove the significant treatment-by-center interactions obtained by the sponsor for the topiramate 200 mg vs placebo and topiramate 400 mg vs placebo comparisons ($p > 0.10$).

Comments:

This trial has established the efficacy of topiramate as adjunctive medication in the treatment of partial onset seizures in two of the dosage groups studied, 400 mg/day and 600 mg/day. During the maintenance phase of the study patients achieved doses approximating the target (means of 391 mg in the 400 mg/day group and 556 in the 600 mg/day group). These conclusions were strengthened by similar results for the analysis of treatment responders as a secondary efficacy variable.

7.2 STUDY YE

TITLE: Double-blind, parallel comparison of three doses of topiramate (600 mg, 800 mg, and 1000 mg) and placebo in refractory partial epilepsy.

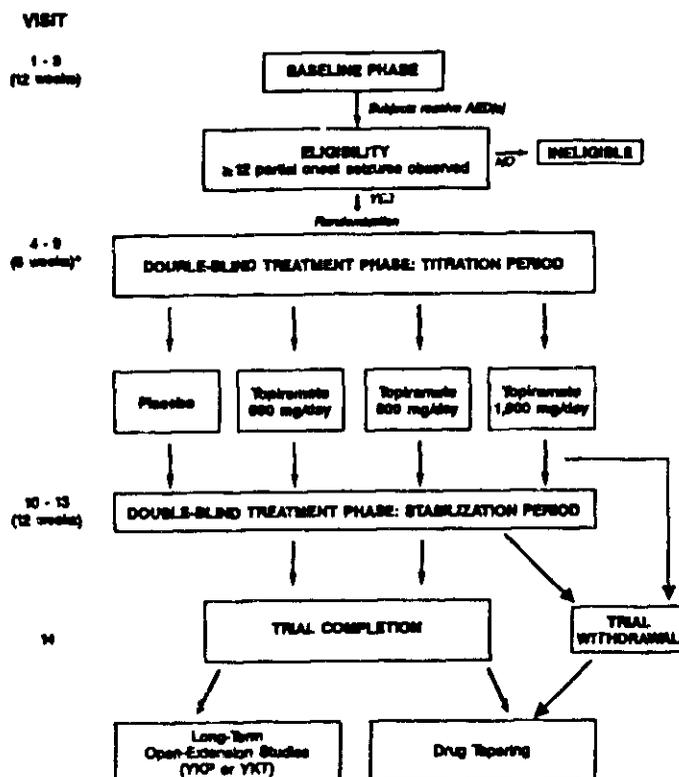
OBJECTIVE to evaluate the efficacy of mid to high dose topiramate as adjunctive therapy in subjects with refractory partial onset seizure.

PROTOCOL

STUDY DESIGN: multicenter, randomized, placebo-controlled, double-blind, parallel-group trial evaluating three oral doses of topiramate* (600 mg/day, 800 mg/day, and 1,000 mg/day) as adjunctive therapy in subjects who had refractory partial seizures

The study schematic for YE is shown below in Sponsor's Figure 1.

Sponsor's Figure 1: Study YE



* If a subject was unable to tolerate the titration schedule, the investigator could do any of the following: reduce the titration increments from 500 mg of topiramate (or two placebo tablets) per day to 100 mg of topiramate (or one placebo tablet) per day, increase the titration interval from one to two weeks, or lengthen the stabilization period after two weeks of a place during titration.

STUDY SCHEDULE

The trial consists of four phases: screening, baseline, double-blind, and tapering. Sponsor's Table 1 below is a tabular summary of the study schedule.

Table 1: Overview of Trial Phases

Study Interval	Planned Duration	Therapy	Purpose
Screening Phase	Prior to baseline phase	Recent history of therapy with one or two standard AED(s) ^a	Determine eligibility and stabilize on background AED(s)
Baseline Phase	12 weeks	Standard AED(s) ^a	Maintain on background AED(s) and further assess eligibility
Double-Blind Phase			
Titration Period	6 weeks (2 to 12 weeks) ^b	Background AED(s) and topiramate or placebo increased at weekly intervals to the assigned (or maximum tolerated) dosage.	Achieve the assigned (or maximum tolerated) dosage of topiramate and conduct efficacy and safety observations
Patients who did not reach their assigned dosage levels during titration were maintained at their maximum tolerated dosage. Stabilization Period	12 weeks	Maintenance on the assigned (or maximum tolerated, if less) dosage of study medication ^c	Efficacy and safety observations
Tapering Phase ^d	Variable	Decreasing dosages of topiramate	Safe withdrawal of topiramate therapy

- ^a Standard AEDs included phenytoin, carbamazepine, phenobarbital, or primidone. Valproic acid was also permitted, but only in combination with one of the above AEDs
- ^b The planned titration period was six weeks. If a subject was unable to tolerate the titration schedule, the investigator could do any of the following: reduce the titration increments from 200 mg of topiramate (or two placebo tablets) per day to 100 mg of topiramate (or one placebo tablet per day), increase the titration interval from one to two weeks, or begin the stabilization period after two weeks of a given dosing regimen.
- ^c Assigned daily dosages of topiramate during the trial were 600 mg/day, 800 mg/day, or 1,000 mg/day.
- ^d All subjects who completed the stabilization period of this trial were permitted to enter one of two open-extension studies (Protocols YKP or YKT) at the discretion of the investigator and medical monitor. Subjects taking topiramate who withdrew the trial or who chose not to enter the open-extension study had their dosages of study medication tapered in decrements of 100 mg/day or 200 mg/day per interval of one week or more.

During the 12-week baseline phase, patients would be required to have at least 12 partial seizures while on adequate doses of concomitant antiepileptic drugs (AEDs) as documented by drug plasma concentrations. Qualified patients would be randomized to receive either placebo or 600 mg/day, 800 mg/day, or 1,000 mg/day of topiramate (while continuing their background AEDs).

The double-blind phase is divided into a titration and stabilization period.

The titration period consists of six weeks permitted for subjects unable to tolerate the dosage schedule. Upward titration occurs on a weekly schedule.¹ An amendment to the original protocol gives patients who are having difficulty tolerating the titration schedule an alternative to reaching the maximum targeted dose. "The patient will be allowed after two weeks on a specific dosing regimen to discontinue the titration and begin the stabilization period." This allows also for titration periods as long as 12 weeks in some cases.

Once patients reach their targeted dose they would be followed for a 12-week stabilization period on this regimen.

Enrollment

Approximately 180 patients with refractory partial epilepsy, maintained on a maximum of two of the following anticonvulsants: carbamazepine, phenytoin, valproic acid, phenobarbital and/or primidone.

The inclusion and exclusion criteria are identical to that in Protocol YD (see section 7.1)

No anti-anxiety agents, antidepressants, neuroleptics or sedatives (other than chloral hydrate) are permitted. No centrally acting drugs (including antihistamines) were to be permitted.

Statistical Analysis Planned:

Primary analysis: "The main measure of efficacy will be the frequency of seizures. Each patient will have a seizure per week (or day) variable computed for the baseline period and each ensuing dose period." (Whether the comparison would be performed between the baseline and entire DB period or just the stabilization period was not specified in the protocol or in the amendments.) "Comparisons among the 4 dose groups will be done by computing change from baseline seizure rates and employing appropriate statistical techniques.

Secondary analyses: In addition efficacy will also be assessed by

¹During the first interval, the initial dose was topiramate 100 mg or one placebo tablet every morning. During the second interval, the dosage was topiramate 100 mg b.i.d. or one placebo tablet b.i.d. Subsequently, the dosage increment for each interval was topiramate 100 mg b.i.d. or one placebo tablet b.i.d. until the assigned dosage or the tolerated dosage, if less, for each subject was achieved.

analyzing the severity of seizures, duration of seizure free intervals, and physician and patient rating scales".¹

A sample size of 45 subjects per treatment group was estimated to provide 90% power to detect a between-group difference in seizure rate change of about six seizures per month assuming a standard deviation of 10 seizures per month for the seizure rate change in each treatment group.

Before initiation of the study, an administrative interim analysis was scheduled to be performed when data were available from one-third of the planned sample size. The interim analysis would not be used to make decisions concerning the design or conduct of this study, but was to be used as an aid for decisions concerning future studies.

STUDY CONDUCT

The study proceeded essentially according to schedule with some minor exceptions. There were 190 patients randomized from an initial 17 centers.

Of those randomized, 152 (80%) were men and 38 (20%) were women. One hundred seventy (90%) patients were white, 16 (8%) were black, and four (2%) were hispanic. The mean age was 35.3 years. All patients were required to have documented refractory partial epilepsy. Most (71%) were receiving carbamazepine either alone or in combination with valproic acid, phenytoin, primidone, or phenobarbital. The median seizure rate at baseline ranged from 9.3 to 16.2 across the treatment groups.

The demographic profiles of the various treatment groups is shown on the next page and is roughly comparable.

¹ An internal correspondence, dated January 4, 1988 (before the trial began) and attached to the protocol in Appendix 1, provided additional statistical information regarding planned analyses and the basis for sample size estimates. The changes in seizure rate from baseline were to be compared among the four treatment groups using two-way analysis of variance. Additionally, analyses of the severity of seizures and physician and subject global ratings of efficacy were planned, as was analysis of responders (subjects with a 50% or greater reduction from baseline in seizure rate). The analysis of the duration of the seizure-free intervals was also planned, but was not performed because this variable is related to, but less informative than, seizure rate.

**Table 3: Demographic and Baseline Characteristics
(All Randomized Subjects; Protocol YE)**

Attribute	Topiramate				Total (N=190)
	Placebo (N=47)	600 mg/day (N=48)	800 mg/day (N=48)	1,000 mg/day (N=47)	
Age (yr) Mean±SD	35.0±10.47	35.7±9.28	34.3±12.86	36.3±11.96	35.3±11.16
Gender % Male/Female	70/30	79/21	85/15	85/15	80/20
Race					
% White	89	90	85	94	90
% Black	11	8	13	4	8
% Other	0	4	2	2	2
Weight (lbs) Mean±SD	169.4±37.78	178.5±47.60	178.5±38.08	182.7±37.74	177.3 ± 40.52
Body Mass Mean±SD	3.7±0.93	3.8±0.79	3.8±0.74 ^d	3.8±0.68	3.8±0.78 ^e
Seizure Type					
% Simple Partial	40	46	46	57	47
% Complex Partial	94	96	88	96	93
% Secondary Generalized	77	60	69	45	63
% Generalized Tonic-Clonic	0	0	0	2	1
Baseline Average Monthly Seizure Rate					
Mean	18.2	23.5	39.8	24.7	26.6
SD	25.81	33.33	56.35	37.05	40.35
Median	9.3	10.0	16.2	11.7	11.0
Range	4.3-131.7	2.7-166.7	4.0-305.0	2.3-238.3	2.3-305.0

As noted, the protocol and amendments allowed for patients who were not tolerating titration to be maintained on less than the dose to which they were randomized. "The third revision gives a[n] ... alternative to patients who are having difficulty tolerating the titration schedule. Therefore, the patient will be allowed after two weeks on a specific dosing regimen to discontinue the titration and begin the stabilization period." The Sponsor's tables below display the mean and median doses reached in each randomized group for the whole double blind period (Sponsor's table 9) and for the stabilization period (Sponsor's Table 10).

**Sponsor's Table 9: Summary of the Average Dosage^a: Double-Blind Phase
(All Randomized Subjects; Protocol YE)**

Treatment	Mean	Standard Deviation	Median
Placebo ^b (N=47)	7.8	1.35	8.4
Topiramate			
600 mg/day (N=48)	431.0	160.91	520.2
800 mg/day (N=48)	611.2	149.29	690.4
1,000 mg/day (N=47)	610.9	249.20	739.8

^a Subject's average over the entire double-blind phase.

^b Placebo dosages are given as number of tablets.

Dosage titration to the assigned or the maximum-tolerated dosage (if less) for each subject over the entire double-blind treatment phase (titration and stabilization periods) resulted in median by-subject average dosages of 520.2 mg/day, 690.4 mg/day, and 739.8 mg/day in the topiramate 600 mg/day, 800 mg/day, and 1,000 mg/day groups, respectively.

The summary of the mean and median by-subject average dosage for the stabilization period is presented by treatment group in Sponsor's Table 10. Average doses achieved by stabilization still fell short of targeted doses. In the 600 mg/day group, the average treatment dose was 543.5 mg/day, in the 800 mg/day group, the average treatment dose was 738 mg/day and in the 1000 mg/day group, the average treatment dose was 798.9 mg/day. The median average dosages during the stabilization period coincided with the target daily dosages (600 mg/day, 800 mg/day, and 1,000 mg/day) for the three topiramate treatment groups.

**Sponsor's Table 10: Summary of the Average Dosage^a:
Stabilization Period
(All Randomized Subjects Who Entered the
Stabilization Period; Protocol YE)**

Treatment	Mean	Standard Deviation	Median
Placebo ^b (N=44)	9.7	0.89	10.0
Topiramate			
600 mg/day (N=40)	543.5	138.81	600.0
800 mg/day (N=45)	738.8	131.82	800.0
1,000 mg/day (N=40)	798.9	292.03	1,000.0

^a Subject's average over the entire stabilization period.

^b Placebo dosages are given as number of tablets; target dosage was 10 tablets/day.

The duration of the double-blind phase was comparable in all four groups.

DISCONTINUATION/COMPLETION INFORMATION:

Thirty six of the 190 patients who entered the randomized portion of the trial withdrew for various reasons (see table below). One center (41) was terminated for administrative reasons and with mutual agreement by the sponsor and investigator. This center had already randomized 9 patients. Of these, two of these patients were discontinued when the center closed out, two completed the trial, three discontinued due to an adverse event, and two chose to discontinue for unknown reasons. No further information is provided to explain the closing of this center.

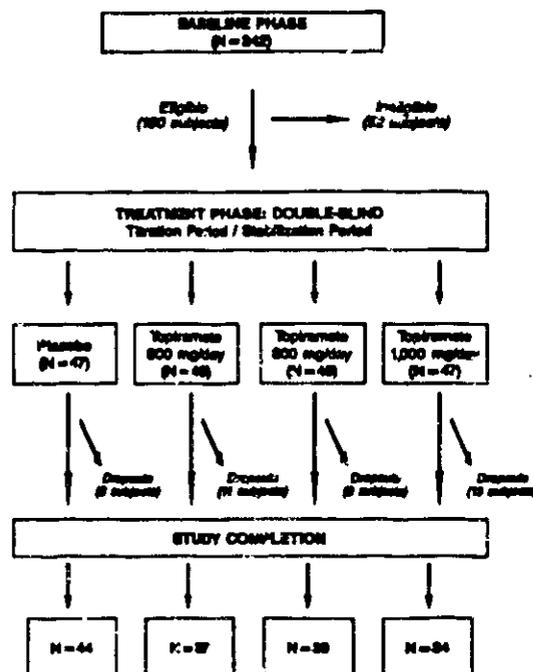
One-hundred fifty-four (81%) of 190 subjects completed the trial. Twenty-four (13%) subjects discontinued from the trial because of adverse events. A summary of the reasons for discontinuation are presented in the table on the following page.

Table 4: Summary of Discontinuation/Completion Information: Double-Blind Phase (All Randomized Subjects; Protocol YE)

Reason	Topiramate									
	Placebo (N=47)		600 mg/day (N=46)		800 mg/day (N=46)		1,000 mg/day (N=47)		Total (N=180)	
	N	%	N	%	N	%	N	%	N	%
Study Completed	44	94	37	77	39	81	34	72	154	81
Study Discontinued										
Limiting adverse events	1	2	10	21	5	10	8	17	24	13
Drug ineffective	0	0	0	0	2	4	0	0	2	1
Intercurrent illness	0	0	0	0	1	2	0	0	1	1
Subject's choice	0	0	1	2	0	0	2	4	3	2
Significant protocol violation	0	0	0	0	0	0	3	6	3	2
Administrative/other	2	4	0	0	1	2	0	0	3	2
Total discontinued	3	6	11	23	9	11	13	28	36	19

A temporal summary of the discontinuations is shown in the schematic below:

Figure 2: Discontinuation/Completion Summary (Protocol YE)



Plasma Levels

The mean (\pm SD) plasma concentrations of topiramate for the entire double-blind phase in subjects randomized to target dosages of 600 mg/day, 800 mg/day, and 1,000 mg/day were 4.5 ± 1.98 μ g/mL, 5.4 ± 2.47 μ g/mL, and 5.1 ± 2.96 μ g/mL, respectively. The relationship between dosage and plasma concentration is impossible to interpret given the variability in the duration of the titration period and the fact that many subjects did not achieve (or maintain) the target assigned dosage level.

Protocol Violations

During the trial, three subjects were discontinued because of protocol violations, all in the 1,000 mg/day group.

Subject 25/13 did not take his study medication according to the schedule. Subject 29/4 used recreational drugs during the trial, and Subject 32/1 failed to disclose a previous suicide attempt.

No other significant protocol violations were identified. There were no significant protocol violations noted which involved the use of additional antiepileptic drugs during the trial or administration of the wrong medications.

Efficacy Criteria: Analysis**Primary****Percent Reduction in Seizure Rate**

The primary efficacy variable was the percent reduction in the average seizure rate from baseline. In this analysis, as in studies YD, Y1, Y2 and Y3, all seizure types were counted, not just partial onset seizures, although the partial onset seizures were by far the majority.

The average monthly (28-day) seizure rates were computed for the baseline and double-blind phases. The average monthly seizure rate for a time period was calculated as (the total number of seizures reported during the period divided by the number of days in the period) multiplied by 28 days. The baseline seizure rate was calculated as the average monthly seizure count for the last 12 pretreatment weeks. For a patient whose baseline was restarted or extended, usually due to a change in background AED dosage, only data from the final 12 weeks were used.

The primary efficacy variable was percent reduction in seizure rate, defined as $100(B-D)/B$, where B=baseline seizure rate and D=double-blind phase seizure rate.

Secondary**Investigator's Global Assessment, Patient's Overall Assessment, Generalized Seizure analysis:**

Please refer to study YD for a description of these measures.

Trial YE: Sponsor's Results

Efficacy analyses in Trial YE were conducted (i) using all double-blind phase data (both titration period and stabilization period); and (ii) using only stabilization period data. These analyses employed identical methods; therefore, the following description will refer to the double-blind phase.

To assess efficacy of the three topiramate dosages, pairwise comparisons to placebo were made using three separate two-factor (treatment, center, and treatment-by-center interaction) analyses of variance on ranks. All randomized patients were used in the efficacy analyses.

The sponsor performed an interim analysis of efficacy data from 61 patients. The interim analysis was not used to make decisions concerning the design or conduct of the trial, but as an aid to decisions concerning future trials.

Medians and ranges for the primary efficacy variable as well as statistical results for pairwise treatment comparisons with placebo are shown below. For the 36 patients who were discontinued early, seizure rates were calculated based on the actual time in the trial.

Results of the Primary Efficacy Evaluation: Percent Reduction From Baseline in Average Monthly Seizure Rate for the Double-Blind Phase (All Randomized Subjects; Protocol YE)

Treatment	Percent Reduction		P-value ^c
	Median	Range ^a	
Placebo (N=47)	1.2	(-139.1, 66.7)	
Topiramate			
600 mg/day (N=48)	40.7	(-142.4, 100.0)	<0.001
800 mg/day (N=48)	41.0	(-11.2, 100.0)	<0.001
1,000 mg/day (N=47)	37.5	(-180.8, 89.3)	<0.001

^a Negative numbers denote an increase in seizure rate.

^c Topiramate vs. placebo; two-factor ANOVA on ranks with type III sums of squares.

Each topiramate daily dosage (600 mg, 800 mg and 1000 mg) was statistically superior ($p < 0.001$) to placebo in reducing the average monthly seizure rate compared to baseline. There were no statistically significant treatment-by-center interactions ($p \geq 0.889$) for any of the comparisons between topiramate and placebo.

Although the treatment-by-center interactions were not significant, the sponsor conducted additional statistical analysis to investigate the consistency of results for the primary efficacy variable across centers. For a given comparison between topiramate and placebo, patients were ranked and the mean ranks calculated for each center and treatment group. Results favored topiramate 600 mg/day over placebo for all 17 centers with randomized patients. For both the topiramate 800 mg and 1000 mg treatment groups, results favored topiramate over placebo for 16 of 17 centers.

Secondary variables

RESPONDER RATE

A patient was defined as a treatment responder if the percent seizure rate reduction during the double-blind phase from baseline was greater than or equal to 50%. The percentage of responders in each topiramate treatment group were compared in a pairwise fashion with placebo using the Cochran-Mantel-Haenszel method stratified by center. A statistically greater percentage of patients in each topiramate treatment group were treatment responders compared with the placebo group. Response rates were 44% for the topiramate 600 mg treatment group, 40% for the topiramate 800 mg treatment group, 38% for the topiramate 1000 mg treatment group and 9% for the placebo group. P-values were < 0.001 , 0.001 and 0.001, respectively.

**Treatment Responders for the Double-Blind Phase
(All Randomized Subjects; Protocol YE)**

Treatment	Treatment Responders ^a		P-value ^b
	N	%	
Placebo (N=47)	4	9	
Topiramate			
600 mg/day (N=48)	21	44	<0.001
800 mg/day (N=48)	19	40	0.001
1,000 mg/day (N=47)	18	38	0.001

^a Subjects with 50% or greater seizure rate reduction from baseline.

^b Topiramate vs. placebo; Cochran-Mantel-Haenszel test stratified by investigator.

Investigator's Global Evaluation

The investigator's global evaluation of improvement at the end of the double-blind phase compared with baseline (5-point scale: 1=worse, 2=none, 3=minimal, 4=moderate, 5=marked) were analyzed by Wilcoxon rank-sum tests stratified by center. All dosages of topiramate were statistically superior to placebo. P-values for each topiramate dose (all mean scores= 3.5) vs placebo (2.4) were <0.001. Refer to the following table.

INVESTIGATOR'S GLOBAL EVALUATION OF IMPROVEMENT AT THE END
OF THE DOUBLE-BLIND PHASE COMPARED WITH BASELINE
(ALL RANDOMIZED SUBJECTS; PROTOCOL YE)

	Placebo (N=47)		Topiramate					
	N	%	600 mg/day (N=47 ^a)		800 mg/day (N=48)		1,000 mg/day (N=47)	
	N	%	N	%	N	%	N	%
Rating								
Worse (1)	2	4	0	0	1	2	4	9
None (2)	32	68	13	28	6	13	9	19
Minimal (3)	8	17	8	17	15	31	9	19
Moderate (4)	4	9	17	36	19	40	12	26
Marked (5)	1	2	9	19	7	15	13	28
Mean	2.4		3.5		3.5		3.5	
P-value^b			<0.001		<0.001		<0.001	

^a One subject was not assessed for this efficacy variable at the final visit.

^b Topiramate vs. placebo; Wilcoxon rank sum test stratified by investigator.

Patient's Overall Assessment

The patient's overall assessment of medication at the end of the double-blind phase compared with baseline (4-point scale: 1=poor, 2=fair, 3=good, 4=excellent) were analyzed by Wilcoxon rank-sum tests stratified by center. The patient's overall assessment of medication was statistically superior for each topiramate dosage compared to placebo.

Mean scores were 2.6 for the topiramate 600 mg treatment group, 2.6 for the topiramate 800 mg treatment group, 2.4 for the topiramate 1000 mg treatment group and 1.9 for the placebo group. P-values were <0.001, <0.001 and 0.015, respectively

Table 15: Subject's Overall Assessment of Medication at the End of the Double-Blind Phase Compared with Baseline (All Randomized Subjects; Protocol YE)

Rating	Placebo (N=47)		Topiramate					
			600 mg/day (N=47 ^a)		800 mg/day (N=47 ^a)		1,000 mg/day (N=47)	
	N	%	N	%	N	%	N	%
Poor (1)	19	40	7	15	7	15	12	26
Fair (2)	16	34	11	23	13	28	13	28
Good (3)	11	23	22	47	21	45	13	28
Excellent (4)	1	2	7	15	6	13	9	19
Mean	1.9		2.6		2.6		2.4	
P-value ^b			<0.001		<0.001		0.015	

^a One subject did not assess this efficacy variable at the final visit.

^b Topiramate vs. placebo; Wilcoxon rank sum test stratified by investigator.

seizures during treatment also.

Plasma concentrations of concomitant antiepileptic drugs
The sponsor investigated changes in plasma concentrations of concomitant antiepileptic drugs from the baseline phase to the double-blind phase. The analysis used a one-way ANOVA to compare

topiramate (all dosages combined) with placebo with respect to the mean change from baseline.

Plasma concentrations of phenytoin, valproic acid, phenobarbital and primidone were comparable ($p \geq 0.274$) between topiramate- and placebo-treated patients. A statistically significant difference ($p = 0.029$) between the combined topiramate groups and the placebo group was detected for carbamazepine. Mean carbamazepine concentrations in both treatment groups declined from baseline mean levels. The mean decrease in the topiramate groups ("double-blind" - baseline = $-0.7 \mu\text{g/ml}$) was larger than the mean decrease in the placebo group ("double-blind" - baseline = $-0.2 \mu\text{g/ml}$). Thus, the statistically significant reduction in seizure rate observed with topiramate could not be attributed, wholly or partially, to higher concentrations of carbamazepine compared to those in the placebo group.

Trial YE: FDA Statistical Reviewer's Analysis

The sponsor submitted efficacy data on diskette to the Agency in the form of three datasets: (1) patient demographics, (2) daily seizure counts for each patient by seizure type, and (3) efficacy variables (including seizure counts and rates) derived from the raw seizure data in dataset 2. The derived variables in dataset 3 formed the basis of the NDA submission.

This reviewer repeated the quality control procedure used in YD, that of attempting to verify the seizure counts and rates in dataset 3. Using the raw seizure data in dataset 2, this reviewer calculated "revised" seizure counts (rates). Twenty-three (23) of the 190 randomized patients had revised seizure counts that disagreed with sponsor-derived counts during the baseline and/or double-blind phases. According to the sponsor, the start and end dates for the different trial phases for some patients were misspecified. These errors resulted in the improper inclusion or exclusion of seizures during certain trial phases. Eleven patients had discrepancies associated with the baseline phase only (i.e., prior to randomization), ten patients had discrepancies associated with the double-blind phase only, and two patients had discrepancies associated with both phases.

The sponsor also scrutinized the raw seizure data (dataset 2) in trial YE. Four patients had incorrect raw seizure data. Zero counts were erroneously assigned for seizure types SP/CL and CP/CL. These data were corrected by changing the number of seizures of type SP/CL from 0 to the correct number for three patients. For the fourth patient, the

number of seizures of type CP/CL was changed from 0 to missing.

Use of the revised data resulted in small changes in the sponsor's percent seizure rate reduction for some patients. These changes sometimes produced small changes in the summary measures.

(Changes in treatment means were more pronounced compared to medians using the revised data, but the mean is less relevant than the median as a summary measure because the data were not normally distributed.) Revised median percent seizure rate reductions are shown below:

**Trial YE: Percent Seizure Rate Reduction From Baseline
Revised Rates**

	Percent Seizure Rate Reduction	
	Median	Range
Placebo (n=47)	1.7	(-139.1, 66.7)
Topiramate		
600 mg/day (n=48)	40.7	(-142.4, 100.0)
800 mg/day (n=48)	41.0	(-11.2, 100.0)
1000 mg/day (n=47)	36.0	(-160.8, 89.3)

This reviewer used the sponsor's statistical model -- two-factor (treatment, center and treatment-by-center interaction) Analysis of Variance (ANOVA) -- for the analysis of the primary efficacy variable using the ranks of the revised data. (Nonparametric analyses were indicated because the distributions of the response variable were highly skewed towards negative values for all topiramate treatment groups ($p < 0.01$). Initially, an F-test comparing all four treatment groups was conducted. Because the F-test was statistically significant ($p = 0.0001$), three pairwise comparisons between each active treatment group and placebo were conducted using a family-wise type I error rate $\alpha = 0.05$ and a Bonferroni adjustment for each comparison with placebo at $\alpha = 0.05/3 = 0.0167$. All active treatment groups (topiramate 600 mg, 800 mg and 1000 mg) were statistically superior to placebo ($p < 0.001$).

Trial YE: P-values for Various Treatment Comparisons

Treatment comparisons	P-value*	
	Revised data	Sponsor's data
All 4 treatment groups	0.0001	0.0001
600 mg vs placebo	0.0001	0.0001
800 mg vs placebo	0.0001	0.0001
1000 mg vs placebo	0.0009	0.0008

* Topiramate vs placebo; two-factor ANOVA on ranks with type III sums of squares

Use of the revised data also did not change the sponsor's results for the primary efficacy variable for individual centers. The number of centers favoring topiramate over placebo remained the same for each pairwise comparison of topiramate and placebo.

Comments

This trial has demonstrated that topiramate is effective at dosages of 600 mg/day and approaching 800 mg/day. No conclusions can be drawn with regard to efficacy using 1,000 mg/day since the doses in this treatment group did not approach target on the average.

The median percent reduction in generalized seizure rate was not statistically significantly different from placebo for the combined treatment groups.

7.3 STUDY Y1

Title: double-blind parallel comparison of topiramate 200 mg twice daily to placebo in patients with refractory partial epilepsy

Objective: to evaluate the safety and efficacy of topiramate 400 mg/day as adjunctive therapy in subjects with refractory partial onset seizures

Protocol

STUDY DESIGN:

This is a multicenter, randomized, placebo-controlled, double-blind, parallel study to evaluate topiramate 400 mg/day as adjunctive therapy in subjects with refractory partial onset epilepsy.

The trial consists of four phases: screening, baseline, double-blind, and tapering. The trial design is summarized on the next page by schematic and by table on the following page.

During the eight-week baseline phase, subjects are required to have at least eight partial seizures, despite adequate doses of concomitant antiepileptic drugs (AEDs) as documented by plasma drug concentrations. Those subjects who qualify for participation in the double-blind phase of the trial are randomized to receive one of two treatments, 400 mg/day of topiramate or placebo, while continuing their background AED regimens. Subjects who do not reach their assigned dosage levels during the titration period are maintained at their maximum tolerated dosage.

The double-blind phase of the trial is divided into two periods, titration and stabilization. The titration period consists of three one-week intervals with some variation permitted for subjects who were unable to tolerate the dosage schedule. (see two previous studies for titration schedule). After the assigned dosage or the maximum tolerated dosage, if less, for each subject is achieved, the subjects are followed for an eight-week stabilization period on this regimen.

The same instructions noted in the previous studies which allowed for adjustment in target dosage or titration rate based on tolerance apply here.

STUDY SCHEMATIC PROTOCOL Y1

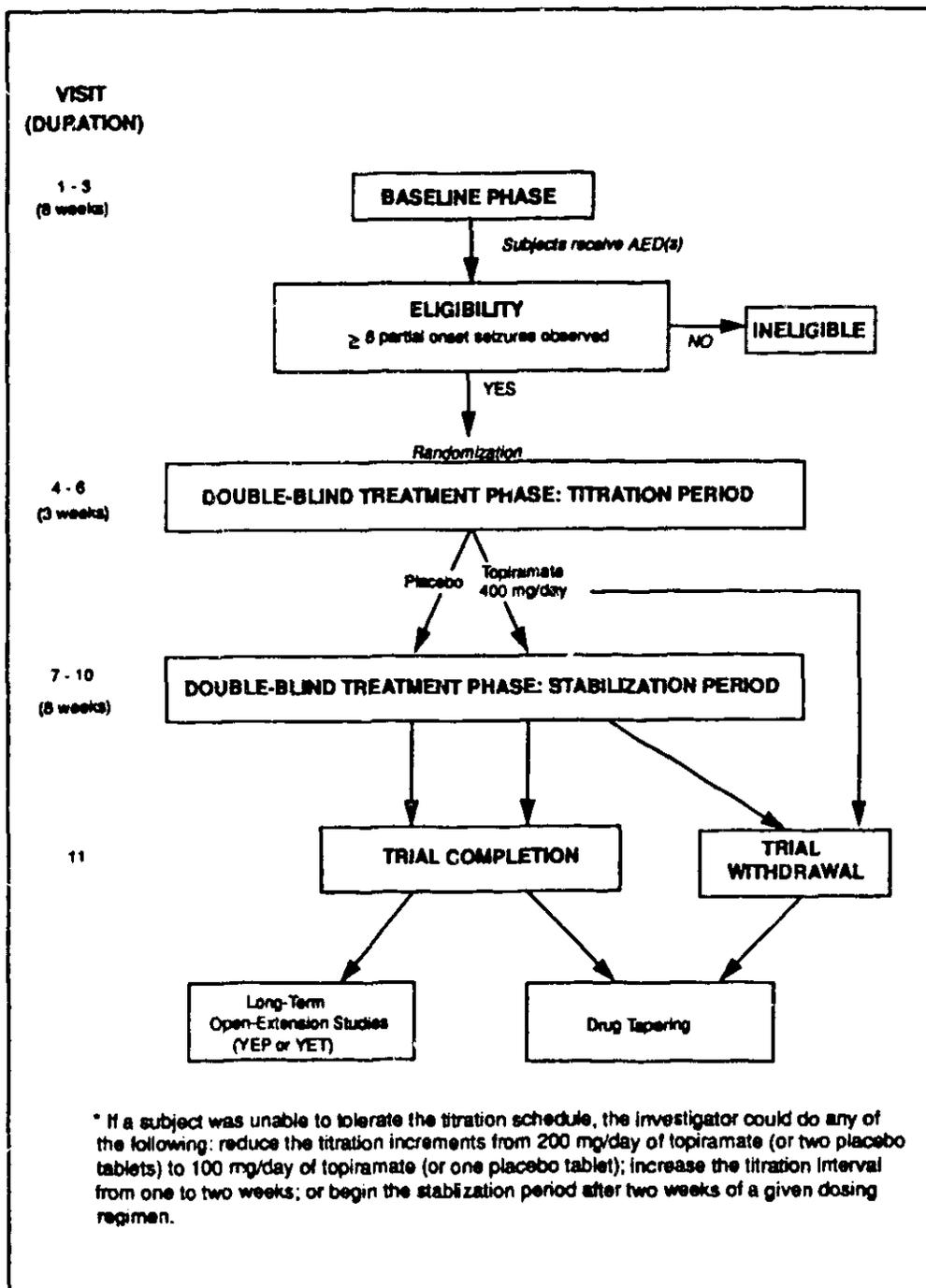


Table 1: Overview of Trial Phases

Study Interval	Duration	Therapy	Purpose
Screening Phase	Prior to baseline phase	Recent history of therapy with one or two standard AED(s)	Determine eligibility and stabilize on background AED(s)
Baseline Phase	8 weeks	Standard AED(s)	Maintain on background AED(s) and further assess eligibility
Double-Blind Phase Titration Period	3 weeks (2 to 6 weeks)	Background AED(s) and topiramate or placebo increased at weekly intervals to the assigned (or maximum tolerated, if less) dosage	Achieve the assigned (or maximum tolerated, if less) dosage of topiramate and conduct efficacy and safety observations
Stabilization Period	8 weeks	Maintenance on the assigned (or maximum tolerated, if less) dosage of study medication	Efficacy and safety observations

Enrollment:

INCLUSION CRITERIA

- Ages 16 and 65 years, inclusive.
- An unequivocal history of simple or complex partial epilepsy that has been adequately described or at least one simple or complex partial seizure must have been witnessed by a professional observer with experience in epilepsy. Observation may be by videotape.
- On study entry, the patient must have an EEG during the preceding five years which has a lateralized epileptiform pattern consistent with the diagnosis of partial epilepsy.
- The patient must have at least eight partial seizures during an eight week baseline period in spite of adequate doses of concomitant anticonvulsants as documented by drug plasma concentrations. The longest seizure free interval can be three weeks in duration with only one such occurrence during the eight week baseline period.
- Minimum steady state plasma concentrations (trough levels) of the allowable concomitant anticonvulsants:

Carbamazepine	4-14 ug/mL
Phenytoin	6- 25 ug/mL
Valproic Acid	40-120 ug/mL
Phenobarbital	15- 40 ug/mL
Primidone	15- 15 ug/mL

- Patients will be in good physical health as determined by a screening medical history, physical examination and laboratory tests.
- Informed consent
- Computerized axial tomography scan (CAT scan) or magnetic resonance imaging (MRI) within the preceding two years to rule out an expanding space occupying lesion or progressive disorder.

EXCLUSION CRITERIA

- Patients who do not have partial epilepsy
- Patients who have only primary generalized seizures
- Patients who have generalized tonic-clonic seizures or other generalized epilepsies in the

- absence of an EEG demonstration of a focal onset
- Patients who clinically have generalized absence seizures which are defined as a three per second spike wave pattern on EEG
 - Patients who have seizures without an abnormal ictal EEG
 - Female patients with a childbearing potential
 - Patients with a treatable cause of seizures, e.g., metabolic, neoplastic or active infection
 - Patients with a progressive neurological disorder
 - Patients with a documented history of status epilepticus while complying with appropriate therapy
 - Patients demonstrating significant acute or chronic confounding physical disease
 - Patients known to have a history of other serious medical diseases, including cardiovascular, hepatic, renal, gastrointestinal, metabolic or endocrine
 - Patients with uncontrolled hypertension or those taking antihypertensive medication other than beta-blockers or ACE-inhibitors
 - Patients who have a history of alcohol or drug abuse within one year prior to the study
 - Patients who are known to be poorly compliant
 - Patients in whom carbonic anhydrase inhibitors are contraindicated
 - Inhibitors (e.g., acetazolamide) or sulfonamides
 - Patients with a history of a serious psychiatric disorder, including rage attacks and violent behavior
 - Patients who are schizophrenic or have exhibited any psychotic symptomatology
 - Patients with a history of a suicide attempt
 - Patients with a malignancy with a metastatic potential
 - Patients who have received an experimental drug or used an experimental device within 60 days prior to admission into this study
 - Patients with abnormal screening laboratory parameters
 - Patients with a history of nephrolithiasis
 - Patients who as a result of the nature of their seizures are unable to take their medication and/or maintain a seizure calendar, independently or with assistance
 - Patients whose mental retardation is severe enough to compromise their ability to independently take their medication and/or keep a seizure count

Efficacy

The main measure of efficacy will be the frequency of seizures. Each patient will have a seizure per week (or day) variable computed for the baseline period and each ensuing dose period. Comparisons between the treatment groups will be done by computing change from baseline seizure rates and employing appropriate statistical techniques. In addition, efficacy will also be assessed by analyzing the severity of seizures, duration of seizure-free intervals, and physician and patient rating scales.

The protocol was silent with regard to methodology for counting seizures, specifically seizures that occurred in clusters.

STUDY CONDUCT

The study was conducted in accordance with the protocol.

ENROLLMENT: demographic and baseline characteristics
 Fifty-two subjects were enrolled in the baseline phase of this trial at four centers within Europe; 47 subjects qualified for randomization and then received study medication. Twenty-three subjects were randomized to receive topiramate 400 mg/day and 24 subjects to receive placebo.

Baseline demographic characteristics including seizure type were comparable between the treatment groups (see table below).

**DEMOGRAPHIC AND BASELINE CHARACTERISTICS:
AGE, AND BASELINE AVERAGE MONTHLY SEIZURE RATE
(ALL RANDOMIZED SUBJECTS; PROTOCOL Y1)**

Attribute	Placebo (N=24)	Topiramate 400 mg/day (N=23)	Total (N=47)
Age (yr)			
Mean	32.6	35.4	34.0
SD	11.12	14.04	12.57
Median	30.0	31.0	31.0
Range	15.0-55.0	17.0-63.0	15.0-63.0
Baseline Average Monthly Seizure Rate			
Mean	23.6	33.4	28.4
SD	34.47	52.60	44.06
Median	10.0	18.0	12.5
Range	1.0-123.0	3.5-208.0	1.0-208.0

Of the 47 randomized subjects, 40 (85%) were men and 7 (15%) were women, and all of the subjects were white. Their mean age was 34.0 years. All subjects were required to have documented refractory partial epilepsy. Most of the subjects (64%) were receiving carbamazepine either alone or in combination with clonazepam, phenobarbital, phenytoin, primidone, or valproic acid. The median seizure rate at baseline was 18 for the topiramate 400 mg/day group and 10 for the placebo group. The demographic and baseline characteristics for all randomized subjects by treatment group are summarized below and were comparable between the treatment groups.

**DEMOGRAPHIC AND BASELINE CHARACTERISTICS:
GENDER, RACE, BACKGROUND AEDs, AND SEIZURE TYPE
(ALL RANDOMIZED SUBJECTS; PROTOCOL Y1)**

Attribute	Placebo		Topiramate 400 mg/day		Total	
	N	%	N	%	N	%
Gender						
Male	15	79	21	71	40	85
Female	5	21	2	9	7	15
Total	24	100	23	100	47	100
Race						
White	24	100	23	100	47	100

Background AED(s)						
Phenytoin	3	13	0	0	3	6
Primidone	0	0	1	4	1	2
Carbamazepine	4	17	3	13	7	15
Clobazam/Phenytoin	1	4	1	4	2	4
Clobazam/Primidone	0	0	1	4	1	2
Clobazam/Barbiturates	1	4	0	0	1	2
Phenobarbital/Phenytoin	1	4	1	4	2	4
Phenobarbital/Carbamazepine	4	17	4	17	8	17
Phenobarbital/Valproic Acid	0	0	1	4	1	2
Phenytoin/Primidone	1	4	0	0	1	2
Phenytoin/Clonazepam	1	4	0	0	1	2
Phenytoin/Carbamazepine	1	4	5	22	6	13
Phenytoin/Valproic Acid	2	8	1	4	3	6
Primidone/Carbamazepine	3	13	3	13	6	13
Clonazepam/Carbamazepine	0	0	1	4	1	2
Clonazepam/Valproic Acid	0	0	1	4	1	2
Carbamazepine/Valproic Acid	2	8	0	0	2	4
Total	24	100	23	100	47	100
Seizure Type*						
Simple Partial	7	29	9	39	16	34
Complex Partial	23	98	20	87	43	92
Secondarily Generalized	16	67	19	83	35	75
All Other Types	3	13	5	22	8	17
Total	24	100	23	100	47	100

Titration schedule

The titration schedule was planned to consist of four one-week intervals with protocol-specific adjustments to this schedule allowed for subjects unable to tolerate the titration schedule as planned. The initial dose administered to subjects during the first titration interval was either 100 mg topiramate or one tablet of placebo every morning. During the second titration interval, subjects were administered either 100 mg topiramate b.i.d. or one tablet of placebo b.i.d. Subsequently, the dose increment for each remaining titration interval was either 100 mg topiramate b.i.d., or one tablet of placebo b.i.d., until the subject reached the assigned maximum dosage (or the maximum tolerated dosage, if less) and the titration period was completed.

Those subjects who qualified for participation in the double-blind phase of the trial were randomized to receive one of two treatments, 400 mg/day of topiramate or placebo, while continuing their background AED regimens. The investigator was permitted to alter the dosing schedule of any subject who could not tolerate the titration schedule by any of the following means: 1) increase the daily dose of study medication by only one tablet of topiramate (100 mg) or one tablet of placebo weekly, 2) increase the dosing interval from one to two weeks, 3) starting at Titration interval 4, change the dosing frequency from twice daily to four times daily, or 4) after two weeks on a specific dosing regimen, discontinue the titration period and begin the stabilization period.

Subjects who did not reach their assigned dosage levels during the titration period were maintained at their maximum tolerated dosage.

Seizure Data

Subjects recorded the date and time of seizures and a description of seizure type in their seizure diaries. The investigator classified each seizure type described in the subject's diary, before the data were recorded on the subject's case report form. The standard seizure classifications used are:

- Simple partial (SP)
- Complex partial (CP)
- Partial evolving to secondarily generalized (PE)

If seizures occurred in a cluster, the investigator added "CL" to the classification. However, because many subjects could not count the seizures in a cluster, it was decided to allow subjects either to estimate the number of seizures in a cluster or to count the cluster as one seizure. Only one of these two approaches was to be adopted and used consistently by the subject throughout the trial. This was not described in the protocol but rather appears to be adopted throughout all of the efficacy trials conducted with topiramate on a regular basis.

No seizure clusters were recorded during this trial.

Global Evaluations and Assessments

Global evaluations and assessments were performed by the investigators and subjects at the final visit of the double-blind phase. The investigator's global evaluation of improvement relative to baseline for each subject was recorded as worse (1), none (2), minimal (3), moderate (4), or marked (5). Likewise, the subject's overall assessment of medication was recorded as poor (1), fair (2), good (3), or excellent (4).

The primary efficacy variable was percent reduction in the average monthly seizure rate from the baseline phase to the double-blind phase. Secondary efficacy variables included percent treatment responders, investigator's global evaluation of improvement, subject's overall assessment of medication, and percent reduction in the generalized seizure rate.

DISCONTINUATION/COMPLETION INFORMATION:

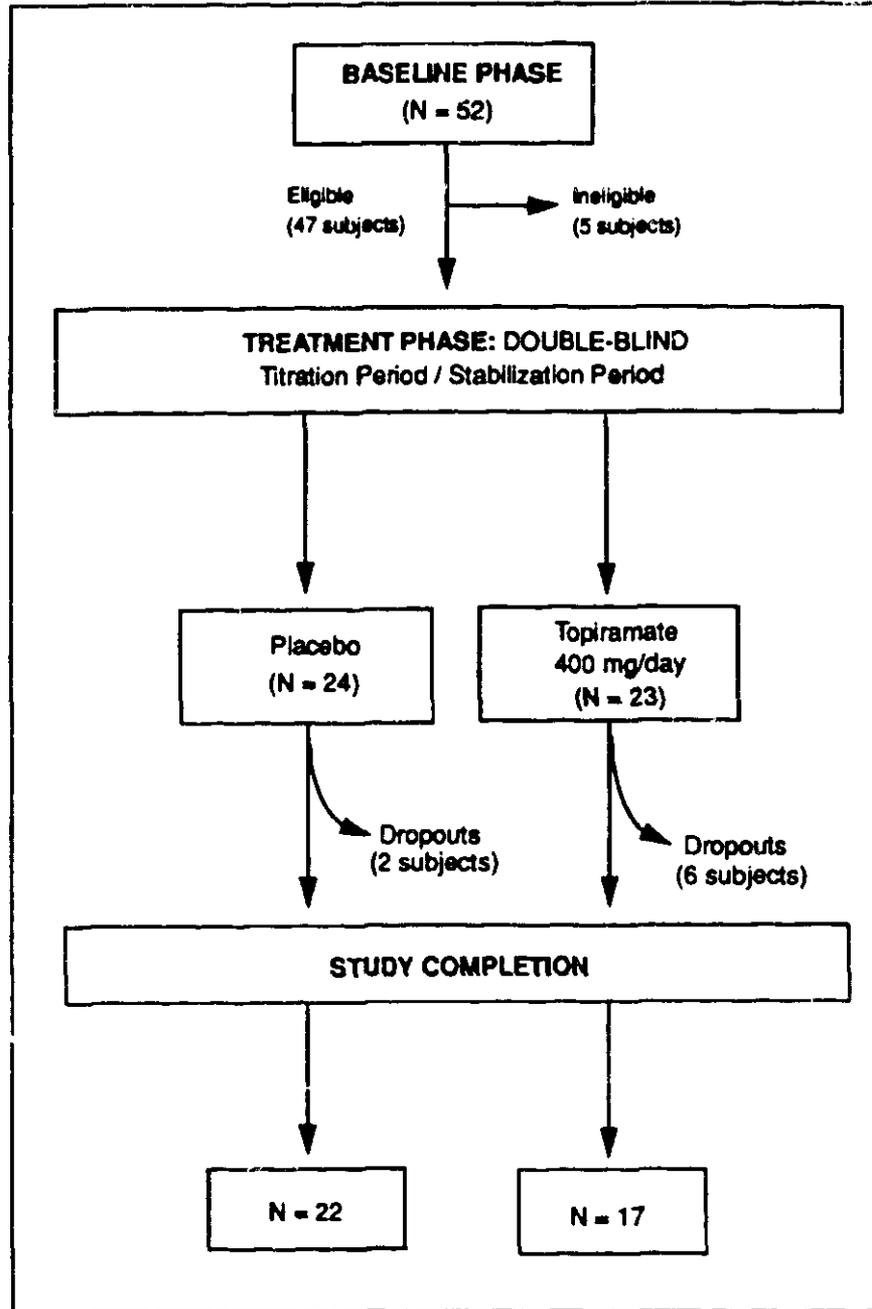
Thirty-nine (83%) of 47 subjects completed the trial. Seven (15%) subjects discontinued from the trial because of adverse events and one discontinued for administrative reasons. A summary of the reasons for discontinuation is presented in the table below.

**SUMMARY OF DISCONTINUATION/COMPLETION INFORMATION: DOUBLE-
BLIND PHASE
(ALL RANDOMIZED SUBJECTS; PROTOCOL Y1)**

Reason	Placebo (N=24)		Topiramate 400 mg/day (N=23)		Total (N=47)	
	N	%	N	%	N	%
Study completed	22	92	17	74	39	83
Study discontinued						
Limiting adverse events	1	4	6	26	7	15
Administrative reasons	<u>1</u>	4	<u>0</u>	0	<u>1</u>	2
Total discontinued	2	8	6	26	8	17

Seventeen (74%) subjects in the topiramate 400 mg/day group and 22 (92%) in the placebo group completed the trial. Eight (17%) of 47 subjects withdrew from the trial prematurely, including seven (15%) because of limiting adverse events. Six of these subjects were in the topiramate 400 mg/day group and one was in the placebo group. Summary Information on completion and discontinuation for the double-blind phase of the trial is presented in the table above and the figure below.

DISCONTINUATION/COMPLETION SUMMARY--PROTOCOL Y1



Dosages

Dosage titration to the assigned dosage or the maximum-tolerated dosage, if less, for each subject over the entire double-blind treatment phase (titration and stabilization periods) resulted in a mean by-subject dosage of only 312 mg/day in the topiramate 400 mg/day group. A summary of the mean and median dosages for the double-blind phase is presented by treatment group in the table below.

**Summary of the Average Dosage^a: Double-Blind Phase
(All Randomized Subjects; Protocol Y1)**

Treatment	Mean	Standard Deviation	Median
Placebo ^b (N=24)	3.3	0.6	3.6
Topiramate 400 mg/day (N=23)	312.0	81.6	352.6

The summary of the average dosage for the stabilization period only is presented by treatment group in the table below. The median average dosage for the topiramate group during the stabilization period was 400 mg/day, which was the target daily dosage.

Summary of the Average Dosage: Stabilization Period

Treatment	Mean	Standard Deviation	Median
Placebo(N=23)	3.8	0.7	4.0
Topiramate 400 mg/day (N=19)	387.0	52.7	400.0

PROTOCOL VIOLATIONS

One subject (no. 905008) was disqualified during the baseline period by investigator 661 because of a protocol violation (suicide attempt). Protocol violations included age-related violations only.

In terms of disallowed concomitant medications, two patients were treated with diazepam during the study. One placebo patient received 5 mg on 4 separate occasions for anxiety, and one topiramate-treated patient received diazepam 5 mg on one occasion for agitation. There were no occasions on which patients were treated for seizures with additional medications.

Trial Y1: Sponsor's Results

The trial was not completed at the time of NDA submission. Because a Final Report of the trial was not available, the sponsor submitted a status report of the on-going trial for the NDA. The report contained data on selected variables (demographics, dropouts and adverse experiences) for the 44 patients who had been randomized by October 31, 1992. On May 15, 1995, the sponsor submitted efficacy data for all randomized patients on diskette to the Agency as well as a Full Clinical and Statistical Report.

Efficacy analyses were conducted (i) using all double-blind phase data (both titration period and stabilization period); and (ii) using only stabilization period data. These analyses employed identical methods; therefore, the following description will refer to the double-blind phase.

The average monthly (28-day) seizure rate for each patient was computed for the baseline and double-blind phases. The average monthly seizure rate for a time period was calculated as (the total number of seizures reported during the period divided by the number of days in the period) multiplied by 28 days. The baseline seizure rate was calculated as the average monthly seizure count for the last 8 pretreatment weeks. For a patient whose baseline was restarted or extended, usually due to a change in background AED dosage, only data from the final 8 weeks were used.

The primary efficacy variable was percent reduction in seizure rate, defined as $100(B-D)/B$, where B=baseline seizure rate and D=double-blind seizure rate. To assess efficacy of topiramate 400 mg, the comparison to placebo was made using a two-factor (treatment, center, and treatment-by-center interaction) analysis of variance on ranks. All randomized patients were used in the efficacy analysis.

Medians and ranges for the primary efficacy variable as well as statistical results for the treatment comparison with placebo are shown below. For the 8 patients who were discontinued early, seizure rates were calculated based on the actual time in the trial.

Topiramate 400 mg had a greater percent reduction from baseline in the average monthly seizure rate compared with placebo. The difference between treatment groups showed a trend toward statistical significance ($p=0.065$). These results were consistent with the results of efficacy analysis on data from the stabilization period ($p=0.070$). There was no statistically significant treatment-by-center interaction ($p=0.833$).

**RESULTS OF THE PRIMARY EFFICACY EVALUATION: PERCENT
REDUCTION FROM BASELINE IN AVERAGE MONTHLY SEIZURE RATE
FOR THE DOUBLE-BLIND PHASE
(ALL RANDOMIZED SUBJECTS; PROTOCOL Y1)**

	Percent Reduction ^a	
	Median	Range
Treatment		
Placebo (N=24)	1.1	(-1347.62, 90.54)
Topiramate 400 mg/day (N=23)	40.7	(-289.74, 100.0)
P-value^b	0.065	

^a Negative numbers denote an increase in seizure rate.

^b Topiramate vs. placebo; two-factor ANOVA on ranks with type III sums of squares.

To investigate the consistency of results for the primary efficacy variable across centers, patients were ranked and the mean ranks calculated for each center and treatment group. Results favored topiramate 400 mg over placebo for all four centers.

Secondary variables

Responder rate

A patient was defined as a treatment responder if the percent seizure rate reduction during the double-blind phase from baseline was greater than or equal to 50%. The percentage of responders in the topiramate 400 mg treatment group was compared with placebo using the Cochran-Mantel-Haenszel method stratified by center.

**TREATMENT RESPONDERS FOR THE DOUBLE-BLIND PHASE
(ALL RANDOMIZED SUBJECTS; PROTOCOL Y1)**

Treatment	Treatment Responders ^a	
	N	%
Placebo (N=24)	2	8
Topiramate 400 mg/day (N=23)	8	35
P-value^b	0.033	

^a Subjects with 50% or greater seizure reduction from baseline.

^b Topiramate vs. placebo; Cochran-Mantel-Haenszel test blocked on investigator.

A statistically greater percentage of patients receiving topiramate were treatment responders compared with the placebo group. Response rates

were 35% (8/23) for the topiramate treatment group and 8% (2/24) for the placebo group ($p=0.033$).

Investigator's Global Evaluation

The investigator's global evaluation of improvement at the end of the double-blind phase compared with baseline (5-point scale: 1=worse, 2=none, 3=minimal, 4=moderate, 5=marked) was analyzed by Wilcoxon rank-sum test stratified by center.

INVESTIGATOR'S GLOBAL EVALUATION OF IMPROVEMENT AT THE END OF THE DOUBLE-BLIND PHASE COMPARED WITH BASELINE (ALL RANDOMIZED SUBJECTS; PROTOCOL Y1)

Rating	Placebo (N=24)		Topiramate 400 mg/day (N=23)	
	N	%	N	%
Worse (1)	4	17	3	13
None (2)	14	58	3	13
Minimal (3)	4	17	4	17
Moderate (4)	1	4	6	26
Marked (5)	1	4	7	30
Mean	2.2		3.5	
P-Value*	0.002			

* Topiramate vs. placebo; Wilcoxon rank sum test stratified by investigator.

The investigator's global evaluation of improvement was statistically superior for topiramate (mean 3.5) compared to placebo (mean 2.2). The p-value was 0.002.

Patient's Overall Assessment

The patient's overall assessment of medication at the end of the double-blind phase compared with baseline (4-point scale: 1=poor, 2=fair, 3=good, 4=excellent) were analyzed by Wilcoxon rank-sum tests stratified by center.

**SUBJECT'S OVERALL ASSESSMENT OF MEDICATION AT THE END OF THE DOUBLE-BLIND
PHASE COMPARED WITH BASELINE
(ALL RANDOMIZED SUBJECTS; PROTOCOL Y1)**

	Placebo (N=24)		Topiramate 400 mg/day (N=23)	
	N	%	N	%
Rating				
Poor (1)	14	58	7	30
Fair (2)	8	33	6	26
Good (3)	0	0	6	26
Excellent (4)	2	8	4	17
Mean	1.6		2.3	
P-value*	0.021			

* Topiramate vs. placebo; Wilcoxon rank sum test stratified by investigator.

The patient's overall assessment of medication was statistically superior for topiramate (mean 2.3) compared to placebo (mean 1.6). The p-value was 0.021.

Plasma concentrations of concomitant antiepileptic drugs

The sponsor investigated changes in plasma concentrations of concomitant antiepileptic drugs from the baseline phase to the double-blind phase. The analysis used a one-way ANOVA to compare topiramate with placebo with respect to the mean change from baseline.

Mean changes in plasma concentrations of each concomitant AED (carbamazepine, phenytoin, valproic acid, phenobarbital, clonazepam, and primidone and its active metabolite (primidone metabolite)) from baseline to the double-blind phases were small and not statistically different between topiramate- and placebo-treated patients ($p \geq 0.278$). Overall, plasma concentrations of all AEDs were comparable over time between the topiramate- and the placebo-treated patients. Thus the greater reduction in seizure rate observed with topiramate could not be attributed to higher concentrations of any of the concomitant antiepileptic drugs compared to concentrations in the placebo group.

Trial Y1: FDA Statistical Reviewer's Results

The sponsor submitted three datasets on diskette for efficacy analyses: (1) patient demographics, (2) daily seizure counts for each patient by seizure type, (3) derived variables (seizure counts and rates) used in the NDA submission. All datasets were without error.

This reviewer replicated the sponsor's results.

Comments

This trial demonstrates the efficacy of topiramate 400 mg/day as adjunctive medication in the treatment of partial onset seizures. The statistical result is not as strong as was observed in YD, but this may be due to the smaller sample size.

7.4 Study Y2

Title: double-blind parallel comparison of topiramate 600 mg/day daily to placebo in patients with refractory partial epilepsy

Objectives:

The objective of this placebo-controlled trial was to evaluate the safety and efficacy of topiramate 600 mg/day as adjunctive therapy in subjects with refractory partial onset seizures

Protocol

Study design:

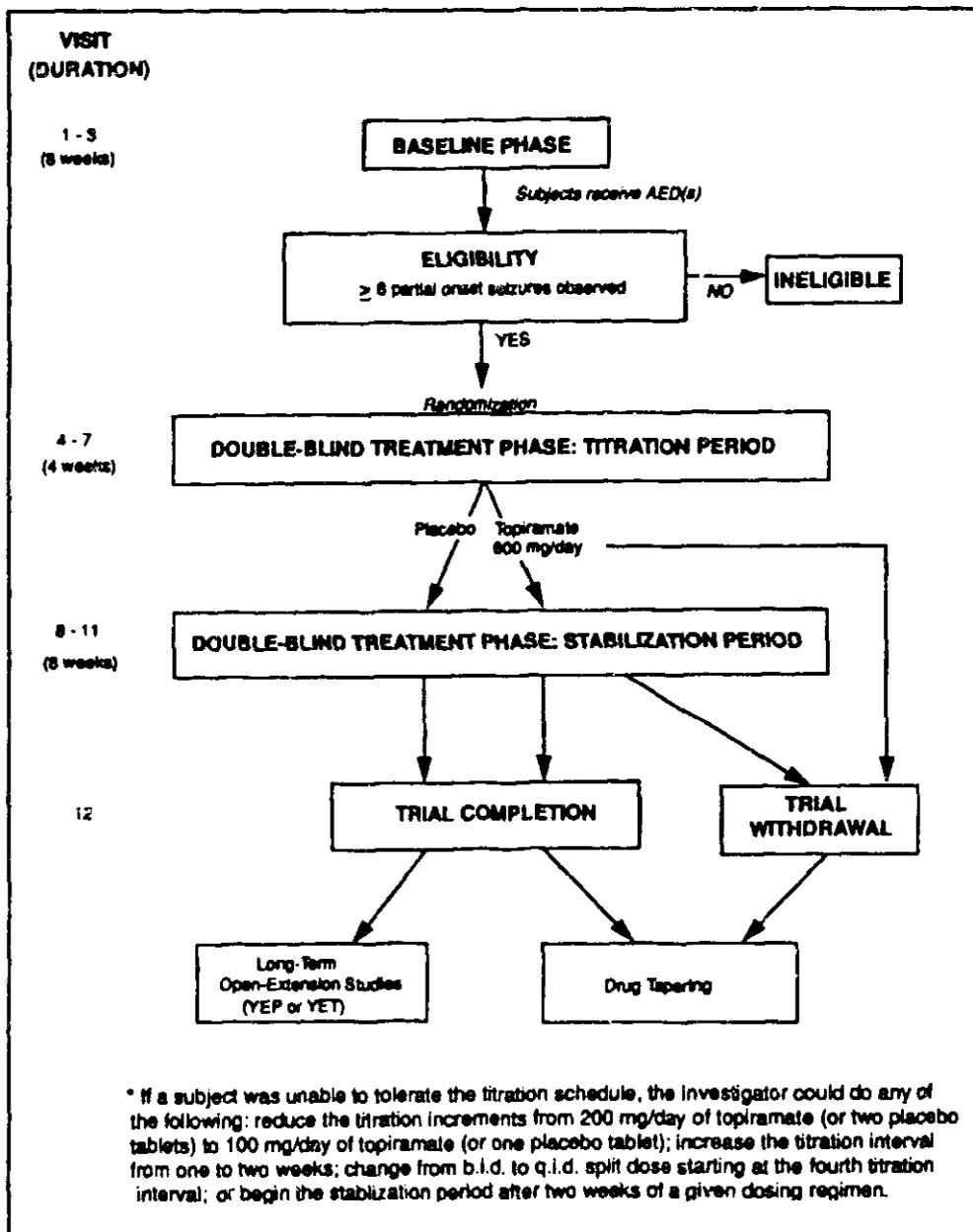
This is a multicenter, randomized, placebo-controlled, double-blind, parallel study to evaluate topiramate 600 mg/day as adjunctive therapy in subjects with refractory partial onset seizures.

The study protocol for Y2 is nearly identical to the protocols for Y1 and Y3, differing only by the dose of topiramate targeted in this study. The protocol is summarized below and the study schematic is shown on the following page.

OVERVIEW OF TRIAL PHASES

Study Interval	Duration	Therapy	Purpose
Screening Phase	Prior to baseline phase	Recent history of therapy with one or two standard AED(s)	Determine eligibility and stabilize on background AED(s)
Baseline Phase	8 weeks	Standard AED(s)	Maintain on background AED(s) and further assess eligibility
Double-Blind Phase Titration Period	4 weeks (2 to 8 weeks)	Background AED(s) and topiramate or placebo increased at weekly intervals to the assigned (or maximum tolerated, if less) dosage	Achieve the assigned (or maximum tolerated, if less) dosage of topiramate and conduct efficacy and safety observations
Stabilization Period	8 weeks	Maintenance on the assigned (or maximum tolerated, if less) dosage of study medication	Efficacy and safety observations

STUDY SCHEMATIC --PROTOCOL Y2



ENROLLMENT

The patient population that would be recruited for this study was the same as described in previous protocols and summarized below.

Key Inclusion Criteria

- 18 to 65 years old, inclusive, and no WCBP
- Unequivocal history of partial seizures with or without secondarily generalized seizures with either clinical or electroencephalographic (EEG) evidence of localized cerebral discharge. An EEG tracing demonstrating a lateralized epileptiform pattern consistent with a diagnosis of partial epilepsy was required within five years before study entry. For entry into the double-blind phase, subjects were required to have at least eight partial seizures during the eight-week baseline phase while maintained at therapeutic AED plasma concentrations. During the eight-week baseline phase of the study, the longest allowable seizure-free interval was three weeks, and only one such seizure-free interval was permitted.
- Steady state trough plasma concentrations of one or two of the following AEDs within a restricted range:

Concomitant AED	Trough Plasma Concentration Range (µg/mL)
Carbamazepine	4-14
Phenytoin	8-15
Phenobarbital	15-40
Primidone	5-15
Valproic Acid	40-120

- Good physical health
- CAT scan or MRI within the preceding two years to exclude potentially progressive neurologic diseases.

Key Exclusion Criteria

- Treatable cause of seizures or progressive neurologic disorder
- Documented history of status epilepticus while complying with appropriate therapy
- Contraindication, hypersensitivity, or known allergy to carbonic anhydrase inhibitors or sulfonamides
- Significant acute or chronic confounding physical disease (e.g., malignancy with metastatic potential, or a history of other serious medical diseases, including cardiovascular, hepatic, renal, gastrointestinal, metabolic, or endocrine diseases)
- History of substance abuse within one year before admission
- History of a serious psychiatric disorder, symptoms of schizophrenia, any psychotic symptomatology, or history of suicide attempt
- History of poor compliance with therapy
- Treatment with an experimental drug or use of an experimental device within 60 days before admission
- Abnormal baseline laboratory parameters

- History of nephrolithiasis
- Inability to take medication or maintain a seizure calendar, independently or with assistance

Efficacy

The primary efficacy variable was to be the frequency of seizures. "Each patient will have a seizure per week (or day) variable computed for the baseline period and each ensuing dose period. Comparisons between groups will be done by computing change from baseline seizure rates and employing appropriate statistical techniques. In addition efficacy will also be assessed by analyzing the severity of seizures, duration of seizure-free intervals, and physician and patient rating scales." There was no specific detail provided for any of these variables.

The protocol was silent with regard to methodology for counting seizures, specifically seizures that occurred in clusters.

Study Conduct

The study was conducted in accordance with the protocol with some additions, which will be alluded to.

ENROLLMENT: demographic and baseline characteristics

Sixty-five subjects were enrolled in the baseline phase of this trial at six centers within Europe; 60 subjects qualified for randomization and then received study medication. Thirty subjects were randomized to receive topiramate 600 mg/day and 30 subjects to receive placebo.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS (ALL RANDOMIZED SUBJECTS; PROTOCOL Y2)

Attribute	Placebo (N=30)	Topiramate 600 mg/day (N=30)	Total (N=60)
Age (yr)			
Mean \pm SD	32.9 \pm 11.71	32.9 \pm 9.21	32.9 \pm 10.44
Gender			
% Male/Female	77/23	80/20	78/22
Race			
% White	93	97	95
% Oriental	3	0	2
% Other	3	3	3

Seizure Type			
% Simple Partial	57	43	50
% Complex Partial	97	93	95
% 2° Generalized	63	57	60
% Other Types	13	20	17
Baseline Average			
Monthly Seizure Rate	72.2	40.3	56.2
Mean	188.93	58.15	139.51
SD	15	16.8	16.0
Median	4.0 - 925.0	4.0 - 230.0	4.0 - 925.0
Range			

Of the 60 randomized subjects, 47 (78%) were men and 13 (22%) were women. All but three of the subjects were white (95%). Their mean age was 32.9 years, their mean weight was 152.7 pounds, and their mean height was 67.8 inches. All subjects were required to have documented refractory partial epilepsy. Most of the subjects (63%) were receiving carbamazepine either alone or in combination with phenobarbital, phenytoin, primidone, or valproic acid. The median seizure rate at baseline was 16.8 for the topiramate 600 mg/day group and 15.0 for the placebo group.

**DEMOGRAPHIC AND BASELINE CHARACTERISTICS:
BACKGROUND AEDs, AND SEIZURE TYPE
(ALL RANDOMIZED SUBJECTS; PROTOCOL Y2)**

Attribute	Placebo (N=30)		Topiramate 600 mg/day (N=30)		Total (N=60)	
	N	%	N	%	N	%
Background AED(s)						
Phenobarbital	1	3	1	3	2	3
Phenytoin	1	3	4	13	5	8
Carbamazepine	9	30	5	17	14	23
Clobazam/Phenytoin	0	0	1	3	1	2
Clobazam/Barbiturates	4	13	2	7	6	10
Phenobarbital/Phenytoin	1	3	1	3	2	3
	8	27	6	20	14	23
Phenobarbital/Carbamazepine	2	7	2	7	4	7
Phenytoin/Primidone	2	7	3	10	5	8
Phenytoin/Carbamazepine	0	0	1	3	1	2
Phenytoin/Valproic Acid	1	3	3	10	4	7
Primidone/Carbamazepine	1	3	0	0	1	2
Primidone/Valproic Acid	0	0	1	3	1	2
Carbamazepine/Valproic Acid						

Seizure Type*						
Simple Partial	17	57	13	43	30	50
Complex Partial	29	97	28	93	57	95
Secondarily Generalized	19	63	17	57	36	60
All Other Types	4	13	6	20	10	17

Titration schedule

The titration schedule was planned to consist of four one-week intervals with protocol-specific adjustments to this schedule allowed for subjects unable to tolerate the titration schedule as planned. The initial dose administered to subjects during the first titration interval was either 100 mg topiramate or one tablet of placebo every morning. During the second titration interval, subjects were administered either 100 mg topiramate b.i.d. or one tablet of placebo b.i.d. Subsequently, the dose increment for each remaining titration interval was either 100 mg topiramate b.i.d., or one tablet of placebo b.i.d., until the subject reached the assigned maximum dosage (or the maximum tolerated dosage, if less) and the titration period was completed.

Those subjects who qualified for participation in the double-blind phase of the trial were randomized to receive one of two treatments, 600 mg/day of topiramate or placebo, while continuing their background AED regimens. The investigator was permitted to alter the dosing schedule of any subject who could not tolerate the titration schedule by any of the following means: 1) increase the daily dose of study medication by only one tablet of topiramate (100 mg) or one tablet of placebo weekly, 2) increase the dosing interval from one to two weeks, 3) starting at Titration Interval 4, change the dosing frequency from twice daily to four times daily, or 4) after two weeks on a specific dosing regimen, discontinue the titration period and begin the stabilization period. Subjects who did not reach their assigned dosage levels during the titration period were maintained at their maximum tolerated dosage.

Seizure Data

Subjects recorded the date and time of seizures and a description of seizure type in their seizure diaries. The investigator classified each seizure type described in the subject's diary before the data were recorded on the subject's case report form. The standard seizure classifications used are:

- Simple partial (SP)
- Complex partial (CP)
- Partial evolving to secondarily generalized (PE)

If seizures occurred in a cluster, the investigator added "CL" to the

classification. However, because many subjects could not count the seizures in a cluster, it was decided to allow subjects either to estimate the number of seizures in a cluster or to count the cluster as one seizure. Only one of these two approaches was to be adopted and used consistently by the subject throughout the trial.

No clusters of seizures were recorded during this trial.

Global Evaluations and Assessments

Global evaluations and assessments were performed by the investigators and subjects at the final visit of the double-blind phase. The investigator's global evaluation of improvement relative to baseline for each subject was recorded as worse (1), none (2), minimal (3), moderate (4), or marked (5). Likewise, the subject's overall assessment of medication was recorded as poor (1), fair (2), good (3), or excellent (4).

The primary efficacy variable was percent reduction in the average monthly seizure rate from the baseline phase to the double-blind phase. Secondary efficacy variables included percent treatment responders, investigator's global evaluation of improvement, subject's overall assessment of medication, and percent reduction in the generalized seizure rate.

DISCONTINUATION/COMPLETION INFORMATION:

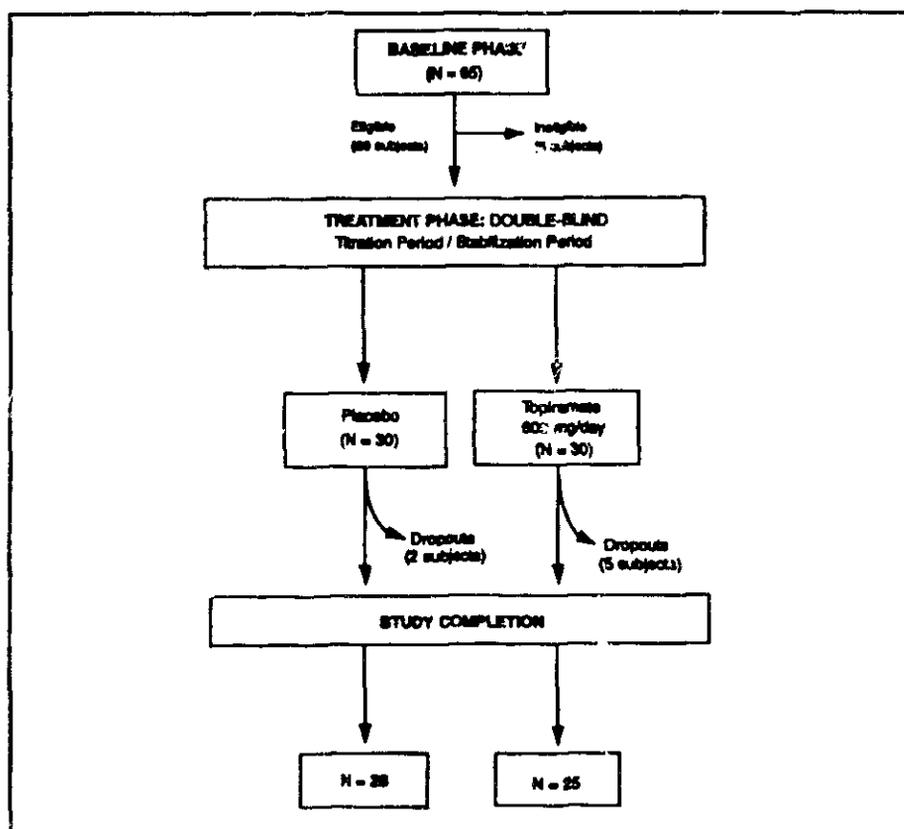
Twenty-five (83%) subjects in the topiramate 600 mg/day group and 28 (93%) in the placebo group completed the trial. Seven (12%) of 60 subjects withdrew from the trial prematurely, including five (8%) because of limiting adverse events. Four of these five subjects were in the topiramate 600 mg/day group and one was in the placebo group.

Patient disposition information is summarized in the table and figure on the following page.

**SUMMARY OF DISCONTINUATION/COMPLETION
INFORMATION: DOUBLE-BLIND PHASE
(ALL RANDOMIZED SUBJECTS; PROTOCOL Y2)**

Reason	Placebo (N=30)		Topimax 600 mg N=30		Total (N=60)	
	N	%	N	%	N	%
Study completed	28	93	25	83	53	88
Study discontinued						
Limiting adverse events	1	3	4	13	5	8
Drug ineffective	1	3	0	0	1	2
Subject's choice	0	0	1	3	1	2
Total discontinued	2	7	5	17	7	12

DISCONTINUATION/COMPLETION SUMMARY--PROTOCOL Y2



Dosages

Dosage titration to the assigned dosage or the maximum-tolerated dosage, if less, for each subject over the entire double-blind treatment phase (titration and stabilization periods) resulted in a mean by-subject average dosage of only 430 mg/day in the topiramate 600 mg/day group. A summary of the mean and median dosages for the double-blind phase is presented by treatment group below.

**Sponsor's Table 10: Summary of the Average Dosage^a: Double-Blind Phase^b
(All Randomized Subjects; Protocol Y2)**

Treatment	Mean	Standard Deviation	Median
Placebo ^c (N=30)	4.8	0.9	5.1
Topiramate 600 mg/day (N=30)	430.0	117.4	505.3

^a Subject's average over the entire double-blind phase.

^b The group for which the intent-to treat analysis was performed

^c Placebo dosages are given as number of tablets.

The summary of the average dosage for the stabilization period only is presented by treatment group in Sponsor's Table 11. The median average dosage for the topiramate group during the stabilization period, 600 mg/day, was equivalent to the target daily dosage of 600 mg/day.

**SPONSOR'S TABLE 11
SUMMARY OF THE AVERAGE DOSAGE^a
STABILIZATION PERIOD
ALL RANDOMIZED SUBJECTS WHO ENTERED THE STABILIZATION PERIOD**

Treatment	Mean	Standard Deviation	Median
Placebo ^b (N=30)	5.7	1.0	6.0
Topiramate 600 mg/day (N=27)	519.3	125.8	600.0

^a Subject's average over the stabilization period.

^b Placebo dosages are given as number of tablets; the target was six tablets/day.

PROTOCOL VIOLATIONS

The sponsor asserts that there were no protocol violations in this study with the exception of one patient who was found to have a disqualifying

condition during baseline, and who was, therefore, discontinued.

In terms of disallowed concomitant medications, there was no record of patients receiving antiepileptic drugs on a pm basis for seizure flurries or status epilepticus. Only one patient was noted to have been treated with a disallowed drug, a placebo patient who received a single dose of nitrazepam for insomnia.

Sponsor's Efficacy Results

The trial was not completed at the time of NDA submission. Because a Final Report of the trial was not available, the sponsor submitted a status report of the on-going trial for the NDA. The report contained data on selected variables (demographics, dropouts and adverse experiences) for the 44 patients who had been randomized by October 31, 1992. On May 15, 1995, the sponsor submitted efficacy data for all randomized patients on diskette to the Agency as well as a Full Clinical and Statistical Report.

Efficacy analyses were conducted (i) using all double-blind phase data (both titration period and stabilization period); and (ii) using only stabilization period data. These analyses employed identical methods; therefore, the following description will refer to the double-blind phase.

The average monthly (28-day) seizure rate for each patient was computed for the baseline and double-blind phases. The average monthly seizure rate for a time period was calculated as (the total number of seizures reported during the period divided by the number of days in the period) multiplied by 28 days. The baseline seizure rate was calculated as the average monthly seizure count for the last 8 pretreatment weeks. For a patient whose baseline was restarted or extended, usually due to a change in background AED dosage, only data from the final 8 weeks were used.

The primary efficacy variable was percent reduction in seizure rate, defined as $100(B-D)/B$, where B=baseline seizure rate and D=double-blind seizure rate. To assess efficacy of topiramate 600 mg, the comparison to placebo was made using a two-factor (treatment, center, and treatment-by-center interaction) analysis of variance on ranks. All randomized patients were used in the efficacy analysis.

Medians and ranges for the primary efficacy variable as well as statistical

results for the treatment comparison with placebo are shown below. For the 7 patients who were discontinued early, seizure rates were calculated based on the actual time in the trial.

**Percent Reduction From Baseline in Average Monthly Seizure Rate for the Double-Blind Phase
(All Randomized Subjects; Protocol Y2)**

Treatment	Percent Seizure Rate Reduction ^a	
	Median	Range
Placebo (N=30)	-12.2	(-327.8, 76.4)
Topiramate 600 mg/day (N=30)	46.4	(-199.4, 95.9)
P-value ^b	0.004	

^a Negative numbers denote an increase in seizure rate.

^b Topiramate vs. placebo; two-factor ANOVA on ranks with type III sums of squares.

Topiramate 600 mg/day had a significantly greater percent reduction from baseline in the average monthly seizure rate compared to placebo ($p=0.004$). There was no statistically significant treatment-by-center interaction ($p=0.775$).

To investigate the consistency of results for the primary efficacy variable across centers, patients were ranked and the mean ranks calculated for each center and treatment group. Results favored topiramate 600 mg/day over placebo at the five centers with patients in both treatment groups.

Secondary variables

Responder Rate

A patient was defined as a treatment responder if the percent seizure rate reduction during the double-blind phase from baseline was greater than or equal to 50%. The percentage of responders in the topiramate 600 mg treatment group was compared with placebo using the Cochran-Mantel-Haenszel method stratified by center.

**Treatment Responders for the Double-Blind Phase
(All Randomized Subjects; Protocol Y2)**

Treatment	Treatment Responders ^a	
	N	%
Placebo (N=30)	3	10
Topiramate 600 mg/day (N=30)	14	47
P-value^b	0.001	

^a Subjects with 50% or greater seizure reduction from baseline.

^b Topiramate vs. placebo; Cochran-Mantel-Haenszel test blocked on investigator.

A statistically greater percentage of patients receiving topiramate were treatment responders compared with the placebo group. Response rates were 47% (14/30) for the topiramate treatment group and 10% (3/30) for the placebo group (p=0.001).

Investigator's Global Assessment

The investigator's global evaluation of improvement at the end of the double-blind phase compared with baseline (5-point scale: 1=worse, 2=none, 3=minimal, 4=moderate, 5=marked) was analyzed by Wilcoxon rank-sum test stratified by center.

**INVESTIGATOR'S GLOBAL EVALUATION OF IMPROVEMENT AT THE END OF THE
DOUBLE-BLIND PHASE COMPARED WITH BASELINE
(ALL RANDOMIZED SUBJECTS; PROTOCOL Y2)**

Rating	Placebo (N=30)		Topiramate 600 mg/day (N=30)	
	N	%	N	%
Worse (1)	0	0	2	7
None (2)	20	67	8	27
Minimal (3)	6	20	5	17
Moderate (4)	4	13	9	30
Marked (5)	0	0	6	20
Mean	2.5		3.3	
P-value^a	0.002			

^a Topiramate vs. placebo; Wilcoxon rank sum test stratified by investigator.

The investigator's global evaluation of improvement was statistically superior for topiramate (mean 3.3) compared to placebo (mean 2.5). The p-value was 0.002.

Patient's Overall Assessment

The patient's overall assessment of medication at the end of the double-blind phase compared with baseline (4-point scale: 1=poor, 2=fair, 3=good, 4=excellent) was analyzed by Wilcoxon rank-sum tests stratified by center.

**SUBJECT'S OVERALL ASSESSMENT OF MEDICATION AT THE END OF THE DOUBLE-BLIND
PHASE COMPARED WITH BASELINE
(ALL RANDOMIZED SUBJECTS; PROTOCOL Y2)**

	Placebo (N=30)		Topiramate 600 mg/day (N=30)	
	N	%	N	%
Rating				
Poor (1)	16	53	10	33
Fair (2)	10	33	6	20
Good (3)	4	13	10	33
Excellent (4)	0	0	4	13
Mean	1.6		2.3	
P-value^a	0.010			

^a Topiramate vs. placebo; Wilcoxon rank sum test stratified by investigator.

The patient's overall assessment of medication was statistically superior for topiramate dosage (mean 2.3) compared to placebo (mean 1.6). The p-value was 0.010.

Plasma concentrations of concomitant antiepileptic drugs

The sponsor investigated changes in plasma concentrations of concomitant antiepileptic drugs from the baseline phase to the double-blind phase. The analysis used a one-way ANOVA to compare topiramate with placebo with respect to the mean change from baseline.

With the exception of carbamazepine, the mean changes in plasma concentrations of each concomitant AED (phenytoin, valproic acid, phenobarbital, and primidone) from the baseline to the double-blind phase were not significantly different ($p \geq 0.175$) between topiramate- and placebo-treated patients. Mean plasma carbamazepine concentrations during double-blind treatment were reduced by 0.7 $\mu\text{g/ml}$ with topiramate treatment (i.e., "double-blind" - baseline = -0.7 $\mu\text{g/ml}$), compared to a slight increase of 0.3 $\mu\text{g/ml}$ with placebo treatment ("double-blind" - baseline = 0.3 $\mu\text{g/ml}$). The difference was statistically significant ($p=0.013$). However, the direction of the changes in carbamazepine concentrations in the respective treatment groups (topiramate \downarrow , placebo \uparrow) indicate that the statistically significant reduction in seizure rate observed with topiramate could not be attributed, wholly or partially, to higher concentrations of carbamazepine compared to those in the

placebo group.

Trial Y2: FDA Statistical Reviewer's Results

The sponsor submitted three datasets on diskette for efficacy analyses: (1) patient demographics, (2) daily seizure counts for each patient by seizure type, (3) derived variables (seizure counts and rates) used in the NDA submission. All datasets were without error.

The statistical reviewer replicated the sponsor's results.

Comments:

This trial demonstrates the efficacy of topiramate as adjunctive therapy in the treatment of partial onset seizures. As in previous studies, the doses targeted were not reached; The average dose of topiramate in this study (during the stabilization phase) was 519 mg, somewhat lower than the targeted 600 mg.

STUDY Y3

TITLE: Double-Blind Parallel Comparison of Topiramate 400 mg Twice Daily To Placebo In Patients With Refractory Partial Epilepsy

OBJECTIVES The purpose of this study is to evaluate the comparative efficacy of oral topiramate 800 mg daily to placebo as add-on therapy in patients with refractory partial epilepsy who are receiving a maximum of two concomitant anticonvulsants.

Protocol

STUDY DESIGN:

This was a multicenter, randomized, placebo-controlled, double-blind, parallel study that evaluated topiramate 800 mg/day as adjunctive therapy in subjects who had refractory partial seizures

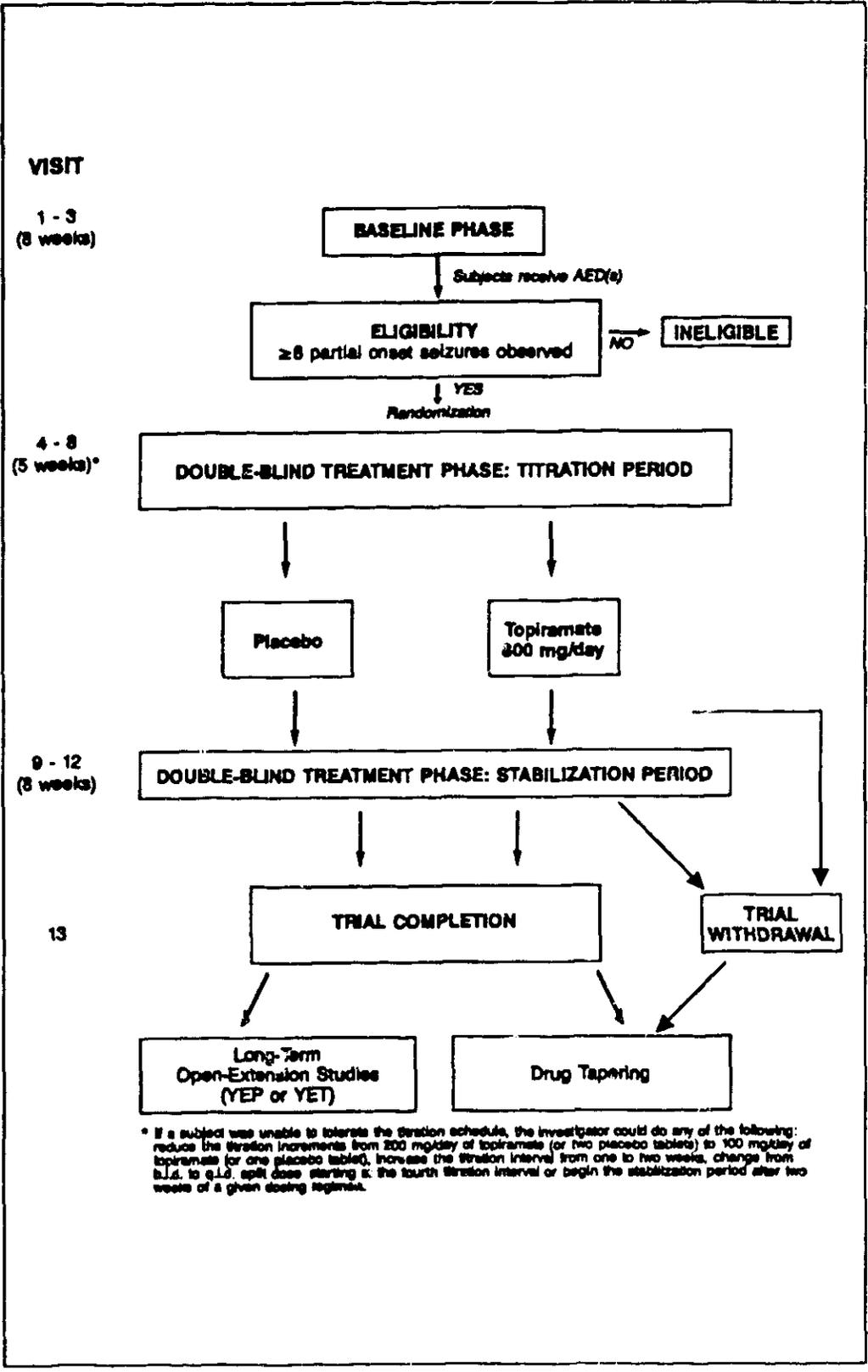
The trial consisted of four phases: screening, baseline, double-blind, and tapering. An overview of the trial phases is presented in Table 1.

The study protocol for Y3 is the same design as protocol Y1 and Y2, differing only in the topiramate dose studied, in this case, 800 mg/day.

Table 1: Overview of Trial Phases

Study Interval	Duration	Therapy	Purpose
Screening Phase	Prior to baseline phase	Recent history of therapy with one or two standard AED(s) ^a	Determine eligibility and stabilize on background AED(s)
Baseline Phase	8 weeks	Standard AED(s) ^a	Maintain on background AED(s) and further assess eligibility
Double-Blind Phase Titration Period	5 weeks (2 to 10 weeks) ^b	Background AED(s) and topiramate or placebo increased at weekly intervals to the assigned (or maximum tolerated, if less) dosage	Achieve the assigned (or maximum tolerated, if less) dosage of topiramate and conduct efficacy and safety observations
Stabilization Period	8 weeks	Maintenance on the assigned (or maximum tolerated, if less) dosage of study medication ^c	Efficacy and safety observations
Tapering Phase ^d	Variable	Decreasing dosages of topiramate	Safe withdrawal of topiramate therapy

The study schematic is shown on the following page.



ENROLLMENT

Approximately fifty patients were planned for participation in this trial who would be on concomitant therapy of one or two of the following anticonvulsants: phenytoin, carbamazepine, valproic acid, phenobarbital or primidone. Clobazam or clonazepam can also be used but only as adjunctive therapy with one of the above.

**TABLE 1: KEY INCLUSION CRITERIA
(PROTOCOL Y3)**

- Eighteen to 65 years old, inclusive, and, if female, postmenopausal or surgically rendered incapable of having children, or not pregnant or nursing and using birth-control methods.
- Unequivocal history of partial seizures with or without secondarily generalized seizures with either clinical or electroencephalographic (EEG) evidence of localized cerebral discharge. An EEG tracing demonstrating a lateralized epileptiform pattern consistent with a diagnosis of partial epilepsy was required within five years before study entry. For entry into the double-blind phase, subjects were required to have at least eight partial seizures during the eight-week baseline phase while maintained at therapeutic AED plasma concentrations. During the eight-week baseline phase of the study, the longest allowable seizure-free interval was three weeks, and only one such seizure-free interval was permitted.
- Steady state trough plasma concentrations of one or two of the following AEDs within a restricted range:

Concomitant AED	Trough Plasma Concentration Range ($\mu\text{g/mL}$)
Carbamazepine	4-14
Phenytoin	8-25
Phenobarbital	15-40
Primidone	5-15
Valproic Acid	40-120

- Good physical health. Note: mild to moderate hypertension was allowed if well-controlled with a stabilized regimen of a β -adrenergic blocking agent (β -blocker) or angiotensin converting enzyme inhibitor.
- CAT scan or MRI within the preceding two years to exclude potentially progressive neurologic diseases.

**Key Exclusion Criteria
(Protocol Y3)**

- Treatable cause of seizures or progressive neurologic disorder
 - Documented history of status epilepticus while complying with appropriate therapy
 - Significant acute or chronic confounding physical disease (e.g., malignancy with metastatic potential, or a history of other serious medical diseases, including cardiovascular, hepatic, renal, gastrointestinal, metabolic, or endocrine diseases)
 - History of alcohol or drug abuse within one year before admission
 - History of a serious psychiatric disorder, symptoms of schizophrenia, any psychotic symptomatology, or history of suicide attempt
 - History of poor compliance with therapy
 - Known allergy or hypersensitivity to carbonic anhydrase inhibitors or sulfonamides, or those in whom carbonic anhydrase inhibitors were contraindicated
 - Treatment with an experimental drug or use of an experimental device within 60 days before admission
 - Abnormal baseline laboratory parameters except for the following: liver function tests of serum glutamate-oxaloacetate transaminase (SGOT), serum glutamate-pyruvate transaminase (SGPT), and alkaline phosphatase, which could be elevated to a level of twice the upper limit of normal; and hematologic parameters including WBC count >3000 cells/mm³; neutrophil count $>1,500$ cells/mm³, hematocrit $>37\%$, and platelet count $>150,000$ cells/mm³
 - History of nephrolithiasis
 - Inability to take medication or maintain a seizure calendar, independently or with assistance
-

The primary efficacy variable was defined imprecisely as in the previous protocols, but was to have its basis in seizure frequency.

STUDY CONDUCT

Fifty-seven subjects entered the baseline phase, 56 of whom qualified for participation in the double-blind phase. Twenty-eight subjects were assigned to the topiramate 800 mg/day group and 28 subjects were assigned to the placebo group. Baseline demographic characteristics including seizure type were comparable between the treatment groups

(Table 3). Most of the subjects (82%) were receiving carbamazepine either alone or in combination with clobazam, clonazepam, phenobarbital, phenytoin, primidone, or valproic acid.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS:

Fifty-seven subjects entered the baseline phase, 56 of whom qualified for participation in the double-blind phase and were randomized. Twenty-eight subjects were assigned to the topiramate 800 mg/day group and 28 subjects were assigned to the placebo group. Baseline demographic characteristics including seizure type were comparable between the treatment groups (Table 3). Most of the subjects (82%) were receiving carbamazepine either alone or in combination with clobazam, clonazepam, phenobarbital, phenytoin, primidone, or valproic acid. The median seizure rate at baseline was 14.2 for the topiramate 800 mg/day group and 11.4 for the placebo group.

**Table 3: Demographic and Baseline Characteristics
(All Randomized Subjects; Protocol Y3)**

Attribute	Placebo (N=28)	Topiramate 800 mg/day (N=28)	Total (N=56)
Age (yr)			
Mean \pm SD	34.7 \pm 11.29	39.7 \pm 11.08	37.2 \pm 11.37
Gender			
% Male/Female	86/14	82/18	84/16
Race			
% White	100	100	100
Weight (lb)			
Mean \pm SD	165.6 \pm 28.33	165.4 \pm 23.10	165.5 \pm 25.61
Body Mass ^a			
Mean \pm SD	3.4 \pm 0.44	3.5 \pm 0.47	3.5 \pm 0.46
Seizure Type ^b			
% Simple Partial	39	39	39
% Complex Partial	86	82	84
% Secondarily Generalized	75	64	70
Baseline Average Monthly Seizure Rate ^c			
Mean	29.2	43.9	36.5
SD	57.44	80.27	69.56
Median	11.4	14.2	12.3
Range	3.9 - 304.1	2.3 - 328.7	2.3 - 326.7

^a Body Mass = 100 (Weight/Height²)

^b Individual subjects may have had a history of more than one seizure type.

^c Monthly = Rate per 28 days.

DISCONTINUATION/COMPLETION INFORMATION:

Forty-nine (88%) of 56 subjects completed the trial. Six (11%) subjects discontinued from the trial because of adverse events and one discontinued due to lack of efficacy. A summary of the reasons for discontinuation is presented in the following table.

**Summary of Discontinuation/Completion Information: Double-Blind Phase
(All Randomized Subjects; Protocol Y3)**

Reason	Placebo (N=28)		Topimax 800 mg (N=28)		Total (N=56)	
	N	%	N	%	N	%
Study completed	27	96	22	79	49	88
Study discontinued						
Limiting adverse events	0	0	6	21	6	11
Drug ineffective	1	4	0	0	1	2
Total discontinued	1	4	6	21	7	13

DOSES ACHIEVED:

Dosage titration to the assigned dosage or the maximum tolerated dosage resulted in a mean by-subject average dosage of 448.0 mg/day in the 800 mg/day group. The mean and median dosages for the double-blind phase are summarized below in Sponsor's Table 10.

**Sponsor's Table 10: Summary of the Average Dosage^a: Double-Blind Phase
(All Randomized Subjects; Protocol Y3)**

Treatment	Mean	Standard Deviation	Median	Range
Placebo ^b (N=28)	6.3	0.45	6.5	4.5 - 6.6
Topiramate 800 mg/day (N=28)	448.0	181.46	448.7	130.0 - 660.0

^a Subject's average over the entire double-blind phase.

^b Placebo dosages are given as number of tablets.

The summary of the average dosage for the stabilization period only is presented by treatment group in Sponsor's Table 11. The mean dosage for the topiramate group during the stabilization period, 567.9 mg/day,

was much lower than the target daily dosage of 800 mg/day.

**Sponsor's Table 11: Summary of the Average Dosage^a: Stabilization Period
(All Randomized Subjects Who Entered the Stabilization Period; Protocol Y3)**

Treatment	Mean	Standard Deviation	Median	Range
Placebo ^b (N=28)	7.9	0.57	8.0	5.0 - 8.0
Topiramate 800 mg/day (N=25)	587.9	230.66	600.0	196.6 - 800.0

^a Subject's average over the stabilization period

^b Placebo dosages are given as number of tablets

Protocol violations

Sponsor has reported no protocol violations and asserts that no patient was withdrawn from a trial because of a protocol violation.

The use of medications during this trial was limited and drugs with antiepileptic properties (except for those daily adjunctive AEDs allowed by protocol) taken on a pm basis were not allowed. The use of additional medications in this trial was reviewed and was limited to only 5 patients with this kind of protocol violation. The medications used were Diazepam or Lorazepam, and in 4/5 patients they were used to treat seizures. The distribution of this violation occurred in both treatment groups and in both phases of the study. While potential inaccuracies are introduced when pm medications are used to treat the primary outcome measure, seizures, in this case there does not, at least, appear to be a systematic error either in favor for or against topiramate.

**Table: Protocol Violations Involving Use of disallowed medication
(with AED properties)***

Pt ID	Treatment Assignment	Baseline	Double blind
900/6	Placebo		Lorazepam (1-2 mg) x3 for seizures
900/10	Topiramate 800 mg	Diazepam pm for anxiety	
901/1	Placebo		Diazepam 5-20 mg x 9 for seizures
901/2	Topiramate 800 mg	Diazepam 5 mg x 2 for seizures	Diazepam 5-20 mg x8 for seizures
901/2*			
901/8	Placebo	Diazepam 10mg x 4 for seizures	Diazepam 10mg x 11 for seizures

Efficacy Data

Seizure counts

Subjects recorded the date and time of seizures and a description of seizure type in their seizure diaries. The duration of each seizure was to have been recorded in the subject's diary; however, because of the difficulty associated with subjects' timing the duration of their seizures, these data were not collected consistently and were not analyzed.

The investigator classified each seizure type described in the subject's diary before the data were recorded on the subject's case report form. The standard seizure classifications used are:

- Simple partial (SP)
- Complex partial (CP)
- Partial evolving to secondarily generalized (PE)

If seizures occurred in a cluster, the investigator added "CL" to the classification. The number of seizures and the duration of the seizures in the cluster were to have been recorded. However, because many subjects could not count the seizures in a cluster, it was decided to allow subjects either to estimate the number of seizures in a cluster or to count the cluster as one seizure. Only one of these two approaches was to be adopted and used consistently by the subject throughout the trial.

Seizure clusters were reported in 4 patients, one placebo and 3

topiramate. Clusters were generally counted as accurately as the patient or caretaker was able. In only two cases did patients use the assignment of "1CL". One patient (assigned to topiramate 800 mg) had two clusters during baseline, for which he assigned "1CL", and another patient also in the topiramate group who reported 4 clusters as "1CL" on the same day, during baseline. The use of this method of assigning counts to seizure flurries would seem inherently inaccurate; however, its use was limited and would not be expected to bias the results.

In reviewing the raw and transcribed data on seizure clusters, it became apparent that not all seizure clusters were recorded as such. Some inaccuracies in transcription were noted and resulted in an internal audit of the seizure data for this trial. The magnitude of errors affecting seizure counts that were not clusters was insignificant.

Global Evaluations

Global evaluations and assessments were performed by the investigators and subjects at the final visit of the double-blind phase. The investigator's global evaluation of improvement relative to baseline for each subject was recorded as worse (1), none (2), minimal (3), moderate (4), or marked (5). Likewise, the subject's overall assessment of medication was recorded as poor (1), fair (2), good (3), or excellent (4).

Trial Y3: Sponsor's Results

Efficacy analyses were conducted (i) using all double-blind phase data (both titration period and stabilization period); and (ii) using only stabilization period data. These analyses employed identical methods; therefore, the following description refers to the double-blind phase only.

The average monthly (28-day) seizure rate for each patient was computed for the baseline and double-blind phases. The average monthly seizure rate for a time period was calculated as (the total number of seizures reported during the period divided by the number of days in the period) multiplied by 28 days. The baseline seizure rate was calculated as the average monthly seizure count for the last 8 to 12 pretreatment weeks. (For some patients, the baseline phase exceeded the planned eight-week duration.) For a patient whose baseline was restarted or extended, usually due to a change in background AED dosage, only data from the final 12 weeks were used.

The primary efficacy variable was percent reduction in seizure rate, defined as $100(B-D)/B$, where B=baseline seizure rate and D=double-blind seizure rate. Comparison between the topiramate- and placebo-

treated groups was by analysis of variance based on ranks of percent seizure rate reduction. All randomized patients were used in the efficacy analyses.

Medians and ranges for the primary efficacy variable during the double-blind phase as well as statistical results for the comparison of topiramate with placebo are shown below. For the 7 patients who were discontinued early, seizure rates were calculated based on the actual time in the trial. Results of efficacy analyses using data from the stabilization period only were, in general, similar to those for the double-blind phase.

Percent Reduction From Baseline in Average Monthly Seizure Rate for the Double-Blind Phase (All Randomized Subjects; Protocol Y3)

Treatment	Percent Seizure Rate Reduction ^a	
	Median	Range
Placebo (N=28)	-17.8	(-152.1, 42.3)
Topiramate 800 mg/day (N=28)	35.8	(-554.6, 100.0)
P-value ^b	0.001	

^a Negative numbers denote an increase in seizure rate.

^b Topiramate vs. placebo; two-factor ANOVA on ranks with type III sums of squares.

To investigate the consistency of results for the primary efficacy variable across centers, patients were ranked and the mean ranks calculated for each center and treatment group. Results favored topiramate 800 mg/day over placebo for all four centers. There was no statistically significant treatment-by-center interaction ($p=0.591$).

SECONDARY VARIABLES

Treatment Responders

A patient was defined as a treatment responder if the percent seizure rate reduction during the double-blind phase from baseline was greater than or equal to 50%. The percentage of responders in the topiramate 800 mg treatment group was compared with placebo using the Cochran-Mantel-Haenszel method stratified by center. A statistically greater percentage of patients receiving topiramate were treatment responders compared with the placebo group. Responder rates were 43% (12/28) for the topiramate treatment group and 0% for the placebo group ($p=0.001$).

**Treatment Responders for the Double-Blind Phase
(All Randomized Subjects; Protocol Y3)**

Treatment	Treatment Responders*	
	N	%
Placebo (N=28)	0	0
Topiramate 800 mg/day (N=28)	12	43
P-value	0.001	

There was no statistically significant treatment-by-center interaction ($p=0.506$) for the analysis of treatment responders, indicating that the relative differences in this variable between topiramate and placebo were consistent across study centers.

Investigator's Global Assessment

The mean score for investigator's global evaluation of improvement was 3.7 for the topiramate 800 mg/day group compared with 2.3 for the placebo group.

**Investigator's Global Evaluation of Improvement at the
End of the Double-Blind Phase Compared With Baseline
(All Randomized Subjects; Protocol Y3)**

Rating	Placebo (N=28)		Topiramate 800 mg/day (N=28)	
	N	%	N	%
Worse (1)	1	4	2	7
None (2)	21	75	6	21
Minimal (3)	3	11	3	11
Moderate (4)	3	11	4	14
Marked (5)	0	0	13	46
Mean	2.3		3.7	
P-value*	<0.001			

* Topiramate vs. placebo; Wilcoxon rank sum test stratified by investigator.

The results of analysis of investigator's global evaluation of improvement showed that 800 mg/day of topiramate was statistically superior to placebo, $p < 0.001$.

Patient's Overall Assessment

The mean score for subject's overall assessment of medication was 2.4 for the topiramate 800 mg/day group compared with 1.8 for the placebo group (Sponsor's Table 16). The results of statistical comparison of scores for subject's overall assessment showed that topiramate 800 mg/day was statistically superior to placebo, $p=0.009$.

Sponsor's Table 16: Subject's Overall Assessment of Medication at the End of the Double-Blind Phase Compared With Baseline (All Randomized Subjects; Protocol Y3)

Rating	Placebo (N=28)		Topiramate 800mg/day (N=28)	
	N	%	N	%
Poor (1)	11	39	8	29
Fair (2)	12	43	6	21
Good (3)	5	18	9	32
Excellent (4)	0	0	5	18
Mean	1.8		2.4	
P-value^a	0.009			

^a Topiramate vs. placebo; Wilcoxon rank sum test stratified by investigator.

Plasma concentrations of concomitant antiepileptic drugs

The sponsor investigated changes in plasma concentrations of concomitant antiepileptic drugs from the baseline phase to the double-

blind phase. The analysis used a one-way ANOVA to compare topiramate with placebo with respect to the mean change from baseline.

Mean changes in plasma concentrations of each concomitant AED (carbamazepine, phenytoin, valproic acid, phenobarbital, and primidone) from baseline to the double-blind phase were small and not statistically different between topiramate- and placebo-treated patients ($p \geq 0.246$). Overall, plasma concentrations of all AEDs were comparable over time between the topiramate- and the placebo-treated patients. Thus the statistically significant reduction in seizure rate observed with topiramate could not be attributed to higher concentrations of any of the concomitant antiepileptic drugs compared to concentrations in the placebo group.

Trial Y3: FDA Statistical Reviewer's Results

Following discussions between the sponsor and FDA involving the accuracy of the derived variables in Trials YD and YE, the sponsor submitted, in addition to three datasets with the same formats as datasets 1-3 for YD and YE, a fourth dataset for Trial Y3. The fourth dataset contained revised derived variables. In summary, the four datasets were: (1) patient demographics, (2) daily seizure counts for each patient by seizure type, (3) derived variables (seizure counts and rates) used in the NDA submission, and (4) revised derived variables.

The sponsor scrutinized the raw seizure data (dataset 2) and did not detect any additional errors.

Use of the revised data resulted in changes in the sponsor's percent seizure rate reduction for some patients. These changes produced changes in the summary measures. Revised median seizure percent reductions and ranges are shown on the next page.

Trial Y3: Percent Seizure Rate Reduction From Baseline Revised Rates

	Percent Seizure Rate Reduction	
	Median	Range
Placebo (n=28)	-20.6 ^a	(-152.1, 40.3)
Topiramate 800 mg/day (n=28)	24.3	(-554.6, 100.0)

^aNegative numbers denote an increase in seizure rate.

The statistical reviewer used the sponsor's statistical model -- two-factor

(treatment, center and treatment-by-center interaction) Analysis of Variance (ANOVA) -- for the analysis of the primary efficacy variable. (Nonparametric analysis of ranks was indicated here because the distributions of the response variable were highly skewed towards negative values for the topiramate treatment group ($p=0.0001$) and somewhat so for the placebo treatment group ($p=0.069$)). The overall statistical result for percent seizure rate reduction remained highly significant using the revised data ($p=0.0008$):

Trial Y3: P-values

	P-value*	
	Revised data	Sponsor's data
topiramate 800 mg vs placebo	0.0008	0.0012

* Topiramate vs placebo; two-factor ANOVA on ranks with type III sums of squares

Use of the revised data did not change the sponsor's results for the primary efficacy variable for individual centers. All four centers (still) favored topiramate 800 mg over placebo.

Comments

This trial demonstrates the efficacy of topiramate as adjunctive medication in the treatment of partial onset epilepsy. It must be noted that the patients in the topiramate-treated group received an average of 568 mg rather than 800 mg during the stabilization period.

14 Pages

Purged

7.7 Integrated Summary

Trials YD, YE, Y1, Y2 and Y3: Sponsor's Review of Required Subgroup Comparisons

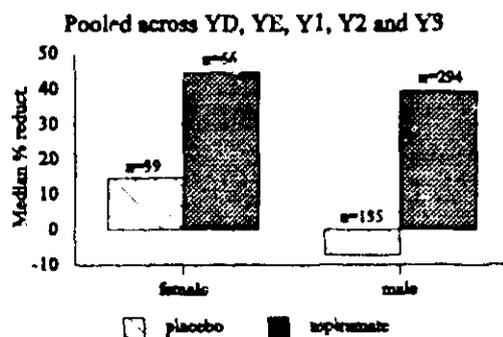
For Trials YD, YE, Y1, Y2, and Y3, the sponsor submitted statistical summaries of the relative efficacy of topiramate and placebo for reducing all seizures or generalized seizures as a function of gender, race and age. No comparable analyses were submitted for

Gender

Eighty-five (105) of the 534¹ randomized subjects in Trials YD, YE, Y1, Y2 and Y3 were female and 429 were male. The median percent reduction in seizure rate following topiramate treatment, pooled across all five trials and dosage groups, was 39% in males and 45% in females. The median reduction observed in placebo-treated male patients was

-7% and in female patients was 15%. The percent of patients demonstrating a therapeutic response to topiramate treatment (i.e., \geq 50% reduction in seizure rate relative to baseline) was similar for males and females (38% and 44%, respectively).

Effect of gender on seizure rate

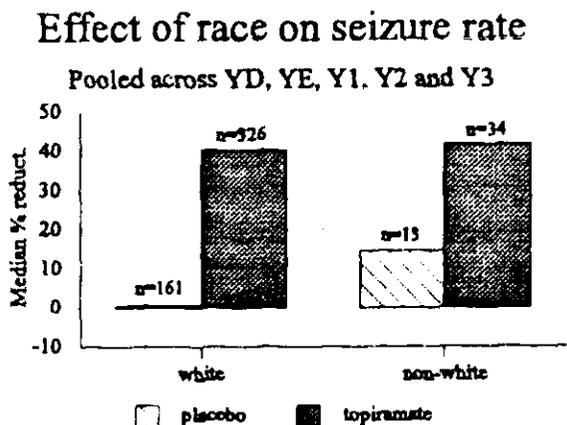


¹This figure does not appear to agree with the figures for the placebo controlled trials reported in the safety data (see section 8.0) and summary of studies in section 5.0. However, this is correct, as this the safety report includes from study YF/G which has not been formally reported to the NDA as an efficacy study and therefore does not contribute to this analysis, but which has contributed safety data from approximately 200 patients.

Of the 137 patients with generalized seizures during baseline in Trials YD, YE, and Y3, 107 were male.

Race

Four hundred eighty-seven (487) of the 534 patients randomized to double-blind treatment were white, with the remainder black (n=47).



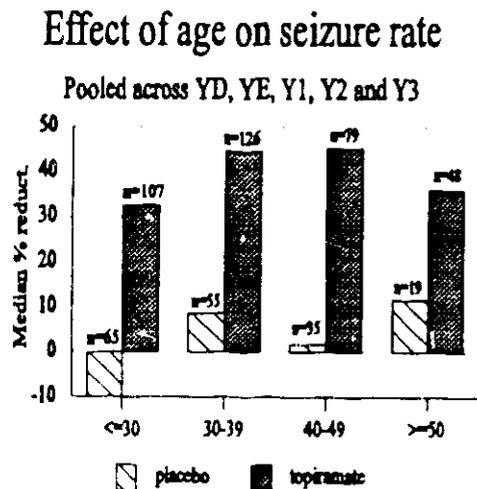
The median percent reduction in seizures during the double-blind phase relative to the baseline phase was 40% for white patients and 42% for non-white patients. Similarly, the percent of topiramate patients demonstrating a therapeutic response (i.e., $\geq 50\%$ reduction in seizures compared to baseline phase) was similar among whites (39%) and non-whites (38%).

reduction in seizure rate. The respective values for placebo-treated patients were 28% of the 39 white patients and 33% of the three non-white patients.

whites). Revised figures incorporating data from Y1 and Y2 have not

Age

In Trials YD, YE, Y1, Y2 and Y3, the median percent reduction from baseline in seizures during double-blind topiramate treatment was 33% for patients under 30 years of age (n=107), 45% for patients 30-39 years (n=126), 45% for 40-49 years (n=79), and 36% for 50 years or older (n=48). The percent of topiramate-treated patients showing a $\geq 50\%$ reduction in seizure rate relative to baseline was also comparable for these four age groups (36%, 43%, 43%, and 31%, respectively).



5.

All Add-on Trials: FDA Statistical Reviewer's Analysis of Required Subgroup Comparisons

The sponsor presented response data in the Integrated Summary of Effectiveness section of the NDA for required subgroups sex, age and race. The data were summarized using tables and graphs. This reviewer conducted statistical tests of subgroup-by-treatment interactions using combined data from all trials with topiramate as adjunctive therapy (YD, YE, Y1, Y2 and Y3).

Methods

Statistical analyses were conducted to evaluate the relative efficacy of topiramate and placebo as a function of gender, race (white, non-white) and age (<30, 30-39, 40-49, >49). Statistical interactions between treatment and a given subgroup were assessed using the ANOVA with two factors (treatment, subgroup of interest) and interaction effect. For the analysis of sex differences, for example, model effects were treatment, sex, and treatment-by-sex interaction. The treatment effect consisted of two levels: Topiramate (topiramate dosages combined across trials) and placebo (placebo groups combined across trials). The SAS procedure for General Linear Models (GLM) was used to analyze the ranks of percent seizure rate reduction. Analyses were conducted using the revised data.

Results

There was no statistical evidence that the relative efficacy of topiramate to placebo varied substantially between males and females ($p=0.27$), whites and non-whites ($p=0.60$), and different age groups ($p=0.46$).

EFFICACY SUMMARY

This section is an effort to consolidate the information provided in the six major phase 2 trials in this NDA evaluating the efficacy of topiramate in the treatment of partial onset seizures. The following tables and text will summarize the findings and conclusions drawn with regard to efficacy at different doses, and for indications beyond adjunctive therapy in partial onset seizures.

The studies and designs of the six major studies are summarized in the table below.

Controlled Clinical Trials of Topiramate

Trial/Dates	Number of centers	Design	Randomized treatment (number of patients randomized)
YD 2/88-12/90	18 US	R, DB, , add-on. 12-week baseline phase 16-week double-blind phase	Placebo (n=45) Topiramate 200 mg (n=45) Topiramate 400 mg (n=45) Topiramate 600 mg (n=46)
YE 3/88-1/91	18 US*	R, DB, , add-on. 12-week baseline phase 18-week double-blind phase	Placebo (n=47) Topiramate 600 mg (n=48) Topiramate 800 mg (n=48) Topiramate 1000 mg (n=47)
Y1 10/89-5/93	4 EUR	R, DB, , add-on. 8-week baseline phase 11-week double-blind phase ^b	Placebo (n=24) Topiramate 400 mg (n=23)
Y2 12/89-2/93	6 EUR	R, DB, , add-on. 8-week baseline phase 12-week double-blind phase ^c	Placebo (n=30) Topiramate 600 mg (n=30)
Y3 5/89-2/92	4 EUR	R, DB, , add-on. 8-week baseline phase 13-week double-blind phase ^d	Placebo (n=28) Topiramate 800 mg (n=28)

Patient accrual and randomization are summarized in the next table.

DISPOSITION OF PATIENTS IN ALL CONTROLLED TRIALS (YD, YE, Y1, Y2, Y3 AND YI): NUMBERS ENROLLED IN BASELINE PHASE AND RANDOMIZED TO DOUBLE-BLIND TREATMENT

Trial	Number enrolled in baseline phase	Number randomized to double-blind treatment							Total randomized
		Pbo	Topiramate (mg/day)						
			100	200	400	600	800	1,000	
YD	223	45		45	45	46			181
YE	242	47				48	48	47	190
Y1	52	24			23				47
Y2	65	30				30			60
Y3	57	28					28		56
YI	51		24					24	48
Total	690	174	24	45	68	124	76	71	582

Before turning to the actual results of the efficacy trials, a summary is provided for the actual doses achieved (mean and median) for each study.

**SUMMARY OF THE AVERAGE DOSES ACHIEVED DURING THE DOUBLE BLIND PHASE
ALL STUDIES--TOPIRAMATE ONLY**

	TARGET DOSE	MEAN \pm SD	MEDIAN
YD	200 mg	187.6 \pm 23.11	193.8
	400 mg	334.4 \pm 76.38	366.9
	600 mg	454.7 \pm 122.54	518.6
YE	600 mg	431.0 \pm 160.9	520
	800 mg	611.2 \pm 149.3	690
	1000 mg	610.9 \pm 249.2	739.8
Y1	400 mg	312 \pm 81.6	352.6
Y2	600 mg	430.0 \pm 117.4	510
Y3	800 mg	448.0 \pm 181.46	448.7
YI	1000 mg		1000 mg

It is evident from the above table that doses were not consistently achieved in clinical studies. These studies have not effectively studied 800 mg since targeted doses for YE and Y3 were never achieved on the average. However, the firm could make a case for the efficacy at higher doses by considering Y1 primarily for its demonstration of efficacy at a dose of 1000 mg, since those doses were largely achieved.

First Claim: Efficacy as adjunctive therapy in the treatment of partial onset seizures in the dosage range of 200-1000 mg/day
The primary efficacy variable for five major studies is summarized in the table below by dose and study.

**Median Seizure Percent Reductions* IN ADD-ON TRIALS: ALL SEIZURES
(ALL RANDOMIZED PATIENTS, USING REVISED DATA)**

Trial	PBO	Topiramate (mg/day)				
		200	400 ¹	600 ²	800 ³	1,000 ⁴
YD	11.6 n=45	27.2 n=45 (0.080)	47.5 n=45 (0.009)	44.7 n=46 (<0.001)		
YE	1.7 n=47			40.7 n=48 (<0.001)	41.0 n=48 (<0.001)	36.0 n=47 (<0.001)
Y1	1.1 n=24		40.7 n=23 (0.065)			
Y2	-12.2 ^b n=30			46.4 n=30 (0.004)		
Y3	-20.6 ^b n=28				24.3 n=28 (<0.001)	

* P-values for two-factor ANOVA on ranks comparing topiramate and placebo, with type III sums of squares, is shown in parentheses below the median value.

¹The actual mean doses achieved in either study where 400 mg was intended to be analyzed was 312 or 334 mg.

²Doses achieved were in the 400 mg range.

³Patients were treated in the range of 400-600 mg in these studies.

⁴The mean dose for this study was in the 600 mg range.

* Negative number denotes an increase in seizure rate.

While efficacy was unequivocally demonstrated statistically in at least one of all but the 200 mg group, the reality does not match the intent. One cannot conclude efficacy about doses that were never received. The range of doses associated with positive results were in the range of 400 - 600 mg. The higher doses were not achieved in these add-on studies because of the flexibility of dosing allowed by the protocol. In order to explore the efficacy of topiramate at higher doses one must

MEDIAN SEIZURE PERCENT REDUCTIONS IN ADD-ON TRIALS

USING REVISED DATA)

Trial	Placebo	Topiramate (mg/day)					P-val
		200	400	600	800	1,000	
YD	-0.6 ^b n=14	55.1 n=14	100.0 n=15	88.8 n=13			0.02
YE	40.0 n=18			65.5 n=12	48.1 n=17	78.0 n=11	0.19
Y1	8.7 n=8		83.9 n=14				0.00
Y2	100.0 n=5			77.8 n=6			1.0
Y3	18.8 n=11				90.0 n=13		0.06

- * Two-factor ANOVA on ranks with type III sums of squares using patients with generalized seizures during baseline phase or double-blind phase (or both). Topiramate groups were combined for this assessment.
- ^b Negative number denotes increase in seizure rate.

Conclusion:

The efficacy results for all studies are summarized in the table below.

**SUMMARY OF EFFECTIVENESS^a IN CONTROLLED TRIALS OF TOPIRAMATE AS ADD-ON THERAPY
(ALL RANDOMIZED PATIENTS, USING REVISED DATA FROM ENTIRE DOUBLE-BLIND PHASE)**

Seizure type	YD			YE			Y1	Y2	Y3
	200 mg/d	400 mg/d	600 mg/d	600 mg/d	800 mg/d	1,000 mg/d	400 mg/d	600 mg/d	800 mg/d
All seizures	T	S	S	S	S	S	T	S	S

^a Effectiveness was measured comparing placebo with topiramate using the primary outcome measure, percent reduction from baseline in the average monthly seizure rate.

^b The analysis compared placebo with the three topiramate treatment groups combined.

KEY: Compared to placebo control:

S = statistical significance, $p \leq 0.05$

T = statistical trend, $0.05 < p \leq 0.10$

NS = no statistical significance, $p > 0.10$

In summary, the sponsor has demonstrated the efficacy of topiramate as therapy for partial onset seizures. The dosage range associated with efficacy are 400- 1000 mg. There is no

The following indicates concurrence with the joint clinical-statistical review of the efficacy data in NDA #20-505, as found in Section 7.

J Todd Sahlroot
J. Todd Sahlroot, Ph.D.
Mathematical Statistician (Biomedical)

S Edward Nevius 11-10-95
S. Edward Nevius, Ph.D. (concur)

S Edward Nevius 11-10-95
for Satya D. Dubey, Ph.D. (concur)

The following indicates concurrence with the joint clinical-statistical review of the efficacy data in NDA #20-505, as found in Section 7.

J. Todd Sahlroot, Ph.D.
Mathematical Statistician (Biomedical)

S. Edward Nevius, Ph.D. (concur)

Satya D. Dubey, Ph.D. (concur)

8.0 SAFETY FINDINGS

8.1 ORIGIN OF SAFETY DATA: GROUPINGS THAT WILL BE USED

This safety summary presents data from 1,679 subjects (1,446 subjects with epilepsy and 249 nonepileptic subjects) who received topiramate in clinical studies that were completed or ongoing as of March 31, 1995. An additional 407 patients contributed information on deaths and serious adverse events, for a total denominator of 2086 patients for those events.

The clinical review of safety data includes data from 44 clinical studies grouped into three pools according to study design as follows:

- Double-blind trial in subjects with epilepsy--
(one study)

Including safety data from all 48 subjects enrolled in the only completed, double-blind, low dose-controlled, parallel-group trial of topiramate in the treatment of adult subjects with partial onset seizures with

One additional was terminated for administrative reasons before adequate patient accrual had taken place.

- Double-blind trials in subjects with epilepsy --Add on (7 studies)

Including safety data from all 527 subjects enrolled in three completed, double-blind, placebo-controlled, parallel-group trials of topiramate as adjunctive therapy in the treatment of adult subjects with partial onset seizures

Protocols YD, YE, YF, YG, Y1, Y2, Y3).

- All Topiramate-Treated Subjects with Epilepsy (Overall Analysis Population)

This population includes 1,446 epileptic subjects who received topiramate therapy in completed double-blind studies, completed or ongoing open-label, studies in patients with epilepsy, and ongoing double-blind studies

This review will attempt to summarize human safety findings, analyses, and interpretations, whether they come from individual studies, pools of relevant studies, the entire population exposed in the sponsor's development program, or any of the secondary sources.

8.1 METHODS

The topiramate NDA Integrated Summary of Safety and 7-month Safety Update provided the foundation from which the safety review emerged. The safety data below was evaluated by looking first at the most serious events reported in patients treated with Topiramate, the deaths, "serious" adverse reactions as defined in 21CFR 312.32 (a), withdrawals due to adverse events, then finally the common and possibly less serious adverse events. Common adverse events were examined through individual study reports and summary tables of adverse events grouped as described in section 8.0. The adverse events were screened by the sponsor for frequency, severity and likelihood of drug attributability based on the expected characteristics of the drug class, chemical class and indication, and from the preclinical profile of the drug. Regardless, all adverse events were considered drug-associated and none were dismissed. Finally unanticipated, possibly serious adverse events were screened for.

Adverse events anticipated from topiramate, as a carbonic anhydrase inhibitor were based on the profile of the prototype, acetazolamide, and included such events as renal calculi, paraesthesias, gastrointestinal upset, and acidosis. Adverse events anticipated from a sulfonamide include rash, renal failure, aplastic anemia and vasculitis. Adverse events expected in the target population include such events as seizures, *status epilepticus*, withdrawal symptomatology, SUDE (sudden and unexplained death in epilepsy), suicide, depression. Adverse events predicted from animal studies: anemia, ataxia, teratogenicity. All of these were anticipated in the review of the topiramate NDA safety data base.

Adverse events not expected but noted in the routine adverse event reports and in the IND safety reports included hearing loss, psychosis, and thrombotic phenomena.

8.2 ASSESSMENT OF DEATHS

This section will focus on deaths that occurred in patients participating in any topiramate clinical trials. There were a total of 19 deaths reported to NDA 20-505 of which the total number of exposed patients or subjects was 2086 (2600 patient years). All patients who died were taking topiramate at the time, and were involved in an open label extension study. The sponsor classified the deaths in one of three categories: accidental, unexplained, and medical. The information about these patients is summarized in the table on the next page.

Summary of Deaths Occurring in Topiramate-Treated Subjects as of March 31, 1995

PtID Study	Age (yr)	Sex	Dosage at Onset of Event (mg/day)	Total Days of Topiramate Therapy ^b	Cause/ Comment
<i>Sudden, Unexplained Deaths</i>					
12/5 Study YKT	24	M	600	171	Cause: Sudden and Unexplained Death Comment: Found dead in his apartment. Up to 18 seizures per day. Refractory. Comeds: Primidone and Phenytoin. <u>No postmortem</u>
31/16 Study YKT	28	M	400	576	Cause: Sudden and Unexplained Death Comment: Found dead at home. Had nearly daily seizures the month before death. Comeds: CBZ and PHT. Postmortem failed to reveal an adequate explanation for death.
188/110 Study YLr	20	F	1,200	129	Cause: Unexplained Comment: The subject was found dead in the bath by a family member.
167/4 Study YF/YG	27	M	800	114	Cause: Unexplained Comment: The subject was found dead after complaining of a number of small seizures. No autopsy was performed.
25/14 YLT	63	M	1600	1768	Cause: Unexplained Comment: Patient complained of dizziness for one week followed by increased confusion. He was found dead in bed and autopsy failed to reveal the cause.
150/4 Study YF/YG	36	M	1,200	864	Cause: Unexplained Comment: On Day 864, the subject experienced two generalized seizures which were not different from his typical seizures. He was later found in an awkward position and could not be awakened. The subject was taken to a hospital where he died an hour later.
29/126 Study YOL	40	M	1,600	258	Cause: Unexplained Comment: The subject was found dead on Day 258. He was last seen by the investigator approximately two weeks before his death and was doing well at that time. An autopsy was not performed.

PtID Study	Age (yr)	Sex	Dosage at Onset of Event (mg/day)	Total Days of Topiramate Therapy ^b	Cause/ Comment
229/291 Study YOL	47	F	400	306	Cause: Unexplained Comment: On Day 306, the subject experienced two generalized tonic/clonic seizures. The next morning, she was found pulseless and was hospitalized with anoxic encephalopathy. The subject died two days later.
2/979 Study YOLE	27	M	200	92	Cause: Unexplained Comment: The subject was found dead in the bath.
43/8 Study YKT	30	M	600	233	Cause: Sudden and Unexplained Death Comment: Found dead in bathtub. Attributed to drowning. Patient had undergone a change in medication from primidone to phenytoin 19 days prior to death. The patient still had barbiturate levels in the therapeutic range at the time of death. Seizure frequency prior to medication change was average 2/week. Postmortem revealed chronic granulomatous changes in spleen, liver and heart. <i>Cause of death could not be determined (AFIP)</i>
743/7 Study YJ	33	M	800	342	Cause: Unexplained Comment: The subject was found dead. The death was attributed to accidental drowning (in a hot tub or pool)
9204/503 Study 64859204 (Japan)	29	M	600	314	Cause: Unexplained Comment: The subject was found dead in his bathroom. The death was presumed by the investigator to be due to drowning.
743/1 Study YJ	40	F	1,600	356	Cause: Unexplained Comment: The subject had a history of hypertension and peptic ulcer disease, and had had a right temporal lobectomy approximately three years before entering this study. She died on Day 356. <i>Autopsy findings</i> were nonspecific, revealing only mild pulmonary edema, moderate coronary atherosclerosis, mild focal hepatic portal triaditis, moderate renal congestion, and focal cerebral gliosis.
Accidental Deaths					
4/14 Study YCO2	40	F	600	1,594	Cause: Multiple trauma secondary to fall Comment: Husband witnessed what he thought was a seizure leading to the fall from tower to roof. Comedications: Phenytoin and CBZ
904/14 Study YEP	38	M	600	111	Cause: Multiple trauma due to MVA Comment: Patient was driver. Patient was experiencing 1-3 seizures per month despite three medications. Comeds: Valproate, phenytoin. <i>No postmortem.</i>
Medical Events					
16/18 Study YKT	40	M	1,300	403	Cause: Pulmonary Embolism Comment: Patient had platelet count on routine lab or 774K and developed thrombophlebitis. One week later he was hospitalized and died of a massive pulmonary embolism. Embolectomy was attempted. One month previously, patient had had a study in which the platelets were clumped and could not be counted. Comed: CBZ

PtID Study	Age (yr)	Sex	Dosage at Onset of Event (mg/day)	Total Days of Topiramate Therapy ^b	Cause/ Comment
24/22 Study YKT	84	M	400	579	Cause: Cancer Comment: Adenocarcinoma of the cecum, squamous cell carcinoma of the chest and basosquamous cell carcinoma of the elbow. Diagnosis of carcinomas was reported on day 362 of treatment. Comedication: CBZ
903/4 Study YEP	31	M	500	1,319	Cause: Astrocytoma Comment: The subject had undergone a partial resection of an astrocytoma and radiotherapy approximately 4 years before enrolling in Protocol Y3. CT scan of the brain on Day 1,045 showed growth of the tumor and edema. The subject was hospitalized for prednisolone treatment and surgery evaluation. The subject was released and treated with prednisolone 70 mg/day for the cerebral edema. On Day 1,318, the subject was hospitalized for markedly severe constipation. An intestinal blockage was confirmed by X-ray film. Because the subject was terminally ill, intravenous morphine treatment was initiated and all other therapy, including topiramate, was discontinued on Day 1,319. The subject died three days after topiramate therapy was discontinued.
904/5 Study YET	63	M	400	1,069	Cause: Pulmonary Embolism Comment: The subject's medical history included paraproteinemia and cardiac failure. He entered the study with a diffuse peripheral neuropathy and ataxia requiring the use of a wheelchair. During the study, the subject experienced weight loss, anorexia, and vomiting. In the ensuing year, the subject became progressively incapacitated despite treatment with folate and intravenous immunoglobulin. On Day 990, the subject was admitted to a hospital for pneumococcal pneumonia, treated with amoxicillin and clavulanic acid, and discharged after five days. While continuing topiramate therapy, the subject's general condition remained poor and he became bedridden. On Day 1,069, bronchitis developed. His general condition deteriorated. No therapy was given and a few hours later the subject died in apparent respiratory distress. The subject's death was attributed to possible pulmonary embolism or acute cardiopulmonary failure. <i>No postmortem.</i>

SUDDEN UNEXPLAINED DEATHS. Using the broadest criteria possible, (defined below) there are 13 of the 19 deaths reported in topimax-treated patients for whom the cause of death or the cause leading to death could not be determined. Patients were classified as SUDE if they were otherwise healthy epileptic patients, and there was no obvious preceding cause of death. As part of the definition (which has been applied to other antiepileptic NDAs in this division), epilepsy-related accidental deaths (especially drownings) are usually considered among the unexplained causes of death. The definition used in previous analyses of SUDE's in this division will be used here, even though it differs somewhat from the sponsor's classification.

Because the two out of three of what the sponsor classified as "accidental deaths" were essentially unobserved, only one can be explained. One patient who fell onto a roof from an TV antennae tower and who died of head injuries sustained during the fall, was witnessed to have had a seizure by her husband. The other two must be considered unexplained. This convention has been retained in the FDA's analysis of sudden unexplained deaths in epilepsy used in all previous NDAs in the past 3 years. Therefore, for the sake of comparison, the same convention will be used. It may be argued that the patient who drowned or the patient who was involved in a MVA were unobserved, were not shown to have had a seizure preceding their death and the autopsy was noncontributory in the former case, the deaths will be considered sudden and unexplained.

All patients were taking topiramate at the time of death. In all of these cases either the patients were not witnessed and were later found dead, or there was an accidental death (drowning, car accident or fall from roof, where the patient's immediate cause of accident was not accurately described.

The total data base of topiramate treated subjects is 2600 patient-years. This rate (5/1000 patient years) is comparable to the rates of sudden unexplained death described for the three most recent antiepileptic drugs approved. The patients who died suddenly in topiramate studies were mostly young males in the range of 24-36 years, were on three antiepileptic drugs and continued to have seizures in spite of their polytherapy. The median dose of topiramate was 600 mg.

The table on the following page demonstrates that the incidence of SUDE in the topiramate NDA is roughly comparable to those in two recently approved antiepileptic drugs, whose demographic profiles closely resemble those of topiramate.

**TABLE: COMPARISON OF SUDE RATES FOR TOPIMAX
COMPARED THAT IN RECENTLY APPROVED DRUGS FOR EPILEPSY**

ANTIEPILEPTIC DRUG (NDA)	SUDE INCIDENCE
Topiramate #20-427 1995	5/1000 pt-years
Felbamate #20- 462 1993	not available ¹
Gabapentin #20-454 1993	2.5/1000 pt-years
Lamotrigine #20-241 1994	5.8/1000 pt-years

DEATHS DUE TO THROMBOTIC PHENOMENA. Two patients died of a pulmonary embolism while on Topiramate therapy. One was in good health up to the time of death, although in the two months prior to therapy he was documented to have one platelet determination for which the platelets were clumped and could not be accurately counted, and a second in which thrombocytosis was documented at 774,000 platelets. A second patient was thought to have died of a pulmonary embolism. There was no indication of such an event or of events preceding the patient's death in the CRF, however the narrative summary, which was clearly derived from sources other than the CRF, indicated a general decline in the patient's health and activity level over the months preceding death. The patient was hospitalized for possible bronchitis, although there were no positive findings on examination, and he died in respiratory distress within hours of admission. Pulmonary embolism was the presumed cause of death. While a determination of drug causality cannot reasonably be ruled out, it cannot be established for certain.

¹The crude rate of 5/1677 patients (3%) for Felbamate is compared to the crude rate for SUDE in Topiramate, that is 12/2086 (6%).

8.3 ASSESSMENT OF DROPOUTS

8.3.1 OVERALL PATTERN OF DROPOUTS

The table below summarizes the predominant reason given for premature discontinuation among patients enrolled in placebo controlled studies with topiramate. Rates of dropout are found in the table enumerating dropouts by reason topiramate-treated patients compared to controls. Adverse experiences were responsible for the majority of dropouts in both groups but topiramate patients far outnumbered placebo patients overall and by dropouts because of adverse events.

RATES OF DROPOUT BY TREATMENT GROUP AND REASON FOR PLACEBO-CONTROLLED STUDIES		
REASON FOR DROPOUT	PERCENT DROPPING OUT	
	TOPIRAMATE (N = 527)	PLACEBO (N = 216)
LACK OF EFFICACY	2 (.4%)	2 (.9%)
ADVERSE EXPERIENCES	89 (17%)	9 (4%)
OTHER	5 (.9%)	3 (1.4%)
ADMINISTRATIVE REASONS	0 (0%)	1 (.5%)
INTERCURRENT ILLNESS	1 (.2%)	0 (0%)
SUBJECT'S CHOICE	6 (1.1%)	1 (.5%)
PROTOCOL VIOLATION	6 (1.1%)	0 (0%)
UNKNOWN	0 (0%)	1 (.5%)
TOTAL DROPOUTS	109 (20.7%)	17 (7.9%)

The table below summarizes the predominant reason given for premature discontinuation among patients enrolled in any clinical study with topiramate. Rates of dropout are found in the table enumerating dropouts by reason for the overall phase 2-3 epilepsy study pool. As the table shows, nearly 25% of patients withdrew from topiramate studies because of adverse events.

**RATES OF DROPOUT BY TREATMENT GROUP AND
REASON FOR ALL TOPIRAMATE TREATED PATIENTS WITH
EPILEPSY N=1446**

REASON FOR DROPOUT	N	%
Limiting adverse event	360	24.9
Drug Ineffective	198	13.7
Other	22	1.5
Subject expired	1	0.1
Administrative reason	17	1.2
Intercurrent illness	11	0.8
Subject's Choice	89	6.2
Protocol Violation	25	1.7
Total	723	50.0

So, as the table demonstrates, approximately 25% of all epilepsy patients enrolled in clinical trials dropped out because of adverse events. Compared to other recent epilepsy drugs approved in the last 5 years, this somewhat exceeds the rates for dropouts for adverse events. For example, gabapentin approved in 1993 had an incidence of 17% dropouts due to adverse events at the time of approval, lamotrigine, 9% and felbamate 12.2%.

**COMPARATIVE RATES FOR WITHDRAWAL DUE TO ADVERSE EVENTS
(COMBINED CLINICAL STUDIES)**

DRUG	N	WDAE
GABAPENTIN (1993)	1746	17%
FELBAMATE (1993)	1677	12.2%
LAMOTRIGINE (1994)	2295	9%
TOPIRAMATE (PENDING)	1446	25%

8.3.2 ADVERSE EVENTS ASSOCIATED WITH DROPOUT

Comparing the reasons given for withdrawal or in some cases the most

recent AE around the time of withdrawal) in placebo controlled studies it was clear that the most frequent reason attributed to withdrawal in the topiramate group was that of cognitive impairment, which was manifest by impaired concentration, confusion, impaired thinking, memory difficulty, word finding difficulty, and delirium. This occurred with an incidence of 5% in the topiramate treated group and 0.9% in the placebo group. A dose-related trend was clearly seen. Not as frequent was the category which encompassed emotional lability, anxiety and nervousness, where no placebo patients withdrew for this reason and approximately 3% of topiramate treated patients did. Here again a clear dose-response relationship was seen. Psychosis, hallucinations and personality changes including aggressiveness and agitation were responsible for 1.5% of withdrawals from topiramate treatment and none from placebo. Other adverse events associated with withdrawal topiramate treatment (in more than one patient) but not placebo were (1) dizziness, (2) abdominal pain/dyspepsia, (3) visual changes (nystagmus, diplopia), (4) abnormal coordination/ataxia, (5) weight loss. The following adverse events were responsible for patients withdrawing from topiramate treatment (in only one patient each) but not placebo, included (1) neutropenia, (2) malaise (3) injury (4) abnormal ECG (5) vasospasm (6) sudden unexplained death (7) polyuria and (8) incontinence.

Adverse Events associated with Withdrawal
Double Blind Placebo Controlled Epilepsy Studies
(YE, YD, YF/G, Y1, Y2, Y3)

Adverse Event	Pbo N=216	Topiramate Treated Group N=627					TPM total
		200 mg N=45	400 mg N=68	600 mg N=124	800 mg N=76	1000 mg N=214	
Rash	2					2	4
Headache	2		1		1	2	4
Fatigue (or somnolence)	1					1	1
Seizures increased	2	1		1			2
Tremor		1					
Impaired Cognition	1		3	6	3	15	27 (5%)
Depression (includes pts with suicidal ideation)	2				1	2	3
Anxiety (includes pts with nervousness, emotional lability)			1	2	1	11	15 (3%)
Personality Change (includes agitation, aggression)		1	1	2			4
Psychosis (includes hallucination)				1		3	4

Weight Loss					2	2
Ataxia (includes abn coordination)			1	1		2
Abdominal Pain (Incl dyspepsia)		1	1	1	1	4
Dizziness		1			5	6
Diplopia (visual changes)		1	2	2	11	16
Malaise			1			1
Polyuria				1		
Incontinence			1			1
Injury			1			
Death					1	1
Vasospasm				1		
Leukopenia						1
Abn ECG					1	1

The above table also clearly demonstrates that some of the most common adverse events associated with withdrawal from placebo controlled trials also demonstrated a dose-response relationship.

In addition to those patients who discontinued topiramate placebo controlled studies because of adverse events, sponsor reveals that 295 (23%) of the 1302¹ patients enrolled in open label studies discontinued topiramate therapy because of adverse events as of March 31, 1994. The most common reasons for discontinuation from topiramate studies were CNS related, such as amnesia, aphasia, anorexia, ataxia, impaired concentration, confusion, depression, dizziness, paresthesias, somnolence, and abnormal thinking. Other reasons included fatigue and weight loss.

The patients identified in the previous section as dropping out for adverse events are shown in the table below. It is not possible to accurately determine the incidence of dropout for those specific adverse events that appear to lead to dropout, because of the manner in which coding took place.

The displays shown below are neither mutually exclusive displays, since individual patients may have experienced more than one event that led to dropout and some patients were coded for the same event by more

¹Number provided by sponsor--cannot be derived.

than one code (although this was rare). The adverse events in related categories are neither mutually exclusive and therefore not additive nor do they maintain a 1-1 correspondence. The numbers in the table below are an artifact of coding to which no intelligent overview was applied. These numbers, therefore serve only as a general guide to the frequency of adverse events which led to withdrawal, as they are by no means accurate or all-inclusive.

ADVERSE EVENTS ASSOCIATED WITH WITHDRAWAL ALL EPILEPSY STUDIES N=1446		
ADVERSE EVENT	TOPIRAMATE N	% ¹
CNS, cognitive impairment		
coded as confusion	59	4.0
coded as thinking abnormal	55	3.8
coded as concentration impaired	30	2.0
somnolence	49	3.3
fatigue	49	3.3
coma or stupor	2	0.1
delirium	1	-
memory difficulty (coded as amnesia)	44	3.0
encephalopathy	1	-
speech disorder (coded as aphasia)	30	2.0
speech disorder	16	1.1
CNS/PNS other		
convulsions aggravated	16	1.1
dizziness	40	2.8
coordination abnormal (coded as ataxia)	35	2.4
coordination abnormal	9	0.6
dyskinesia	2	0.1
headache	22	1.5
hypokinesia	7	0.5
involuntary movements	3	0.2
neuropathy	2	0.1
paresthesias	2	0.1

¹ The percentages represent the patients who withdrew as a percent of the whole 1446 exposed cohort, not against the 360 who withdrew because of adverse events.

hypoesthesias	2	0.1
hyperesthesias	1	—
dystonia	1	—
hypertonia	1	—
weakness	3	0.2
tremor	11	0.8
vertigo	3	0.2
PSYCHIATRIC		
Depression	43	3.0
Emotional Lability	25	1.7
Nervousness	27	1.9
Anxiety	21	1.5
Psychosis	12	0.8
Hallucination	10	0.7
Paranoid reaction	5	0.3
depersonalization	3	0.2
delusion	6	0.4
insomnia	14	1.0
Aggressive reaction	11	0.8
agitation	7	0.5
apathy	5	0.3
personality disorder/behavior change	9	0.6
Suicide attempt	11	0.8
overdose	4	0.3
euphoria	3	0.2
hyperkinesia	2	0.1
decreased libido	3	0.2
dreaming abnormal	2	0.1
GENERAL		
Fatigue	49	3.4
asthenia	9	0.6
Hot flashes	1	—
sweating abnormality	3	0.2
rigors	1	—
dry mouth	3	0.2
malaise	3	0.2

weight loss	15	1.0
CARDIOVASCULAR		
ECG abnormal	3	0.2
atrial fibrillation	1	—
chest pain	1	—
vasospasm	1	—
PULMONARY		
dyspnea	1	—
GASTROINTESTINAL		
abdominal pain	9	0.6
anorexia	34	2.4
constipation	3	0.2
diarrhea	4	0.3
dyspepsia	6	0.4
esophagitis	1	—
hepatic dysfunction	4	0.3
nausea	18	1.2
pharyngitis	1	—
increased salivation	1	—
stomatitis	1	—
taste perversion	4	0.3
vomiting	8	0.6
rinitis	1	—
GENITOURINARY		
renal calculi	6	0.4
renal colic	2	0.1
urinary incontinence	6	0.4
urinary retention	1	—
impotence	5	0.3
polyuria	1	—
oliguria	1	—
dehydration	1	—
thirst	2	0.1
pregnancy unintended	1	—
HEMATOLOGIC		
anemia	1	—

thrombocytopenia	1	-
granulocytopenia	1	-
pancytopenia	1	-
bleeding abn (epistaxis, gingival bleeding)	2	0.1
thrombotic phenomena, thrombophlebitis	2	0.1
thrombotic phenomena, pulmonary embolism	1	0.1
SKIN DISORDERS		
alopecia	3	0.2
rash (NS)	11	0.8
urticaria	2	0.1
pruritus	4	0.3
erythema multiforme		
Stevens Johnson's syndrome		
Visual Disturbances		
abnormal accommodation	2	0.1
diplopia	6	0.4
iritis	1	-
mydriasis	1	-
vision abnormal	14	1.0
nystagmus	4	0.3
visual field defect	2	0.1
myopia	1	-
eye pain	1	-
eye abnormality	3	0.2
Musculoskeletal		
arthralgia	2	0.1
arthritis	1	-
chest pain	2	0.1
leg pain	2	0.1
osteoporosis	1	-
pain (N/S)	2	0.1
Special Senses		
hearing loss	2	0.1
tinnitus	1	-
Other		

Injury	6	0.4
cancer	2	0.1

†Aphasia does not appear to be used specifically here.

‡This represents the only AE leading to discontinuation

Note that the frequency of events in certain cases (pregnancies, for example) is known to exceed that which was reported here as an adverse event leading to withdrawal. This was an artifact of coding which should have been overridden by careful review of the data, but appears to have been overlooked. This adds to the unreliability of these numbers, which, again, should be used only as a crude guide to adverse events which led to dropout.

The most common adverse events leading to dropout are confusion, abnormal thinking, impaired concentration, somnolence, fatigue, abnormal speech, ataxia, dizziness, depression, emotional lability and anxiety, nervousness, insomnia, headache, increased convulsions and abnormal vision. This parallels the spectrum of all adverse events reported in the topiramate-exposed epilepsy cohort.

8.4 Other Safety Findings

8.4.1 ADR Incidence Tables

8.4.1.1 Common and Drug-Related Adverse Events

INCIDENCE IN CONTROLLED CLINICAL TRIALS: The table below and continued on the following pages enumerates adverse events that occurred at a frequency of 1% or more among topiramate-treated patients who participated in placebo-controlled studies of similar design. Reported adverse events were classified using a modified WHOART preferred terminology. These figures provide some basis for estimating the relative contribution of topiramate vs. nondrug factors to the side effect incidence rate in the population studied.

TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS WITH AN INCIDENCE OF AT LEAST 1%

BODY SYSTEM/PREFERRED TERM	TOPIRAMATE	PLACEBO
TOTAL NUMBER OF SUBJECTS	527	218
# WHO EXPERIENCED ADVERSE EVENT	511 (97.0)	185 (85.6)
CENTR & PERIPH NERV SYST DISORDERS		
Dizziness	165 (31.3)	33 (15.3)
Headache	142 (26.9)	60 (27.8)
Paraesthesia	86 (18.2)	10 (4.6)
Ataxia	84 (15.9)	15 (6.9)
Nystagmus	63 (12.0)	20 (9.3)
Aphasia	64 (10.2)	1 (0.5)
Speech Disorder	63 (10.1)	5 (2.3)
Tremor	49 (9.3)	13 (6.0)
Coordination Abnormal	21 (4.0)	6 (2.3)
Hypokinesia	12 (3.6)	-
Convulsions Aggravated	13 (2.5)	10 (4.6)
Gait Abnormal	11 (2.1)	3 (1.4)
Muscle Contractions Involuntary	11 (2.1)	3 (1.4)
Hypertonia	8 (1.5)	1 (0.5)

Hypoaesthesia	8 (1.5)	2 (0.9)
Vertigo	8 (1.5)	2 (0.9)
Stupor	6 (1.1)	-
NEUROPSYCHIATRIC DISORDERS		
Somnolence	149 (28.3)	21 (9.7)
Thinking Abnormal	112 (21.3)	6 (2.3)
Nervousness	93 (17.6)	18 (7.4)
Confusion	84 (15.9)	9 (4.2)
Amnesia	69 (13.1)	7 (3.2)
Concentration Impaired	69 (13.1)	4 (1.9)
Depression	61 (11.8)	11 (5.1)
Emotional Lability	58 (11.0)	7 (3.2)
Anorexia	57 (10.8)	8 (3.7)
Anxiety	48 (9.7)	13 (6.0)
Insomnia	29 (5.5)	10 (4.6)
Agitation	19 (3.6)	3 (1.4)
Aggressive Reaction	15 (2.8)	1 (0.5)
Apathy	15 (2.8)	-
Depersonalization	11 (2.1)	2 (0.9)
Impotence	10 (1.9)	-
Hallucination	8 (1.5)	-
Euphoria	7 (1.3)	-
BODY AS A WHOLE: GENERAL DISORDERS		
Fatigue	135 (25.6)	29 (13.4)
Injury	70 (13.3)	33 (15.3)
Pain	27 (5.1)	14 (6.5)
Asthenia	22 (4.2)	3 (1.4)
Back Pain	19 (3.6)	9 (4.2)
Influenza-Like Symptoms	19 (3.6)	7 (3.2)
Leg Pain	19 (3.6)	5 (2.3)
Chest Pain	15 (2.8)	6 (2.8)
Allergy	13 (2.5)	-
Fever	13 (2.5)	4 (1.9)

Drug Level Increased	6 (1.1)	-
Hot Flashes	6 (1.1)	4 (1.9)
Malaise	6 (1.1)	1 (0.5)
Edema	6 (1.1)	2 (0.9)
GASTRO-INTESTINAL SYSTEM DISORDERS		
Nausea	63 (12.0)	16 (7.4)
Diarrhoea	59 (11.2)	16 (7.4)
Abdominal Pain	35 (6.6)	8 (3.7)
Dyspepsia	35 (6.6)	14 (6.5)
Vomiting	35 (6.6)	15 (6.9)
Constipation	20 (3.8)	5 (2.3)
Mouth Dry	19 (3.6)	2 (0.9)
Gingivitis	7 (1.3)	1 (0.5)
Gastroenteritis	6 (1.1)	4 (1.9)
Tooth Ache	6 (1.1)	6 (2.8)
RESPIRATORY SYSTEM DISORDERS		
Upper Resp Tract Infection	80 (15.2)	34 (15.7)
Rhinitis	34 (6.5)	15 (6.9)
Sinusitis	28 (5.3)	9 (4.2)
Coughing	24 (4.6)	11 (5.1)
Pharyngitis	21 (4.0)	6 (2.3)
Dyspnoea	12 (2.3)	2 (0.9)
Bronchitis	6 (1.1)	8 (3.7)
VISION DISORDERS		
Diplopia	59 (11.2)	12 (5.6)
Vision Abnormal	58 (11.0)	6 (2.8)
Eye Pain	8 (1.5)	4 (1.9)
Eye Abnormality	7 (1.3)	-
METABOLIC AND NUTRITIONAL DISORDERS		
Weight Decrease	61 (11.6)	6 (2.8)
SKIN AND APPENDAGES DISORDERS		
Rash	19 (3.6)	12 (5.6)
Pruritus	16 (3.0)	3 (1.4)

URINARY SYSTEM DISORDERS		
Urinary Tract Infection	13 (2.6)	-
Micturition Frequency	11 (2.1)	1 (0.5)
HEARING AND VESTIBULAR DISORDERS		
Tinnitus	8 (1.6)	-
Hearing Decreased	7 (1.3)	2 (0.9)
MUSCULO-SKELETAL SYSTEM DISORDERS		
Myalgia	9 (1.7)	2 (0.9)
SPECIAL SENSES OTHER, DISORDERS		
Taste Perversion	17 (3.2)	-
REPRODUCTIVE DISORDERS, FEMALE		
Dysmenorrhea	6 (3.5)	4 (6.8)
WHITE CELL AND RES DISORDERS		
Leukopenia	8 (1.5)	1 (0.5)

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2 Pages

Purged

8.4.1.2 ADVERSE EVENT INCIDENCE OVER THE ENTIRE EPILEPSY DATABASE
 During the premarketing assessment multiple doses of topiramate were administered to 1446 epileptic patients. The conditions and duration of exposure to topiramate differed and included (in overlapping categories) open and double-blind studies, fixed dose and titration studies. The adverse events reported in the pool of all epilepsy studies are grouped by system and summarized below. Adverse events reported in >10% of the treated population are shaded.

**ADVERSE EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF
 TOPIRAMATE:**

PSYCHIATRIC DISORDERS	
Somnolence	464 (32.1)
Thinking Abnormal	344 (23.8)
Nervousness	288 (19.9)
Anorexia	277 (19.2)
Confusion	264 (18.3)
Amnesia	241 (16.7)
Depression	225 (15.6)
Concentration Impaired	184 (12.7)
Emotional Lability	163 (11.3)
Insomnia	150 (10.4)
Anxiety	127 (8.8)
Aggressive Reaction	53 (3.7)
Agitation	52 (3.6)
Apathy	39 (2.7)
Hallucination	39 (2.7)

Personality Disorder	36 (2.5)
Psychosis	34 (2.4)
Impotence	27 (1.9)
Euphoria	24 (1.7)
Depersonalization	22 (1.5)
Libido Decreased	16 (1.1)
Suicide Attempt	16 (1.1)

CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS

Headache	431 (29.8)
Dizziness	419 (28.9)
Paresthesia	309 (21.4)
Ataxia	246 (17.0)
Aphasia	171 (11.8)
Tremor	156 (10.8)
Speech Disorder	155 (10.7)
Nystagmus	146 (10.1)
Convulsions Aggravated	120 (8.3)
Coordination Abnormal	71 (4.9)
Hypokinesia	59 (4.1)
Gait Abnormal	54 (3.7)

MUSCLE CONTRACTIONS INVOLUNTARY

Hypesthesia	33 (2.3)
Hypertonia	32 (2.2)
Vertigo	31 (2.1)
Convulsions Grand Mal	26 (1.8)
Stupor	25 (1.7)
Cramps Legs	16 (1.1)
Neuropathy	16 (1.1)

BODY AS A WHOLE - GENERAL DISORDERS

Fatigue	419 (29.0)
Injury	295 (20.4)
Pain	174 (12.0)
Influenza-like Symptoms	130 (9.0)

Back Pain	126 (8.7)
Leg Pain	93 (8.4)
Fever	89 (8.2)
Asthenia	79 (5.5)
Chest Pain	64 (4.4)
Allergy	35 (2.4)
Malaise	30 (2.1)
Edema	30 (2.1)
Edema Peripheral	22 (1.5)
Hot flashes	21 (1.5)
Drug Level Increased	18 (1.2)
GASTRO-INTESTINAL SYSTEM DISORDERS	
Nausea	232 (16.0)
Diarrhea	218 (15.1)
Abdominal Pain	143 (9.9)
Vomiting	123 (8.5)
Dyspepsia	115 (8.0)
Constipation	109 (7.5)
Mouth Dry	44 (3.0)
Gastroenteritis	43 (3.0)
Tooth Disorder	40 (2.8)
Tooth Ache	34 (2.4)
Gingivitis	26 (1.8)
Flatulence	23 (1.6)
GASTRO-INTESTINAL DISORDER NOS	16 (1.1)
Tooth Caries	15 (1.0)
RESPIRATORY SYSTEM DISORDERS	
Upper Resp Tract Infection	370 (25.6)
Rhinitis	137 (9.5)
Coughing	127 (8.8)
Sinusitis	123 (8.5)
Pharyngitis	112 (7.7)
Bronchitis	54 (3.7)

Dyspnoea	38 (2.6)
Pneumonia	33 (2.3)
VISION DISORDERS	
Vision Abnormal	171 (11.8)
Diplopia	157 (10.9)
Eye Abnormality	32 (2.2)
28 (1.9)	Eye Pain
Conjunctivitis	23 (1.6)
Accommodation Abnormal	20 (1.4)
METABOLIC AND NUTRITIONAL DISORDERS	
Weight Decrease	287 (19.8)
SKIN AND APPENDAGES DISORDERS	
Rash	79 (5.5)
Pruritus	48 (3.3)
Acne	40 (2.8)
Alopecia	39 (2.7)
Skin Disorder	37
Dermatitis	19 (1.3)
Nail Disorder	19 (1.3)
Folliculitis	18 (1.2)
URINARY SYSTEM DISORDERS	
Urinary Tract Infection	78 (5.4)
Micturition Frequency	45 (3.1)
Urinary Incontinence	39 (2.7)
Dysuria	30 (2.1)
Renal Calculus	24 (1.7)
Hematuria	22 (1.5)
Urine Abnormal	18 (1.2)
MUSCULO-SKELETAL SYSTEM DISORDERS	
Arthralgia	36 (2.5)
Muscle Weakness	36 (2.5)
Myalgia	35 (2.4)
HEARING AND VESTIBULAR DISORDERS	

Ear Disorder Nos	49 (3.4)
Hearing Decreased	48 (3.3)
Tinnitus	39 (2.7)
Earache	26 (1.8)
REPRODUCTIVE DISORDERS, FEMALE	
Dysmenorrhoea	24 (4.8)
Vaginitis	21 (4.2)
Amenorrhoea	16 (3.2)
RESISTANCE MECHANISM DISORDERS	
Infection Viral	20 (1.4)
Otitis Media	20 (1.4)
Infection	15 (1.0)
PLATELET, BLEEDING & CLOTTING DISORDERS	
Epistaxis	33 (2.3)
SPECIAL SENSES OTHER, DISORDERS	
Taste Perversion	43 (3.0)
WHITE CELL AND RES DISORDERS	
Leucopenia	16 (1.1)
RED BLOOD CELL DISORDERS	
Anemia	26 (1.8)

8.4.1.3 Dose Response Data for Adverse Events

Data from fixed dose studies are available and the sponsor made an effort to view these data against adverse events in an effort to detect evidence of dose dependency for specific events. However this tabulation is of limited usefulness, since the randomized doses were not largely the doses achieved by patients during the double blind trials. The sponsor has been requested to perform an analysis of the incidences of treatment-emergent adverse events not by randomized dosage but by mean dosage achieved during the double blind portion of the trials. This evaluation is outstanding.

8.4.1.4 Demographic Interactions

The sponsor has made an effort to evaluate treatment emergent adverse events as a function of race, sex, and age. There were no apparent demographic risk factors.

8.5 LABORATORY FINDINGS AND VITAL SIGNS

Clinical laboratory data were obtained at pre and post baseline phase and at regular intervals throughout therapy during the controlled studies and at pre and post dose visits in a majority of the Topiramate trials, yielding a sample of approximately 1446 topiramate-treated patients with at least some laboratory data. This section will focus on a subgroup of exposed patients, those in controlled epilepsy trials, in order to explore contrasts in laboratory changes in the treated and control groups. In this group, the relationship to the concomitant drugs to the laboratory changes will be evaluated.

8.5.1 CLINICAL CHEMISTRY

The table below provides criteria for identifying patients with changes from baseline in clinical chemistry variables of possible clinical significance.

	LOW	HIGH
Albumin	≤2.5 g/dl	
Alkaline Phosphatase		≥390 U/L
BUN		≥30 mg/dl
Calcium	<8.2 mg/dl	≥12 mg/dl
Chloride	≤90 meq/L	≥118 meq/L
Cholesterol		≥600 mg/dl
CPK		≥200 I.U./L
Creatinine		≥2 mg/dl
Globulin	≤1 g/dl	
Glucose		≥175 mg/dl
LDH		>750 u/ml
Phosphorous	≤1.7 mg/dl	
Potassium	≤3 meq/L	≥6 meq/L
SGOT		≥150 U/L
SGPT		≥165 U/L
Sodium	≤126 meq/L	≥156 meq/L
Total Bilirubin		≥2 mg/dl

Total Protein	≤4.5 g/dl	≥10 g/dl
Triglycerides		≥600 mg/dl
Uric Acid		
Female		≥8.5 mg/dl
Male		≥10.5 mg/dl

The table below provides the proportions of patients who were relatively normal at baseline and who then exceeded these criteria during treatment. There appeared to be no significant differences between the frequencies of specific abnormalities between the two groups, with the exception of alkaline phosphatase and serum phosphorus.

Proportions of Patients Having Potentially Clinically Significant Changes¹ in Clinical Chemistry Variables in Placebo-Controlled Studies

CLINICAL CHEMISTRY VARIABLES	TOPIRAMATE			PLACEBO		
	TOTAL PATIENTS	ABNORMAL #	%	TOTAL PATIENTS	ABNORMAL #	%
Albumin - High	361	0	0	173	1	.6
Albumin - Low	361	0	0	173	0	0
Alk. Phos. - High	527	15	2.8	215	2	0.9
Bicarbonate - High	122	0	0	48	0	0
Bicarbonate - Low	122	0	0	48	0	0
BUN - High	527	9	1.7	215	5	2.3
BUN - Low	527	0	0	215	0	0
Calcium - High	361	1	0.3	174	0	0
Calcium - Low	361	2	0.6	174	1	0.6
Chloride - High	493	0	0	184	0	0
Chloride - Low	493	0	0	184	1	0.5
Cholesterol - High	360	0	0	173	1	0.6
Cholesterol - Low	360	0	0	173	0	0
Creatinine - High	527	0	0	215	0	0
GGTP - High	33	0	0		0	0
Glucose - High	527	0	0		1	0.5
Glucose - Low	527	12	2.3	215	14	6.5
LDH - High	38	0	0	15	0	0

Phosphorous - High	360	7	1.9	172	0	0
Phosphorous - Low	360	21	5.8	172	3	1.7
Potassium - High	527	4	0.8	215	4	1.9
Potassium - Low	527	1	0.2	215	0	0
SGOT - High	514	7	1.4	204	1	0.5
SGPT - High	521	6	1.2	208	3	1.4
Sodium - High	527	3	0.6	215	0	0
Sodium - Low	527	2	0.4	215	1	0.5
Total Bilirubin - High	360	0	0	173	0	0
Total Protein - High	360	0	0	173	0	0
Total Protein - Low	360	0	0	173	0	0
Triglycerides - High	62	0	0	43	0	0
Uric Acid - High	360	0	0	173	1	0.6
Uric Acid - Low	360	2	0.6	173	2	1.2

In addition the entire topiramate-exposed population was screened for patients who discontinued, died, or reported serious adverse events related to or because of abnormalities in clinical chemistry variables. The following patients were identified for the following laboratory abnormalities:

Hypokalemia

Pt 115/14 (YLT) reported hypokalemia as a serious adverse event. The CRF was submitted for the previous study YD, and therefore has no information about the severity and course of the hypokalemia, nor even that it had been reported.

Because of uncertainty as to whether this patient had actually experienced hypokalemia, the CANDA was queried regarding patients who reported hypokalemia. There were indeed 9 patients in the entire topimax database with hypokalemia. Further information about these was requested.

Pancreatic Enzymes Increased:

Pt. 362/20 (YK) reported pancreatitis as a serious adverse event. No CRF could be found on this patient, and therefore the course, complicating factors, and outcome are not known. The sponsor was asked to provide the CRF.

Prothrombin decreased

Pt. 45/2 (YP) reported decreased PT as a serious AE. No CRF could be found on this patient, and therefore the course, complicating factors, and outcome are not known. The sponsor was asked to provide the CRF.

Hepatic Enzymes elevated

All of the following patients reported this as a serious adverse event. Only the last patient did not withdraw from topiramate therapy.

Pt. 10/5 (MS 174) This patient was diagnosed with hepatitis A within the first week of topiramate treatment. He was withdrawn from topiramate for that reason.

Pt. 144/1 (YF/YG) This patient was discontinued from topiramate therapy because of elevated liver enzymes which rose from normal to 489 SGOT and 346 SGPT after many months of therapy (exact duration unknown) without warning and with no apparent explanation. There was no accompanying jaundice.

Pt. 2/1 (YB)

This patient had elevated liver function studies which increased slightly during treatment from a normal baseline to a peak SGOT was 160, SGPT was 72 and LDH was 392. Viral studies were inconclusive. Patient was discontinued from medication. Concomitant medications (if any) were not identified. This patient was not found in the CANADA.

Pt 355/ 26 (YOL/YH)

Six additional patients experienced recurrent markedly abnormal SGOT and SGPT elevations. Three had been noted as serious adverse events (above).

Patient 33/11 discontinued topiramate therapy because of documented hepatitis A.

The remaining 5 patients remained in studies.

Pt 21/8 (YKP) had a history of elevated liver function studies in the past, attributed to valproic acid therapy. The elevated liver function studies recurred during therapy remaining in the range of 213 (SGOT) and >110 (SGOT). Alkaline phosphatase was also elevated. These were never fully explained, however, as his medications were tapered (valproate first) his liver functions began to normalize.

Pt. 4/10 (YC,CO2) Elevated LFTs and alkaline phosphatase, glucose.

Range of abnormality (GGTP 300 IU/L). No CRF could be found on this patient, and therefore the course, complicating factors, and outcome are not known. The sponsor was asked to provide the CRF.

Pt. 178/11 (MS-218) elevated liverfunction studies were documented during comedication with valproate and topiramate. Upon withdrawal of valproate, LFTs returned to normal.

Pt 171/6 (YF/G) SGPT elevations in the range of 279 and SGOT of 626. Pt was asymptomatic, treatment was continued. No CRF could be found on this patient, and therefore the course, complicating factors, and outcome are not known. The sponsor was asked to provide the CRF.

Pt. 743/1 (YJ) Peak SGOT and SGPT were 189 and 309 respectively, after 1 month on therapy. The elevations started to resolve but were not followed to normal. No alternative etiology found.

Alkaline Phosphatase Increased

Pt 904/6 had persistent mild elevation of Alkaline phosphatase throughout treatment. It was unaccompanied by any other relevant laboratory abnormalities or relevant symptoms. (Although the patient experienced the typical slowness of thought and common weight loss seen with topiramate). This patient withdrew from topiramate therapy.

In addition 15 patients (of the total epilepsy population of which 79 reported some abnormality of alkaline phosphatase) had recurrent elevations of alkaline phosphatase levels. Those patients with abnormal alkaline phosphatase had mild elevations in the range of 300-345 and these were unassociated with abnormalities of other liver enzymes. These were unexplained and asymptomatic.

RECURRENT MARKED ABNORMALITIES: Some patients reported recurrent marked laboratory abnormalities. Of the 527 subjects who received topiramate during double-blind trials 21 (4%) repeated recurrent treatment-emergent laboratory abnormalities, compared to 5 (2%) placebo patients. These included 5 patients with elevated alkaline phosphatase levels, 2 elevated BUN, six with elevated SGOT/SGPT, and one each with abnormal phosphorus and uric acid.

BUN elevations were in the range of 50-52. Patients completed therapy with topiramate. (904/6 (Y1) and 911/7 (Y1). While a case report form exists for the latter (corresponding to his later enrollment in study YET), there is no discussion of this abnormality. No information is available regarding elevated BUN in patients on topiramate. The sponsor has been asked to comment on this area,

Two patients had recurrent hypophosphatemia, unassociated with abnormal calcium or symptoms. Phosphorus was in the range of 1.6-2.0 (normal 2-5.3 mg/dL). Pt. 20/3 (YD) and Patient 17/21 (YD) were so identified. Further details are unavailable. There does not appear to have been any investigation of the patients' hypophosphatemia.

One patient reported a recurrently low uric acid, with which he was asymptomatic. The patient had numerous determinations within the normal range as well.

Among all topiramate treated subjects with epilepsy (N=1446) the most commonly reported markedly abnormal laboratory values were low phosphorus (14% of patients reported this), low bicarbonate (10% reported this), low serum glucose (6% of patients reported this). The decrease in bicarbonate levels was anticipated as consistent with the known effects of carbonic anhydrase inhibitors. The significance of the decreased phosphorus levels was not evaluated by the sponsor. As noted, a difference between topiramate and placebo in the incidence of marked decrease in serum phosphorus was also noted during double blind therapy for decreased phosphorus levels.

8.5.2 HEMATOLOGY

The table below provides criteria for identifying patients with changes from baseline in hematology variables of possible clinical significance.

CRITERIA FOR IDENTIFYING PATIENTS WITH POTENTIALLY CLINICALLY SIGNIFICANT CHANGES IN HEMATOLOGY VARIABLES		
	LOW	HIGH
Hemoglobin		
Female	≤9.5 g/dl	
Male	≤11.5 g/dl	
Hematocrit		

Female	≤32%	
Male	≤37%	
White Blood Cells	≤2.8 tha/mm	≥16 tha/mm
Neutrophils	≤15%	
Lymphocytes		≥75%
Monocytes		≥15%
Eosinophils		≥10%
Basophils		≥10%
Platelets	≤75 tha/mm	≥700 tha/mm
Bands		≥10%

The table below provides the proportions of patients in placebo controlled trials who were relatively normal at baseline and who then exceeded these criteria during treatment. There appeared to be no significant differences between the frequencies of specific abnormalities between the two groups.

Proportions of Patients Having Potentially Clinically Significant Changes¹ in Hematology Variables in Placebo-Controlled Studies

Hematology Variable	TOPIRAMATE			PLACEBO		
	Total Patients	Abnormal #	Abnormal %	Total Patients	Abnormal #	Abnormal %
Hemoglobin - High	527	0	0	214	0	0
Hemoglobin - Low	527	1	0.2	214	0	0
Hematocrit - High	512	0	0	199	0	0
Hematocrit - Low	512	0	0	199	0	0
WBC - High	527	2	0.4	213	1	0.5
WBC - Low	527	32	6.1	213	7	3.3
RBC - High	527	0	0	214	0	0
RBC - Low	527	2	0.4	214	1	0.5
Neutrophils - High	527	2	0.4	214	0	0

Neutrophils - Low	527	8	1.5	214	6	2.8
Lymphocytes - High	527	8	1.5	214	8	2.8
Lymphocytes - Low	527	4	0.8	214	1	0.5
Monocytes - High	524	0	0	214	1	0.5
Eosinophils - High	520	7	1.3	210	4	1.9
Basophils - High	516	0	0	206	0	0
Platelets - High	527	3	0.6	214	0	0
Platelets - Low	527	2	0.4	214	1	0.5
Immature Cells - High	144	0	0	64	0	0

In addition, the entire topiramate population (N=1446) was screened for patients who discontinued, were hospitalized, or died because of abnormalities in hematology variables and the following patients were identified:

Pancytopenia

Pt. 744/15 (YOL/YH) This patient withdrew from therapy because of pancytopenia. The patient's hemoglobin dropped from a baseline of 15.3 gm to 10.8, platelets were normal at baseline and fell to 71,000 and WBC from a normal range and differential (maximum 13,300) to 3,400. The patient was maintained on valproate and carbamazepine as well. Onset of the pancytopenia was 88 days after onset of treatment, and at a dose of 600 mg of topiramate. No clear etiology has been forthcoming, and the investigator assessed the cause as probable related to topiramate. The sponsor should provide some followup on this patient as well as others with laboratory abnormalities which have not normalized by study termination.

Thrombocytopenia:

Pt. 11/13 (YZL) withdrew from treatment because of thrombocytopenia which reached a nadir of 62,000. The patient had been maintained on valproate, and upon withdrawal of valproate, the abnormality resolved. It might be noted, however that the patient also discontinued treatment with topiramate at the same time. Either drug could be responsible.

Pt. 178/6 (MS 218) reported thrombocytopenia as a serious adverse event. This patient's platelet count reached a nadir of 28,000 by one

month on therapy. Concomitant medication was valproate. There was resolution of the thrombocytopenia with discontinuation of valproate and topiramate monotherapy. This patient also experienced anemia.

In addition, eight (.6%) patients (among the total exposed group of 1446 epileptics) were reported as having markedly low platelet counts. Of these subjects, 7 were maintained on valproate and/or carbamazepine comedication. Two patients reported the thrombocytopenia as an adverse event (see above)

Leukopenia:

Pt. 152/1 YF/YG withdrew from treatment because of leukopenia. No CRF could be found on this patient, and therefore the course, complicating factors, and outcome are not known. The sponsor was asked to provide the CRF.

In addition, recurrent low WBCs were noted in five topiramate-treated patients and in one placebo patient in double blind studies.

Pt 115/1 (YD) had a significant decline in WBCs from 8,400 to 2,200 over 146 days of therapy. There was no follow-up, although there was a slight improvement in WBC while still on therapy.

Pt. 151/3 (YF/G) had a baseline WBC of 3.9×10^3 which fell to 2.6×10^3 (day 42). Return to baseline occurred during therapy

The other patients had a similar pattern with low baseline and consistently two counts, and no documented return to normal.

In review of patients (among all exposed epileptic patients (N=1446)) who had recurrent abnormalities in hematology laboratory studies, 54(4%) had abnormalities in hematologic parameters, mainly low WBCs. Of these there were 22 (2%) of patients who reported recurrent markedly low WBC's including four in whom the low WBC was reported as an adverse event. Of these 22 patients, only two (**Pt 24/1 YKT**) and **115/11 (YKT)**) had a value less than 2,000 white cells/mm³. This abnormality was recorded in both cases on only one occasion and neither patient was discontinued from therapy.

ANEMIA

Pt. 30/8 (YKP) withdrew from treatment because of anemia. The patient's hemoglobin fell and continued to fall from the normal range to 9.5gm during treatment.

Five patients (.3%) of the 1446 topiramate-exposed epileptic patients experienced recurrent markedly low hemoglobin, hematocrit or RBC counts. None of these patients were reported as having adverse events and none discontinued therapy because of anemia.

They are described below:

Pt 12/7 (YKT) Hematocrit values ranged from 23-30 and were accompanied by decreased lymphocytes and increased neutrophils. This occurred following a serious accident and spinal cord compression. Pt also developed DVT. The patient was withdrawn from therapy for multiple reasons.

Pt 114/2 This patient had gradual decline in HGB over 2 years on therapy. The patient's lowest hemoglobin recorded was 9.7 g. The patient was not documented as having resolution of this side effect. No CRF could be found on this patient, and therefore the course, complicating factors, and outcome are not known. The sponsor was asked to provide the CRF.

Pt. 178/6 (MS 216) described above.

Pt 905/13 (YEP) This patient had a hemoglobin of 10.3 which returned to a normal 14.8 during therapy.

Pt. 912/6 (YET) This patient had decreased RBCs and anisocytosis. The etiology of this abnormality is not known and no resolution was described.

Thrombocytosis

Pt.16/18 (YKT) Reported pulmonary embolism as a serious AE and death. Patient found to have a platelet count of 744,000 one month before the event, and on a later smear platelet clumping was described, precluding an accurate count.

RECURRENT MARKED ABNORMALITIES

Eosinophilia

Occasional recurrent eosinophilia (>0%) was also noted in 7 patients.

8.5.3 URINALYSIS

The table below provides criteria for identifying patients with changes from baseline in urinalyses of possible clinical significance.

Urinalysis Variable	TOPIRAMATE		PLACEBO	
	Total Patients	Mean Change	Total Patients	Mean Change
pH	475	-0.2	191	0.1
Protein	435	-0.3	174	0.0
Glucose	471	0.2	195	0.0
Specific Gravity	453	0.0	171	0.0
WBC	338	0.4	125	0.4
RBC	324	-0.4	125	0.2
Casts	90	0.1	49	-0.5

The table below provides the proportions of patients who were relatively normal at baseline and who then exceeded these criteria during treatment. There appeared to be no significant differences between the frequencies of specific abnormalities between the two groups.

Proportions of Patients Having Potentially Clinically Significant Changes¹ in Urinalysis Variables in Placebo-Controlled Studies

Urinalysis Variable	TOPIRAMATE			PLACEBO		
	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%
pH - High	514	12	2.3	203	12	5.9

pH - Low	514	1	0.2	203	0	0
Specific Gravity - High	492	8	1.6	177	10	5.3
Specific Gravity - Low	492	6	1.2	177	1	0.5
RBCs - High	459	27	5.9	166	5	3.0
WBCs - High	469	23	4.9	173	7	4.0
Protein - High	517	15	2.9	207	9	4.4
Glucose - High	520	2	0.4	210	1	0.5
Casts - High	146	4	2.7	63	0	0

In addition, the entire topiramate population N=1446 was screened for patients who discontinued, were hospitalized, or died because of abnormalities in urinalyses and the following patients were identified:

Hematuria:

Pt 12/1 (YKT) This patient withdrew because of hematuria. The patient was evaluated by urology consultants and evidence of calculi were seen on ultrasound. Because this was information contained in a radiology report, and it was not included as an adverse event, it was not included among the 32 calculi reports.

Renal Calculi:

There were 16 patients who either reported this as a serious adverse event or withdrew from therapy because of this adverse event. Please refer to the section on serious adverse events. Additional patients reported renal colic but did not report this adverse event as a renal stone.

Abnormal Urine:

Pt. 433/300 (YOLE) . Further details about this patient are not available in this NDA.

UTI

Pt. 356/153 (YOL/YH) This patient had a urinary tract infection, bladder cancer and urinary obstruction. Relationship to drug is remote.

No one died because of complications related to abnormalities in urinalysis.

SUMMARY

The changes seen in clinical laboratory evaluations during topiramate therapy were infrequent, small in magnitude and generally not clinically significant. While in general laboratory abnormalities of possible clinical significance were infrequent in controlled clinical trials, there were rare reports of withdrawals due to abnormal laboratory variables which reached clinical significance in the eyes of the investigator such that they led to discontinuation of drug. In most (? but not all cases, return to normal was seen upon withdrawal of the drug.

The most common findings in clinical laboratory evaluations of the urine were hematuria and calculi.

8.5.4 VITAL SIGNS

The table on the following page provides criteria for identifying patients with vital signs changes from baseline of potential clinical significance.

CRITERIA FOR IDENTIFYING PATIENTS WITH POTENTIALLY
CLINICALLY SIGNIFICANT CHANGES IN VITAL SIGNS VARIABLES

	LOW	HIGH
Systolic Blood Pressure	< 90 mm Hg	> 180 mm Hg
Change in Systolic BP	Decrease \geq 30 mm Hg	Increase \geq 40 mm Hg
Diastolic Blood Pressure	< 50 mm Hg	> 105 mm Hg
Change in Diastolic BP	Decrease \geq 20 mm Hg	Increase \geq 30 mm Hg
Pulse	< 50 bpm	> 120 bpm
Change in Pulse	Decrease \geq 30 bpm	Increase \geq 30 bpm
Temperature		> 101 Fah
Change in Temperature	Decrease \geq 2 Fah	Increase \geq 2 Fah

Those patients in controlled studies who were relatively normal at baseline and who then exceeded the criteria as noted above at some time during treatment are listed in the table below.

PROPORTIONS OF PATIENTS HAVING POTENTIALLY CLINICALLY SIGNIFICANT CHANGES¹ IN

VITAL SIGNS VARIABLES IN PLACEBO-CONTROLLED STUDIES

VITAL SIGNS VARIABLE	TOPIRAMATE			PLACEBO		
	TOTAL PATIENTS	ABNORMAL #	%	TOTAL PATIENTS	ABNORMAL #	%
SYSTOLIC BP - HIGH	525	2	0.4	216	2	0.9
SYSTOLIC BP - LOW	525	12	2.3	216	0	0
DIASTOLIC BP - HIGH	525	6	1.1	216	1	0.5
DIASTOLIC BP - LOW	525	7	1.3	216	1	0.5
PULSE - HIGH	524	2	0.4	216	0	0
PULSE - LOW	524	7	1.3	216	3	1.4
TEMPERATURE - HIGH	359	2	0.6	173	1	0.6
RESPIRATION - HIGH	301	1	0.3	160	1	0.6
RESPIRATION - LOW	301	0	0	160	0	0
WEIGHT INCREASED	485	3	0.6	206	5	2.4
WEIGHT DECREASED	485	121	24.9	206	1	0.5

The table on the next page applies to all patients in topiramate studies, including those in open label studies and provides the proportions of patients who had relatively normal vital signs at baseline and who then exceeded the criteria during treatment.

**PROPORTIONS OF PATIENTS HAVING POTENTIALLY CLINICALLY SIGNIFICANT CHANGES¹ IN
VITAL SIGNS VARIABLES IN ALL TOPIRAMATE TREATED PATIENTS WITH EPILEPSY**

VITAL SIGNS VARIABLE	TOPIRAMATE		
	TOTAL PATIENTS	ABNORMAL #	%
SYSTOLIC BP - HIGH	1384	6	0.4
SYSTOLIC BP - LOW	1384	81	5.9

DIASTOLIC BP - HIGH	1384	23	1.7
DIASTOLIC BP - LOW	1384	40	2.9
PULSE - HIGH	1380	3	0.2
PULSE - LOW	1380	31	2.2
TEMPERATURE - HIGH	518	3	0.6
RESPIRATION - HIGH	485	7	1.4
RESPIRATION - LOW	485	1	0.2
WEIGHT INCREASED*	1236	48	3.9
WEIGHT DECREASED*	1236	384	31.1

The only notable difference between the placebo (.5%) and the topiramate (24.9%) treated group was in the report of weight loss in the latter. Weight loss was cited as the only reason or among the reasons for withdrawal in 25 patients. See discussion of weight loss in Section 8.7.

8.5.5 ECGs

The occasional changes in ECG waveforms among patients in a pool of placebo-controlled studies and in open extension studies were not clinically significant. Below mean changes ECG waveform measurements from baseline to study end are noted.

CHANGES IN ECG WAVEFORM MEASUREMENTS FROM BASELINE TO END OF TREATMENT IN PLACEBO-CONTROLLED STUDIES

VARIABLE	TOPIRAMATE			PLACEBO		
	N	MEAN CHANGE	SD	N	MEAN CHANGE	SD
Heart Rate	474	-1.979	10.672	208	-0.654	10.451
PR Interval	474	-0.603	13.756	208	-0.002	0.038
QRS Interval	474	-0.329	8.807	208	0.011	0.087
QT Interval	467	-1.738	36.849	205	0.005	0.036

CHANGES IN ECG WAVEFORM MEASUREMENTS FROM BASELINE TO END OF TREATMENT IN ALL TOPIRAMATE TREATED PATIENTS WITH EPILEPSY

TOPIRAMATE			
VARIABLE	N	MEAN CHANGE	SD
HEART RATE	731	-1.513	11.455
PR INTERVAL	727	-0.393	11.107
QRS INTERVAL	727	-0.207	7.112
QT INTERVAL	718	-1.127	29.719

One patient reported atrial fibrillation as a serious adverse event and withdrew from treatment.

(Pt. 180/2, YOL/YH). This patient was a 59 year old woman with no prior history of atrial arrhythmia. She had onset of palpitations on day 9 of topiramate 400 mg/day therapy and was evaluated in the local emergency room. She was found to have atrial flutter with a rate of 140-150 bpm. Topiramate was discontinued immediately. She was treated with Idoquad and digoxin, which controlled the arrhythmia. The attending could find no alternative etiology and considered that topiramate may have been responsible for her arrhythmia.

Two other patients withdrew from topiramate therapy because of abnormal ECGs.

Pt 345/507, (YOLE). Developed incomplete RBBB in one of the early examinations of the study. No prior ECG was available to compare but the reader suggested that this was a change. There were no other comments and it is not clear whether the patient actually dropped out of the study because of this, or rather because of the cognitive impairment he was experiencing.

Pt 129/2 (YF/G)

No CRF could be found on this patient, and therefore the course, complicating factors, and outcome are not known. The sponsor was asked to provide the CRF.

8.6 SPECIAL STUDIES

8.6.1 WITHDRAWAL PHENOMENA/ABUSE POTENTIAL

There has been no systematic evaluation of the abuse potential of this drug in humans or in animal studies.

8.6.2 HUMAN REPRODUCTION DATA

The reproductive toxicity profile of topiramate in animal studies appears to be similar to acetazolamide and other carbonic anhydrase inhibitors in terms of its pattern of teratogenicity-- right sided ectrodactyly in rats and rib and vertebral malformations in rabbits.

The sponsor asserts that CA anhydrase inhibitors have not been associated with malformations in humans, however no human data is submitted to support this.

In the topiramate NDA, two patients withdrew from topiramate therapy because of pregnancy, one of whom conceived a child with multiple congenital anomalies. (177/12 YLT and 357/66 YOL/YH) . In addition two other patients reported pregnancy as an adverse event. There is no information on any of these four patients with regard to outcome and no case report forms were provided.

No study has been done to determine the effect of topiramate in pregnant women. According to the Sponsor, seven women have become pregnant while receiving topiramate in clinical studies¹. The duration of topiramate therapy in these seven women ranges from 24 days to approximately 3 years. Three women had normal deliveries of normal infants, one had a spontaneous abortion within the first four weeks of pregnancy, and three voluntarily terminated their pregnancies. One of these patients, a 19 year-old woman, became pregnant while participating in Protocol YOL terminated her pregnancy; an autopsy report on the fetus noted clenched fists with flexion of upper extremities and widened space of the first and second toes. No other gross

¹Specific information has not been provided by the sponsor. It has been requested for review and is currently outstanding.

abnormalities or dysmorphic features were present. Exposure of the fetus to topiramate was estimated to be 50 to 58 days.

8.6.3 OVERDOSE EXPERIENCE

There have been four cases of intentional overdose and one accidental overdose associated with topiramate therapy. The topiramate overdoses range from 1.8 to 100 g. Symptoms associated with overdose included confusion, ataxia, hyperreflexia, and lethargy.

Pt 135/1 (YF/G) This patient ingested 3.2 grams of topiramate was treated symptomatically with gastric lavage and activated charcoal. She recovered without sequelae.

Pt 30/1 (YKT) This patient ingested 3.9 grams of topiramate and presented with confusion, ataxia, hyperreflexia, all of which resolved following supportive measures.

Pt. 24/16 (YKP) This patient took an accidental overdose of 1800 mg in a postictal confusional state. She presented with confusion, lethargy and memory lapse. She recovered without sequelae.

Pt. 139/1 (YF/G) This patient ingested 100 g of topiramate and was hospitalized in *status epilepticus*, was treated with ipecac, activated charcoal, IV midazolam 2 mg and pentothal 250 mg. The patient developed a metabolic acidosis, treated with NaHCO_3 .

Pt.29/179 (YOL) This patient was found unresponsive, and obtunded with an empty bottle of 100 mg topiramate next to her. She was treated with activated charcoal and gastric lavage. She recovered without sequelae.

Supportive measures have been successful in treating the overdoses reported thus far. The firm notes that topiramate is hemodialyzable if the necessity arises.

8.7 SUMMARY OF POTENTIALLY IMPORTANT EVENTS (SERIOUS ADVERSE EVENTS)

As required by 21 CFR 312.32 (a), the sponsor used the term "serious" in the IND to describe certain kinds of adverse events. Adverse events were reported as serious if they were thought to be immediately life threatening, permanently disabling, or requiring hospitalization, cancer, overdose, congenital anomalies, or other events deemed of medical concern by the sponsor.

A total of 221 (15%) patients in all trials (N=1446) reported events which were considered serious. Not all of these events resulted in withdrawal from treatment. Serious events which occurred most often were psychiatric and neurologic (mirroring the overall adverse event profile and that for withdrawals).

The table below summarizes the types of adverse events reported as serious and details of their occurrence. Patients occasionally were reported as having more than one serious adverse event at a time. In the table below, patients are listed only once, groups of similar adverse events, therefore are additive (for example, suicide + suicide and depression can be added to determine the number of suicide attempts were reported as serious).

While attribution cannot be ascribed with absolute certainty in all cases, some of the serious adverse events described can be reasonably associated with this medication. Events that are considered possibly or probably drug-related are psychosis, aggressive behavior, depression, personality change, injury (indirectly), weight loss, and renal calculi. Possible drug related events which have not been adequately characterized by the sponsor are thrombotic and thromboembolic phenomena, such as DVT, and pulmonary embolism. Serious adverse events considered possibly drug related are summarized in the table below.

SUMMARY OF SERIOUS ADVERSE EVENTS OCCURRING IN TOPIRAMATE-TREATED SUBJECTS AND CONSIDERED POSSIBLY DRUG-RELATED

STUDY #/ PT	AGE (YRS)	SEX	DOSE (MG)	ONSET (DAYS)	ADVERSE EVENT
METABOLIC & NUTRITION					
YOLE 814/201	18	F	300	73	WEIGHT LOSS

0101	29	M	300	68	WEIGHT LOSS
YK 1178	18	M	700	38	WEIGHT LOSS
OVERDOSE					
YFYQ- QL1372	33	M	1600	730	THERAPEUTIC RESPONSE INCREASE ¹
YKI 3071	33	F	700	372	SUICIDE ATTEMPT
YFYQ- QL1387	18	F	1400	302	THERAPEUTIC RESPONSE INCREASED
PSYCHIATRIC					
MS-218 1788	40	M	1400	87	PSYCHOSIS
YFYQ- DB 1518	51	M	1000	117	PSYCHOSIS
YLI 11424	30	M	500	1281	PSYCHOSIS
YA 171"	25	M	400	1	PSYCHOSIS
YI 23079	29	F	1000	77	PSYCHOSIS
0062	25		800	139	PSYCHOSIS
YKI 2777	32	F	1100	350	PARANOID REACTION
18"	32	M	1200	1	AGITATION
YB 2731"	32	M	200	3	EMOTIONAL LABILITY
				17	PARANOID REACTION
YEP 9018	20	M	1000	535	EMOTIONAL LABILITY
YEI 9048	63	M	400	245	ANOREXIA
9118	43	M	500	150	DEPRESSION
YFYQ- DB 13871	30	M		122	SUICIDE ATTEMPT DEPRESSION
YKI 1148	56	M	700	623	DEPRESSION

¹SPONSOR'S EUPHEMISM FOR OVERDOSE.

					643	SUICIDE ATTEMPT
27/11	21	M	400	499		DEPRESSION
27/8	24	M	900	872		DEPRESSION
YOLE18 60/216	38	F	800	141		DEPRESSION
YOLYH 28/178	43	F	600	59		SUICIDE ATTEMPT/ (INTENTIONAL TOPIRAMATE OVERDOSE)
387/89	33	F	900	82		DEPRESSION
YK 11/13	11	F	325	31		AGGRESSIVE REACTION
11/15	18	M	700	38		SOMNOLENCE
YKP 23/8	26	M	1100	778		PERSONALITY DISORDER
MS-228 186/102	27	F	200	9		CONFUSION
YD 74/3	45	M	400	33		PERSONALITY DISORDER
YEI 924/11	35	M	1000	1065		PERSONALITY DISORDER AGGRESSIVE REACTION
YK 357/5	15	M	150	10 19		SOMNOLENCE ANOREXIA
YLI 26/28	30	M	350	1463		PERSONALITY DISORDER
YOLYH 252/217	39	F	800	253		HALLUCINATION DEPERSONALIZATION
384/233	20	M	1800	316		AGITATION
389/43	30	M	800	361		DELUSION
YOLYH 170/144	33	M	300	98		THINKING ABNORMAL
YOLYH 28/136	43	M	1600	188		PSYCHOSIS
28/210	17	M	800	56		EMOTIONAL LABILITY
364/233	20	M	1400	245		PSYCHOSIS
369/43	30	M	800	361		PSYCHOSIS
44/228	36	M	800	55		AGITATION
YOLE11 64/306	40	M	600	277		PSYCHOSIS
YOLE 328/324	27	M	100	108		CONFUSION/ PSYCHOSIS/ HALLUCINATIONS

343/234	51	M	400	156 159	CONFUSION PERSONALITY DISORDER
618/207	57	M	600	81 114	NERVOUSNESS CONFUSION
618/208	30	M	600	80 109	NERVOUSNESS DELIRIUM
020/228	18	M	300	35	AMNESIA
84101	28	M	300	95	AGGRESSIVE REACTION

PLATELET & CLOTTING

<u>MS-218</u> 1788	33	F	400	28 880	THROMBOCYTOPENIA SUICIDE ATTEMPT?
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INJURY

<u>YG</u> 472	22	M	300	41	INJURY (NEAR DROWNING)
<u>YE</u> 4173	44	F	600	51	INJURY
<u>YET</u> 903/12	44	M	1100	1024	INJURY
<u>YFYQ-</u> <u>QL</u> 1804	38	M	1200	333	INJURY SLEEPING, TANDEN GAIT
<u>YKP</u> 178	40	M	300	1347	INJURY (AUTOMOBILE ACCIDENT)
<u>YQLE16</u> 884408	24	M	200	22	INJURY NO CRF
328/323	22	M	700	207	INJURY NO CRF
402/808	41	M	200	32	INJURY NO CRF
818/223	35	M	300	42	INJURY
<u>YQ22</u> 474	40	F	600	1594	DEATH ACCIDENTAL FALL
<u>YET</u> 904/8	63	M	400	711	INJURY/SOMNOLENCE NOT CODED BUT REPORTED IN CRF/ PSYCHOMOTOR SLOWING
<u>YFYQ-</u> <u>QL</u> 1848	46	M	1600	366	INJURY NO REAL SIGNIF. MSAs
<u>YQLYH</u> 286/118	22	M	1400	266	INJURY
<u>YMI</u> 288	47	M	800	488	FATIGUE COMA (AUTOMOBILE ACCIDENT)
<u>YKE</u> 337/3	16	M	250	439D	INJURY NO CRF

<u>YEP</u> 904/14	36	M	600	111	DEATH (AUTOMOBILE ACCIDENT)
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REPRODUCTIVE

<u>YET</u> 902/15	36	M	600	297	PROSTATIC DISORDER
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RESPIRATORY

<u>YE 393</u>	58	M	200	8	DYSPNEA
<u>YFYQ- QL1447</u>	52	F	1300	554	DYSPNEA

SKIN & APPENDAGES

<u>YOLE</u> 345/506	50	F	100	69	ECZEMA
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URINARY

<u>YR</u> 2/32--	28	M	200	17	RENAL CALCULUS
<u>YEP</u> 903/4	31	M	600	1143	RENAL CALCULUS
<u>YET</u> 902/21	27	M	600	79	RENAL PAIN
<u>YLI</u> 14/10	49	M	800	1462	RENAL CALCULUS
<u>178/1</u>	32	M	800 900	119 279	RENAL CALCULUS RENAL CALCULUS
<u>24/1</u>	36	M	900	673	RENAL CALCULUS
<u>28/2</u>	34	M	1000	1603	RENAL CALCULUS
<u>YOLYH</u> 204/262	37	M	200	152	RENAL CALCULUS

VASCULAR

<u>YFYQ- OL 93/1</u>	33	M	900	181	THROMBOPHLEBITIS DEEP
<u>YD</u> 24/2	59	M	400	53	PRESUMPTIVE CVA
<u>YET</u> 901/5	30	M	800	216	THROMBOPHLEBITIS DEEP
<u>YL*</u> 52/14	32	M	1300	1006	THROMBOPHLEBITIS DEEP

VISION

<u>YOLE18</u> 60/216	38	F	800	107	DIPLOPIA
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BODY AS A WHOLE

<u>YR</u> 2/32--	28	M	200	22	RIGORS
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YOL/YH 367/88	26	F	600	253	FATIGUE
YOLE 343/234	51	M	600	57	ASTHENIA
620/228	18	M	100	4	ASTHENIA
9101	28	M	300	95	FATIGUE

CENTRAL AND PERIPHERAL NERVOUS SYSTEM

YC 44	29	M	200	18	DIZZINESS (SUSPECTED CARBAMAZEPINE TOXICITY)
YEP 905/2	31	M	1000	698	ATAXIA
YF/YQ- QL 127/2	18	F	800	239	PARESTHESIA
154/8	46	M	1600	366	TREMOR
YK 341/8	6	M	100	55	CONVULSION-GRAND MAL
YLI 178/6	33	F	1600	237	PARESTHESIA
YOLE 343/234	51	M	400	159	ATAXIA

GASTROINTESTINAL/LIVER & BILIARY

YE 30/14	25	M	600	35	ABDOMINAL PAIN
YET 904/6	63	M	400	245	VOMITING
YF/YQ- QL 154/8	46	M	1600	485	ABDOMINAL PAIN
YB 2/1**	32	M	50	12	HEPATIC FUNCTION ABNORMAL

HEARING & VESTIBULAR

YOLE 618/206	30	M	600	109	EAR DISORDER
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HEART RATE & RHYTHM

YI 2/11**	27	M	100	17	PALPITATION
YOL/YH 180/2	59	F	400	9	FIBRILLATION, ATRIAL

Some of the more common serious adverse events, were evaluated with the aid of the CANDAs database. The summaries follow. Much work is needed for the sponsor to characterize the adverse event profile that relates to CNS toxicity. Time and limitations of the database did not

permit a more detailed analysis by FDA.

SERIOUS AE THAT SUGGEST CENTRAL NEUROTOXICITY

COGNITIVE DYSFUNCTION

Cognitive dysfunction is an important issue in epilepsy drug treatment. It is also one which is difficult to quantify. Terms such as thinking abnormal, confusion, concentration impaired, aphasia, slowed thinking and memory loss were used to describe the mental status of a large number of patients on topiramate. Indeed, one or more of these adverse events was experienced by a full 62% of the entire topiramate-exposed population.¹ The rates of cognitive impairment reflected by these adverse event reports are compared within the treatment groups and clearly the topiramate groups exceed placebo in rates reported of somnolence: topiramate 149 (28.3%), placebo 21 (9.7%); thinking abnormal: topiramate 112 (21.3%), placebo 5 (2.3%); confusion: topiramate 84 (15.9%), placebo 9 (4.2%); amnesia: topiramate 69 (13.1%), placebo 7 (3.2%), concentration impaired:topiramate 69 (13.1%), placebo 4 (1.9%).

Whether there is a sustained effect or not cannot be determined for sure with the data as it stands.

The sponsor might have undertaken some formal psychometric studies in the context of a placebo controlled trial, once the picture of a sedating drug emerged. This would have provided more tangible quantification of the problem of cognitive dysfunction with this drug.

According to the sponsor, the mean plasma topiramate concentration was statistically significantly greater for subjects who experienced the adverse events such as abnormal thinking, speech disorder, aphasia, confusion, amnesia, and impaired concentration, than those who did not. However, for individual patients in those add-on trials, the topiramate concentration had little predictive value. The sponsor has been asked to provide further documentation of this assertion, however it has not been received as of the completion of this review.

While it would not at first appear that aphasia and amnesia should be included among the more generalized adverse events affecting mental

¹CANDA was queried for the number of patients who reported one or more of the adverse events of somnolence, thinking abnormal, concentration impaired, confusion and amnesia.

status, such as concentration, delirium, and so on, when the data was examined more in depth, it appeared that coding such as "aphasia" and "amnesia" were not being used accurately but were used because of an inability to find the proper word for coding. Indeed, aphasia was used to relate to a patient who has such slowness of thought that he is unable to speak fluently or searches for the words. It is part of a more global cognitive impairment. Similarly, amnesia is not used specifically but rather to describe a confused patient or one with such poor concentration that he cannot recall simple things. The sponsor has been asked to provide further documentation of this assertion, however it has not been received as of the completion of this review.

ACCIDENTAL INJURY

Accidental injury is listed as an adverse event for 295/1446 patients (20% of the topiramate-exposed epileptic population) and as a serious adverse event for 25 patients. For those injuries reported as serious adverse events which were related to seizures, or the case of one patient involved in a motor vehicle accident in which he was a passenger, the adverse event of injury was considered unrelated to topiramate therapy. However for the remainder, there appeared to be at least a reasonable chance that drug contributed to the adverse event. For all patients for whom case reports were available or information listed in the CANDAs, all had some degree of cognitive dysfunction reported in addition to the accident, specifically, somnolence, fatigue, confusion, concentration impaired, or delirium. In some cases the adverse event was not coded in the database, but was found on serial examinations of the patient.

While this does not establish that the injuries were all definitely related to the sedative effects of topiramate, it bears further scrutiny. Time does not permit such an analysis by FDA, but the firm would do well to consider this further in its analyses of topiramate.

PSYCHIATRIC ADVERSE EVENTS

Psychiatric adverse events that were reported as serious were numerous and were of three types--depression (with or without suicidal ideation), psychosis, and behavioral change.

Depression

Depression is not an unexpected occurrence in the population under study--the patients with refractory partial epilepsy. The question that arises when one views a an occurrence rate of 12% in placebo

- controlled trials or 16% overall, that of a drug-disease interaction, that is, is whether the rate is expected or exceeds that which is expected.

Depression was viewed as a function of dose, concomitant antiepileptic medication and latency (time on treatment). Reports of depression occurred in 238 patients in the entire topiramate treated epilepsy population. There was no clear relationship between dose of topiramate and incidence of depression. Rate of depression was evaluated as a function of antiepileptic drug therapy. The patients on carbamazepine monotherapy or carbamazepine in addition to one or more AEDs reported 62.4% of the cases of depression. Patients on phenytoin alone or in combination reported 43% of the cases of depression (note that some patients were on carbamazepine and phenytoin combined). Given the frequency of use of carbamazepine and phenytoin in this population, this is likely a spurious relationship, and one that mirrors the baseline treatment in the topiramate treated population (see Section 5.0).

Latency from onset of therapy to first report of depression was explored. The table below displays first reports of depression against duration of therapy. The resolution of depression is not taken into account here. The table shows that if depression is seen, it commonly occurs in the first year of treatment, earlier rather than later, and thereafter the rate plateaus.

INCIDENCE OF FIRST REPORT OF DEPRESSION AS A FUNCTION OF DURATION OF THERAPY ALL TOPIRAMATE-TREATED EPILEPSY PATIENTS N=1446			
INTERVAL	NO PATIENTS	N	%
0-3 MOS	1446	122	8.4%
3-6 MOS	1083	38	3.5%
6-12 MOS	845	42	5%
1-2 YEARS	616	19	3%
2-3 YEARS	244	9	3.7%
3-4 YEARS	176	7	3.9%
>4 YEARS	119	1	.8%

The incidence of treated depression in the NDA population is unknown, but probably can be generated by the sponsor. The sponsor would do

well to perform further analyses to determine the incidence of depression, particularly depression severe enough to require treatment and compare it to the background incidence in the relevant population, that is, the refractory patients with partial epilepsy, to determine whether the incidence is higher than expected with this drug.

A comparison of the crude rate for depression against the background rate in the relevant population can be obtained for the short-term in the placebo controlled data. Here the rate of depression in the placebo group is 5% (11 reports) and 12% in the topiramate group (61 reports). In addition one can look at rates in comparable cohorts. The following table compares the crude rates of depression across 4 comparable NDA's.

COMPARISON OF CRUDE RATES OF DEPRESSION ACROSS RECENT NDA'S		
NDA #/YEAR	N	REPORTS (%)
Felbamate #20-189 1993	786 (excluding pediatric)	33 (4.2%)
Gabapentin #20-454 1993	2048	78 (5.3%)
Lamotrigine # 20-241 1994	2601	116 (4.5%)
Topiramate #20-505 pending	1446	238 (16%)

According to the sponsor, the mean plasma topiramate concentration was statistically significantly greater for subjects who experienced depression than those who did not. However, for individual patients in those add-on trials, the topiramate concentration had little predictive value. The sponsor has been asked to provide further documentation of this assertion, however it has not been received as of the completion of this review.

PSYCHOSIS:

Psychosis occurred in one (0.4%) of the 216 placebo-treated epileptic subjects and in fifteen (2.8%) of the 527 epileptic subjects who received

topiramate in double-blind studies. Psychosis, hallucination or paranoid reaction was reported as an adverse event in 75 patients (5% of the topiramate-exposed epilepsy population), and as a severe adverse event in 15 (see section 8.7) and a reason for discontinuing form topiramate therapy in 4 (there may be some overlap between these two groups). This probably represents a significant underestimate of the true incidence of psychosis, since there was obvious miscoding of some of these adverse events and the true numbers were dispersed over several terms. For example, one patient, coded as having "agitation" was actually found to have been homicidal. He indeed became significantly agitated, underwent psychiatric evaluation, and discharged during which time he became homicidal and killed his mother. The extent to which this kind of subtle miscoding took place cannot be documented in the time frame allotted.

The psychiatric adverse effects of topiramate were evaluated by the sponsor. These results are shown below based on the Kaplan-Meier method estimating the cumulative incidence rates of these adverse events over time. These results are summarized for all topiramate-treated subjects in sponsor's Table 19.

Sponsor's Table 19: Estimated Incidence Rates of First Occurrence of Treatment-Emergent Psychosis
(All Topiramate-Treated Subjects With Epilepsy; N=1,446)

Adverse event	Estimated Percentage of Subj. With First Occurrence of AE During Interval:						
	0-6 mos.	6mos.-1yr	1-2 yr.	2-3 yr.	3-4 yr.	4-5 yr.	>5 yr.
Psychosis	1.8	1.0	0.7	0.5	1.9	0.0	0.0

a Based on Kaplan-Meier method.

The sponsor asserts that diverse psychoses are reported to occur in about 7% of subjects with epilepsy. Thus, topiramate administered as adjunctive therapy in subjects with epilepsy does not appear to increase the risk of psychosis. Again, the rates on which the sponsor bases its conclusions are thought to be an underrepresentation. A more careful examination of the psychiatric adverse events should be undertaken by the sponsor. This was requested and is expected.

PERSONALITY CHANGE

Personality change is cited as an adverse event frequently in this NDA. While it may appear benign on its face, it is often seen in company with irritability, agitation, aggressiveness or personality disorder. The coding is diffuse and thus it is difficult to define much less quantify this entity. It has not been really been acknowledged by the sponsor.

In an attempt to more completely understand the nature of the adverse events which were so coded, those available CRFs wherein the adverse events of personality change, agitation and aggressiveness were coded. The personality changes were uniformly negative, generally aggressive or antisocial, and included such behaviors as acute spells of violence, aggressive attacks on mother, bizarre behavior, frontal lobe syndrome, unpredictable behavior, aggressiveness toward spouse, rage, argumentativeness, violent outbursts, maliciousness, boisterous behavior, an episode of "out of control", attacks of anger, violent behavior, and homicidal behavior. In some cases, psychiatric and/or pharmacologic intervention was sought.

The CANDAs were queried for all patients who reported either personality change, agitation or aggressive behavior both in the double blind and combined double blind and open label studies for the first time. The table on the following page summarizes what was found.

**FIRST REPORTS OF PERSONALITY CHANGE IN DOUBLE BLIND STUDIES
N=743**

Interval	Placebo (N=216)	Topiramate (N=527)
0-3 mos	4 (1.9%)	30 (5.7%)
3-6 mos	0	6 (1.1%)
Total	4 (1.9%)	36 (6.8%)

The first reports of personality change were more likely to occur in the topiramate-treated patients than in the placebo patients, and early onset was more common than later. This does not address the question of persistence of the adverse event.

In the total topiramate-exposed epilepsy population (N=1446) the incidence of personality change, aggression, and/or agitation was 127/1447 (8.8%).

This adverse event deserves a closer look and careful evaluation by the sponsor, so that appropriate labeling can be developed.

Gastrointestinal Effects

Because carbonic anhydrase has been involved in gastric acid function and is important in gastric acid secretion, chronic preclinical studies were done to evaluate the effect of topiramate on the gastric mucosa in animals. In chronic studies in mice and rats, gastric mucosal hyperplasia were noted along with slightly elevated serum gastrin levels. Humans, therefore were evaluated with endoscopic gastric investigation including histologic evaluation and measurement of serum gastrin levels. This was done in only 8 subjects receiving long-term treatment with topiramate in the range of 200-500 mg/day. All were evaluated for 15 months, and 7 patients were evaluated after 3 years. The status of the 8th patient is not known. There were no abnormal mucosal changes reported, according to the sponsor. This statement is somewhat ambiguous and therefore the sponsor was asked to provide the study report for review. ¹ It is still outstanding.

Weight loss

Reductions in body weight were observed based on analysis of adult subjects with epilepsy who received topiramate treatment in the completed double-blind studies and in the open-label studies. In the double-blind trials, mean decreases from baseline to the end of therapy, ranging from 2.5 to 5.1 kg (approximately 3% to 6% decrease from baseline), were noted for subjects in the topiramate groups, compared with almost no change (0.8% increase from baseline) in the placebo group). Among the 206 placebo-treated subjects for whom both pre- and post-therapy body weights were available, 78 (36%) subjects lost between 0 and 5 kg and 2 (1%) lost between 5 and 10 kg. Of the remaining 126 placebo-treated subjects, 120 (56%) gained between 0 and 5 kg, 5 (2%) gained between 5 and 10 kg, and 1 (<1%) gained more than 15 kg. Among 485 topiramate-treated subjects for whom both pre- and post-therapy body weights were available, 281 (53%) subjects lost between 0 and 5 kg and 101 (19%) lost between 5 and 10 kg, 24 (5%) lost between 10 and 15 kg, and 6 (1%) lost more than 15 kg.

In the six completed double-blind trials, 8 placebo-treated and 57 topiramate-treated subjects reported anorexia. An analysis was done to determine whether there was an association between the reporting of

¹Abrahamsson and Ben Menachem "Gastrosopic evaluation of patients with epilepsy treated with topiramate." , an unpublished report 1994. NDA volume 13.1 p. 212 reference #122. References cited p.189 summary of GI effects

weight decrease and anorexia as adverse events during these trials. This association between weight decrease and anorexia is summarized for topiramate-treated subjects in the Sponsor's Table 36. Subjects with decreased weight were more likely to have reported anorexia (17/61; 28%) compared with those who did not show a decrease in weight (40/466; 9%); thus, there is an apparent association between weight decrease and anorexia.

Sponsor's Table 36: Relationship Between Weight Loss and Anorexia
(All Topiramate-Treated Subjects;
Protocols YD, YE, Y1, Y2, Y3, and YF/YG)

Weight Decrease	Anorexia		Total
	Yes	No	
Yes	17	44	61
No	40	426	466
Total	57	470	527

All Topiramate-Treated Subjects With Epilepsy

To further assess the relationship between topiramate treatment and weight loss, an analysis was undertaken of body weight changes in the overall population of adult epileptic subjects treated with topiramate. As shown in the Sponsor's Table 37 reductions in body weight appeared to be related to mean topiramate dosage as well as to baseline weight. Mean decreases in body weight from baseline to the end of topiramate therapy ranged from 1.3 kg (1.7% decline) in the lowest dosage group (average dosage <200 mg/day) to 6.1 (7.2% decline) in the highest dosage group (average dosage ≥800 mg/day). Changes in body weight varied with initial body weight; subjects who weighed the most (>100 kg) prior to topiramate therapy showed the greatest weight loss (mean decrease of 8.6 kg or 7.6%); those in the lowest (<60 kg) baseline weight group showed the least weight loss (mean decrease of 1.3 kg or 2.5%). Changes in body weight were also examined by sex for each of four baseline body weight categories. Within each of the baseline weight groups, women showed a greater mean percent decrease in body weight when compared to men of comparable weight.

TABLE 37: MEAN CHANGE IN WEIGHT FROM BASELINE TO THE END OF TOPIRAMATE THERAPY BY DOSAGE GROUP, BASELINE WEIGHT, AND NUMBER AND TYPE OF CONCOMITANT AEDs (TOPIRAMATE-TREATED ADULT SUBJECTS WITH EPILEPSY)^a

Parameter	N	Mean Baseline (kg)	Mean (%) Change from Baseline (kg)
Dosage Group (mg/day)			
<200	186	72.1	-1.3 (-1.7)
200-499	399	74.2	-2.6 (-3.4)
500-799	344	76.4	-4.1 (-5.1)
≥800	307	81.8	-6.1 (-7.2)
Baseline Weight (kg)			
>0-60	221	53.1	-1.3 (-2.5)
>60-80	551	70.6	-3.1 (-4.4)
>80-100	343	88.1	-4.5 (-5.1)
>100	121	111.9	-8.6 (-7.6)
Number of Concomitant AEDs^b			
1	661	76.1	-3.8 (-4.7)
2	481	76.7	-3.5 (-4.2)
≥3	78	77.8	-4.5 (-5.6)
Specific Concomitant AEDs^c			
Carbamazepine	424	77.4	-4.1 (-5.1)
Phenytoin	149	74.9	-2.5 (-3.2)
Valproic acid	48	75.0	-5.5 (-7.3)
Phenobarbital	14	85.4	-2.3 (-3.2)
Primidone	26	70.9	-2.9 (-3.4)
Carbamazepine/valproic acid	142	77.2	-4.6 (-5.7)
Carbamazepine/phenytoin	125	77.1	-2.8 (-2.9)
Other combinations	292	76.6	-3.6 (-4.5)

^a Based on subject's average daily dose.

^b Includes 1,236 adult subjects with weight recorded at baseline and at the end of therapy. Subjects 18 years of age and under are excluded.

^c Excludes 16 subjects for whom no concomitant AEDs were recorded.

Additionally, an analysis was done to determine whether there was an association between the reporting of weight decrease and anorexia as adverse events for all topiramate-treated subjects with epilepsy (Sponsor's Table 39). Subjects with decreased weight were more likely to have reported anorexia (107/287; 37%) compared with those who did not show a decrease in weight (170/1,159; 15%). As was seen in the

double-blind population, there is an apparent association between weight decrease and anorexia.

**Sponsor's Table 39: Relationship Between Weight Loss and Anorexia
(Topiramate-Treated Subjects with Epilepsy)**

Weight Decrease	Anorexia		Total
	Yes	No	
Yes	107	180	287
No	170	989	1,159
Total	277	1,169	1,446

For the adverse events of weight loss and anorexia, the mean plasma topiramate concentration was statistically significantly greater for subjects who experienced the adverse event than those who did not. However, for individual patients in those add-on trials, the topiramate concentration had little predictive value.

Renal Calculi

Summary: Clinical trials indicate that topiramate increases the risk of nephrolithiasis by approximately 10-fold due to its effects on carbonic anhydrase.

Chronic administration of topiramate to rats resulted in an increased incidence and severity of phosphate urolithiasis which caused urothelial hyperplasia. The hyperplasias were not considered preneoplastic, and carcinogenicity studies confirmed that urothelial hyperplasia did not progress to neoplasia.

The renal changes observed in rodent studies with topiramate appear to be consistent with carbonic anhydrase inhibition. Carbonic anhydrase inhibitors promote stone formation (primarily calcium phosphate) by increasing urinary pH and reducing the urinary excretion of citrate as a consequence of systemic and intracellular acidosis. Topiramate has been shown to have the same effects in animals and humans.

Renal calculi were reported as adverse events in 32/2086 topiramate-treated epileptic patients and as serious adverse events in 14 patients. A total of 18 (1.5%) subjects, all males ages 21 to 54, had definite renal calculi (stone recovered or positive imaging study). One of the 18 subjects had two episodes of stone passage and another had three

episodes for a total of 21 episodes and an overall annualized rate of occurrence of 196 per 10,000 persons based on these 21 episodes. This rate of occurrence of renal calculi is comparable to that associated with acetazolamide treatment (reportedly 235 per 10,000 persons) and is approximately 10-fold higher than that reported in the general population (reportedly 7 to 21 cases per 10,000 persons).

Data from completed and ongoing clinical studies reported in this four-month safety update were reviewed for clinically significant cases of renal calculi through March 31, 1995. At the time of this analysis, approximately 2,086 healthy and epileptic subjects had been exposed to topiramate, some for more than 7 years. A total of 32 subjects, mostly men (84%), ages 21 to 54, had definite renal calculi for an overall annualized incidence rate of 123 per 10,000 persons. Four subjects had two episodes of renal calculi, two had three episodes, and one had four episodes for a total of 43 episodes of renal calculi and an overall annualized rate of occurrence of 165 per 10,000 persons. There was no apparent relationship between stone formation and duration of topiramate therapy; 30 (70%) of the 43 episodes of renal calculi developed within the first two years of treatment. Annualized incidence rates and rates of occurrence of renal calculi over time are presented in the Sponsor's Table 42.

Sponsor's Table 42: Annualized Incidence Rates and Rates of Occurrence of Renal Calculi Over Time^a
(All Topiramate-Treated Subjects Through March 31, 1995)

Duration of exposure	Annualized incidence rate	Annualized rate of occurrence
0 - 1 yr	143/10,000	202/10,000
1 - 2 yr	63/10,000	63/10,000
2 - 3 yr	127/10,000	190/10,000
3 - 4 yr	58/10,000	58/10,000

^a Beyond four years, the subject sample size was too small to make a valid estimate of the incidence rate of renal calculi.

Eight subjects with definite renal calculi required hospitalization, these cases were therefore considered to be serious adverse events

Contributing factors were present in some of the subjects in whom calculi

were reported, including personal or family history of nephrolithiasis or prior treatment with other CA inhibitors. Renal calculi occurred at dosages from 200 to 1,600 mg/day; 18 of the 32 subjects who developed definite renal calculi did so at dosages of 800 mg/day or greater. The stone was passed spontaneously in 29 (67%) of 43 cases. Only one subject underwent surgery for the placement of a stent following his fourth renal calculus; this subject had a history of renal calculi prior to topiramate therapy. Twenty-five (78%) subjects chose to continue topiramate treatment after passing a renal calculus.

Renal calculi consisted predominantly or entirely of calcium phosphate and occurred mostly in men. The individuals with renal calculi are found in Sponsor's table 43 (attachment 1).

Thrombotic Phenomena:

There were a total of seven reports of deep vein thrombosis or thromboembolic phenomena reported to this NDA. Of these 4 were reported as serious adverse events, and two as deaths. There has not been a systematic look at this event by the sponsor, clotting studies were not routinely done during any of the trials, there were no evaluations for possible vasculitides. In review of the case report forms, there appear to be plausible explanations for some of these events, but others remain unexplained. For example, in one case the patient had fallen off the roof and sustained a spinal cord injury. His deep vein thrombosis occurred in that setting. One patient developed a pulmonary embolism after he had a documented thrombocytosis for one month. None of the other patients with thrombotic or thromboembolic phenomena had thrombocytosis or obvious predisposing conditions.

While the rate described here is low, and some cases may be easily dismissed it is something that bears watching.

Pancytopenia

Pancytopenia was reported as a serious adverse event in only one patient. One cannot rule out topiramate as a possible etiologic agent in this case of pancytopenia based on the available information. See section on laboratory abnormalities.

Hepatotoxicity

Hepatitis, abnormal hepatic function studies, or hepatotoxicity was reported as a serious adverse event in one patient and a reason for

withdrawal from treatment in five. In some cases a viral etiology was likely but in the remainder the etiology could have well been medication effect. One cannot rule out topiramate as a possible etiologic agent in some cases of hepatic insufficiency based on the available information. SEE SECTION ON LABORATORY ABNORMALS.

8.8 Summary of Drug Interactions

8.8.1 Drug-Demographic Interactions

No interactions could be identified which would lead to increased toxicity in any particular demographic group with regard to age, sex, or race, that would not be readily expected (such as prevalence of SUD in men as seen in this small series, similar to published reports).

8.8.2 Drug-Disease Interactions

The pharmacokinetics was shown to be affected by renal impairment, as one would expect. Topiramate was effectively removed from the plasma by hemodialysis.

In subjects with moderate to severe hepatic impairment, both C_{max} and AUC of topiramate increased by 29%.

8.8.3 Drug-Drug Interactions

Antiepileptic Drugs

Please refer to Biopharmaceutics review for details of drug interaction studies. The only drug-drug interaction of significance which has been discovered is that of phenytoin and topiramate. Specifically, clinical studies designed to look for drug interaction have shown that when topiramate and phenytoin are administered together, there is a 20% increase in the clearance of phenytoin. This might be expected to manifest itself by increased seizure activity as phenytoin levels under certain circumstances might be expected to fall. Practically speaking, however, in the course of practice, as one drug is added to a regimen the actions and levels of existing drugs are usually measured during the course of titration. Therefore such a drop would be expected to be adjusted for if it did occur. Such a drop was not noted during clinical efficacy trials with topiramate. Adequate labeling should, however, warn of the potential for this to occur.

Oral Contraceptives

Studies of escalating doses of topiramate 100 to 400 mg q12h had no significant effect on norethindrone pharmacokinetics parameters

compared to baseline parameters in the absence of topiramate in 12 women with epilepsy stabilized on VPA.

Ethinyl estradiol serum C_{max} and AUC were decreased and CL/F increased with concomitant topiramate therapy compared to corresponding values in the absence of topiramate. The C_{max} was decreased by a maximum of approximately 25%, the AUC decreased by a maximum of approximately 30%, and the CL/F increased a maximum of approximately 33% at a topiramate dosage of 400 mg q12h.

Serum progesterone concentrations from cycle Day 21 before add-on topiramate therapy and during concomitant topiramate dose escalation were close to or at the limit of quantification. No apparent differences were observed among cycles.

Since no effect on the progestin component was observed and only a maximum mean 30% reduction in ethinyl estradiol concentrations occurred, which would give similar ethinyl estradiol concentrations as seen with a 20 µg ethinyl estradiol dose (known to be effective), there is likely to be no clinically significant effect on the contraceptive efficacy of ORTHO-NOVUM® 1/35□28 by concomitant administration of topiramate. The selective reduction of only the estrogen serum concentrations may result in an increase in breakthrough bleeding for the subject.

9.0 Conclusions

This NDA contains sufficient information to determine that topiramate is more effective than placebo in the treatment of partial onset seizures by the parameters chosen. These parameters are commonly used and do provide assurance that at least one measure of efficacy has been addressed.

The data in this NDA has been screened for accuracy though an internal audit of case record forms in two efficacy trials. The data has some problems but there does not appear to be any systematic error or error sufficiently large as to render its interpretation invalid.

With that the sponsor has demonstrated (1) effectiveness for the adjunctive treatment of partial onset seizures within a dose range of 400 to 1000 mg.

The sponsor has generated a reasonable number of exposures for an adequate time period to be able to determine that there is reasonable safety for the product in adults. The central neurotoxicity which has manifested itself so prominently should be addressed by the sponsor before final labeling can be accepted.

10.0 Recommendations

This drug should be recommended as approvable pending labeling changes that reflect the efficacy as established in adequate and well controlled trials, specifically as adjunctive therapy for partial onset seizures in the doses ranging from 400-1000 mg/day.

The labeling should reflect the sedative nature of this medication and provide adequate warning regarding the serious adverse events that have occurred, such as psychosis, depression, renal stones, hepatic dysfunction, and hearing loss, pancytopenia, and possible thrombotic phenomena.

Appendix 1

Table 43: Definite Cases of Renal Calculi in Topiramate Clinical Trials

Investigator Subject	Protocol No.	Sex	Age*	Investigator (location)	Medication and Doses	Date of Stone Occurrence	Stone Composition	Days of Exposure to Topiramate at Time of Event	Continue Topiramate	Date of D/C from Study	Urological Procedure Used	Reported in NDA 20-505 (Y/N)
13/6	YKT	M	34	Bergan (Chicago, IL)	800 mg/day topl 1,900 mg/day CBZ 175 mg/day PB 500 mg pm TYLENOL*	3/1/90	Calcium 100%	256	Yes	12/07/90 (Subject Choice)	Spontaneous passage	Y
12/7	YKT	M	40	Barr (Chicago, IL)	1,000 mg/day topl 180 mg/day PB 1,400 mg/day CBZ ranitidine HCL, dexamethasone Necospirin [®] , desipramine HCl morphine, magaldrate, heparin glycopyrrolate, hydrocortisone phytonadione, Decadron [®] , cetazolin ticarcillin, gentamicin, Vicodin [®] milk of magnesia, Dulcolax [®] meperidine, atropine, bisacodyl docusate, Lidax [®] , warfarin Darvocet [®] -100, methyprednisolone	8/14/90	None passed (had positive IVP)	353	Yes	10/14/90 (intercurrent illness, Significant Protocol Violation)	None passed	Y
<p>Subject fell from a ladder and was paralyzed on 6/29/90. An IVP done in 7/90 was normal. An IVP done in 8/90 showed multiple right renal calculi. Subject tapered off of topiramate in 10/90. Subject expired in 12/90.</p>												
900/6*	YEP	M	28	Ben-Menachem (SWEDEN)	500 mg/day topl 1,400 mg/day CBZ 200 mg/day PB	3/3/91	None collected (had positive IVP)	451	Yes	Therapy cont.	Spontaneous passage	Y
903/4	YEP	M	35	Dam (DENMARK)	500 mg/day topl	5/27/93	NAV	1,059	Yes	Therapy cont.	NAV	N
	second episode				600 mg/day topl 900 mg/day CBZ	8/19/93	None collected (had positive ultrasound)	1,143	No	2/11/94 (intercurrent illness)	Spontaneous passage	N

(Continued)

* Age at onset of renal calculus.

* Patient has personal or family history of renal stones.

Key: topl = topiramate, CBZ = carbamazepine, PB = phenobarbital, IVP = intravenous pyelogram, NAV = information not available.

Table 43: Definite Cases of Renal Calculi in Topiramate Clinical Trials (Continued)

Investigator/Subject	Protocol No.	Sex	Age*	Investigator (location)	Medications and Doses	Date of Stone Occurrence	Stone Composition	Days of Exposure to Topiramate at Time of Event	Continue Topiramate	Date of D/C from Study	Urological Procedure Used	Report in ND/ 20-50: (Y/N)
215/10 ^b	YI	F	39	Sachdeo (New Brunswick, NJ)	1000 mg/day topi 500 mg TYLENOL [®] pm	11/3/93	Ca. Ox. Dihydrate 5% Ca. Apatite 5% Ca. Ox. Monohydrate 90%	201	Yes	Therapy cont.	Spontaneous passage	N
171/4	YF	M	53	Browne (Boston, MA)	800 mg/day topi 1000 mg/day CBZ	7/26/93	None collected (had positive ultrasound)	209	No	8/7/93 (renal calculus)	Spontaneous passage	N
21/2 ^a	YD	M	21	Ramsay (Miami, FL)	400 mg/day topi 800 mg/day CBZ 2,000 mg/day VPA 1,000 mg/day Cipro [®] 2,000 mg/day ampicillin 500 mg pm TYLENOL [®] Diamox [®] X 33 months (ended 39 months before stone occurrence)	11/3/88	None collected (had positive IVP)	112	No	11/03/88 (completed YD study)	Spontaneous passage	Y
2/32	YB	M	28	Tolman (Salt Lake City, UT)	200 mg/day topi	2/17/87	None collected (had positive IVP)	22	No	6/3/17/87 (renal calculus, report)	Spontaneous passage	Y
17/22	YKT	M	43	Faught (Birmingham, AL)	800 mg/day topi 750 mg/day VPA	6/25/92	Protein 2% Carbonate Apatite 10% Hydroxyl Apatite 88%	1,063	Yes	Therapy cont.	Spontaneous passage	Y
178/1 ^a	MS-218	M	33	Rosenfeld (Chesterfield MO)	800 mg/day topi 2,000 mg/day Depakote [®]	7/23/82	None collected (had painful hematuria)	35	Yes	Therapy cont.	Spontaneous passage	Y
	YLT			second episode	800 mg/day topi	10/15/92	None collected (had painful hematuria)	119	Yes	Therapy cont.	Spontaneous passage	Y
	YLT			third episode	900 mg/day topi	3/23/93	None collected (had painful hematuria)	279	Yes	Therapy cont.	Spontaneous passage	Y
	YLT			fourth episode	900 mg/day topi	4/19/93	Calcium phosphate	305	Yes	Therapy cont.	Stone manipulation & stent placement	N

^a Age at onset of renal calculus.
^b Information collected during double-blind treatment and not represented in adverse event data listings.

^c Patient has personal or family history of renal stones.

Key: topi = topiramate, CBZ = carbamazepine, VPA = valproic acid, IVP = intravenous pyelogram

Table 4J: Definite Cases of Renal Calculi in Topiramate Clinical Trials (Continued)

Investigator/Subject	Protocol No.	Sex	Age ¹	Investigator (location)	Medications and Doses	Date of Stone Occurrence	Stone Composition	Days of Exposure to Topiramate		Urological Procedure Used	Reported in NDA 20-805 (Y/N)
								Continuous Topiramate	Date of D/C from Study		
142/6	YF	M	33	Krumholz (Ballimore, MD)	600 mg/day topi	7/25/93	None collected (had positive ultrasound)	117	Therapy cont.	Spontaneous passage	N
355/273*	YOL	M	20	Rak (Allentown, PA)	800 mg/day topi multivitamin Retin-A benzoyl peroxide (topical)	3/23/94	Protein/blood 3% Ca. Oxalate Dihydrate 5% Ca. Oxalate Monohydrate 10% Ca. Phosphate (carbonate form) 10% Ca. Phosphate (hydroxyl form) 72%	120	Therapy cont.	Spontaneous passage	N
					800 mg/day topi multivitamin Retin-A benzoyl peroxide (topical)	6/3/94	Ca. Oxalate Monohydrate 2% Protein 3% Ca. Phosphate (carbonate form) 13% Ca. Phosphate (hydroxyl form) 82%	192	Therapy cont.	Spontaneous passage	N
					NAV	10/94	NAV	NAV	NAV	NAV	N
215/44*	YI	F	39	Sachdeo (New Brunswick, NJ)	5 tabs bid (blinded) 2,100 mg/day FBM Rolids [®] pm TYLENOL [®] pm	10/6/94	None collected (had positive IVP)	42	Therapy cont. passage	Spontaneous passage	N
802/441*	YOLE	M	22	Tarraz (Italy)	800 mg/day topi 175 mg/day PHT 1400 mg/day CBZ 15 mg/day nitrazepam	9/23/94	None collected (had positive urography)	245	Therapy cont.	Spontaneous passage	N
328/335	YOLE	M	27	Crawford (U.K.)	700 mg/day topi 500 mg/day PHT 150 mg/day PB 10 mg/day clobazam	5/25/93	None collected (had positive ultrasound)	157	Therapy cont.	Spontaneous passage	N

¹ Age at onset of renal calculus.

* Information collected after the March 31, 1994 data cutoff for this safety update.

² Patient has personal or family history of renal stones.

(key): topi = topiramate, CBZ = carbamazepine, PHT = phenytoin, PB = phenobarbital, FBM = febamate, NAV = information not available.

(Continued)

REVIEW AND EVALUATION OF CLINICAL DATA

NDA	20 505
Sponsor	RW Johnson Pharmaceutical Research Institute
Brand Name (generic name)	Topamax (Topiramate)
Indication	Partial Onset Epilepsy
NDA Classification	IS
Original Receipt Date	December 29, 1994
Clinical Reviewer	Cynthia G. McCormick, MD <i>Cynthia G. McCormick MD</i>
Labeling Review	November 9, 1995

LABELING REVIEW

Labeling was received with the original NDA and unsolicited additions have been made by the sponsor throughout the review period. The final version of the sponsor's labeling was received on October 19, 1995. This version includes the new dosage form submitted to the NDA on October 19, 1995. This version will serve as the basis for review. Appended to this summary is that version of labeling incorporating clinical changes which in the opinion of this reviewer the NDA supports.

Description

This section requires no clinical additions, deletions, or changes.

Clinical Pharmacology

Mechanism of Action

This section requires no clinical additions, deletions, or changes.

Pharmacodynamics:

This section requires no clinical additions, deletions, or changes.

Biopharmaceutics changes are noted.

39 Pages

Purged

Draft
Label

Pharmacokinetics

Changes to the current version recommended by Biopharmaceutics were included in small print. There are no other clinical additions, deletions, or changes required in this section.

Clinical Studies

The sponsor has included a detailed description of all 5 clinical studies of a placebo-controlled, parallel, add-on design. These studies differ only in doses and in some cases the length of the baseline or titration period. Because of their similarity, nothing substantive appears to be gained by describing each one individually. While it is difficult to consolidate the information, an attempt has been made (see attached labeling and next page).