

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

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

^a Individual subjects may have received one or more AEDs.

^b Individual subjects may have had more than one seizure type during the baseline phase.

^c Includes both valproic acid and divalproex sodium.

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

	Placebo (N=45)		Topiramate (N=41)		Total (N=86)	
Age (yr)	N	%	N	%	N	%
1-7; No. (%)	15	(33)	17	(41)	32	(37)
8-11; No. (%)	20	(44)	13	(32)	33	(38)
≥12; No. (%)	10	(22)	11	(27)	21	(24)
Mean	9.0		8.8		8.9	
SD	3.35		3.64		3.47	
Median	10.0		9.0		9.0	
Range	2-16		2-16		2-16	
Weight (kg)						
15-24.9 kg	13	(29)	15	(37)	28	(33)
25-31.9 kg	13	(29)	7	(17)	20	(23)
32-42.9 kg	9	(20)	10	(24)	19	(22)
≥43 kg	10	(22)	9	(22)	19	(22)
Mean	35.1		34.7		34.9	
SD	16.32		15.79		15.98	
Median	32.0		30.0		31.5	
Range	15.0-90.0		15.0-76.0		15.0-90.0	
Height (cm)						
Mean	132.6		131.8		132.2	
SD	19.05		23.90		21.27	
Median	134.0		133.0		134.0	
Range	94.0-178.0		90.0-178.0		90.0-178.0	
Baseline Average Monthly Seizure Rate: ^a						
Partial Onset Seizures						
Mean	84.5		45.6		65.9	
SD	190.1		56.18		143.5	
Median	19.0		21.5		21.3	
Range	2.0-1132.6		1.8-231.5		1.8-1132.6	
Secondarily Generalized Seizures						
Mean	17		17		34	
SD	41.1		16.4		28.8	
Median	87.95		25.32		64.95	
Range	5.0		6.3		5.6	
All Seizures						
Mean	0.5-272.8		0.9-89.1		0.5-272.8	
SD	84.2		46.0		67.0	
Median	189.82		57.20		143.52	
Range	23.0		21.5		22.2	
Rate per 28 days	2.0-1132.6		1.8-244.0		1.8-1132.6	

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Table 7: Subjects Who Prematurely Discontinued Study Medication
(All Randomized Subjects; Protocol YP)

Investigator/ Subject No.	Age (yrs)	Sex	Duration of Therapy (Days)	Daily Dosage at Discontinuation (mg/day)	Duration of Double-Blind Participation (Days) ^a	Reason for Discontinuation
Wyllie/113	4	M	14	25	29	AE: rash
Edwards/662	10	M	18	100	28	Subject choice; uncooperative
Wyllie/110*	5	M	93	125	119	Other: noncompliance

* Number of days from the beginning of the double-blind phase until withdrawal from or completion of the trial.

• Discontinued study medication prematurely but completed the trial per protocol.

Table 8: Percent Reduction From Baseline in Average Monthly Seizure Rate
During the Double-Blind Phase

(All Randomized Subjects; Protocol YP)

Seizure Type/Treatment	Median	Percent Seizure Rate Reduction ^a
Partial Onset Seizures		
Placebo (N = 45)	10.5	-17.4 to 42.6
Topiramate (N = 41)	33.1	6.9 to 67.0
p-value ^b		0.034
Secondarily Generalized Seizures		
Placebo (N = 20)	-10.6	-376.6 to 52.1
Topiramate (N = 20)	31.6	-49.9 to 87.1
All Seizures		
Placebo (N = 45)	10.5	-15.0 to 43.5
Topiramate (N = 41)	31.9	3.2 to 67.0
p-value ^b		0.077

^a Negative numbers denote an increase in seizure rate.

^b TPM vs. placebo: two factor (treatment and center) ANOVA on ranks.

Table 9: Treatment Responders for the Double-Blind Phase
(All Randomized Subjects; Protocol YP)

Seizure Type/Treatment	No.	%	Treatment Responders ^a	p-value ^b
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Partial Onset Seizures

Placebo (N=45)

Topiramate (N=41)

Secondarily Generalized Seizures

Placebo (N=20)

Topiramate (N=20)

All Seizures

Placebo (N=45)

Topiramate (N=41)

Subjects with 50% or greater reduction from baseline.

^a TPM vs. placebo; Cochran-Mantel-Haenszel test stratified by center.

^b TPM vs. placebo; Wilcoxon-Rank Sum test stratified by center.

Table 10: Distribution of Subjects by Percent Reduction
in Average Monthly Seizure Rate for the
Double-Blind Phase

(All Randomized Subjects; Protocol YP)

Seizure Type/ Percent Reduction	Placebo (N=45)	Topiramate (N=41)
Partial Onset Seizures		
100	0	2
75	1	7
50	9	16
25	18	22
0	29	32
≥25	34	35
Secondarily Generalized Seizures		
100	2	5
75	3	5
50	6	9
25	7	11
0	9	13
≥25	12	15
All Seizures		
100	0	2
75	1	7
50	10	16
25	19	22
0	30	31
≥25	35	35

* Placebo: N=20; Topiramate: N=20.

Table 11: Parental Global Evaluation of Improvement in Seizure Severity
(All Randomized Subjects; Protocol YP)

Improvement Rating (Score)	Placebo (N=45)	Topiramate (N=41)
Worse	4	3
No Change	26	14
Minimally	7	8
Moderate	3	4
Marked	5	12
p-value		0.025 ^a 0.019 ^b

^a TPM vs. placebo; Wilcoxon-Rank Sum test stratified by center.

^b TPM vs. placebo; Wilcoxon-Rank Sum test unstratified.

Table 12: Changes in Plasma Concentrations of Concomitant AEDs From the
Baseline Phase to the Double-Blind Phase

(Randomized Subjects With Available Data; Protocol YP)

Concomitant AED	Baseline Mean (SD)	Change (SD)	N	Baseline Mean (SD)	Change (SD)	N	p-value ^a
Carbamazepine	26	9.3 (2.49)	25	-0.3 (1.60)	8.9 (2.46)	25	0.428
Valproic Acid	12	75.6 (40.34)	10	-4.2 (16.28)	83.3 (34.78)	10	0.389
Lamotrigine	5	3.5 (1.36)	5	0.7 (0.96)	7.8 (5.99)	5	0.017
Phenytoin	9	12.8 (7.36)	9	-1.2 (3.66)	9.8 (6.70)	6	0.101

^a One-way ANOVA comparing topiramate with placebo with respect to mean change from baseline.

Table 13: Seizure Rate Reduction and Treatment Responders by Plasma Topiramate Concentration Stratum (All Available Plasma Samples During Stabilization; Protocol YP)

Seizure Type	N	Median Percent Reduction	Percent Respondent No.	%
Partial Onset Seizures	13	18.1	5	38
3.2 to <4	14	51.5	8	57
≥4	14	30.3	5	36
All Seizures	13	10.6	5	38
3.2 to <4	14	51.5	8	57
≥4	14	30.4	5	36

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

Primary Variable	Placebo (N=45)	Topiramate (N=41)	p-value
Percent reduction from baseline in average monthly seizure rate for partial onset seizures	10.5	32.1	0.034 ^a
Percent reduction from baseline in average monthly seizure rate for:			
All seizures	10.5	31.9	0.077 ^a
Generalized seizures	-10.6	31.6	
Percent treatment responder ^b :			
Partial onset seizures	20.0	39.0	0.080 ^c
All seizures	22.0	39.0	0.127 ^c
Percent global evaluation of improvement in seizure severity ^d	33	59	0.025 ^e
Percent responder is defined as subject whose seizure rate was reduced 50% or more during the double-blind phase.			0.019 ^f

Table 15: Actual Target Doses Based on Subjects' Baseline Weight

Target Dose (mg/kg per day)	Placebo (N=45)	Topiramate (N=41)	Total (N=86)
4 to <5	1 (2)	0 (0)	1 (1)
5 to <6	21 (47)	20 (49)	41 (48)
6 to <7	12 (27)	13 (32)	25 (29)
7 to <8	8 (18)	5 (12)	13 (15)
8 to 9	3 (7)	3 (7)	6 (7)
Mean	6.3	6.3	6.3
SD	0.93	0.94	0.93
Median	6.1	6.0	6.1
Range	4.4-8.7	5.2-8.9	4.4-8.9

Table 16: Daily Dosage of Study Medication: Double-Blind Phase (All Randomized Subjects; Protocol YP)

Treatment	Mean	Standard Deviation	Median	Range
Average Daily Dosage ^a (mg/kg/day)				
Placebo ^b (N=45)	4.8	1.12	4.8	1.4 - 6.8
Topiramate (N=41)	4.8	0.88	4.8	1.8 - 6.7
Maximum Daily Dosage ^c (mg/kg/day)				
Placebo ^b (N=45)	6.3	1.49	6.1	1.4 - 10.0 ^d
Topiramate (N=41)	6.3	1.20	6.0	3.9 - 10.4 ^d

Table 17: Daily Dosage of Study Medication: Stabilization Period (All Randomized Subjects; Protocol YP)

Treatment	Mean	Standard Deviation	Median	Range
Average Daily Dosage ^a (mg/kg/day)				
Placebo ^b (N=43)	6.2	1.13	6.2	2.3 - 8.7
Topiramate (N=41)	6.0	1.21	5.9	2.0 - 8.9
Maximum Daily Dosage ^c (mg/kg/day)				
Placebo ^b (N=43)	6.4	1.12	6.2	4.2 - 10.0 ^d
Topiramate (N=41)	6.2	1.36	6.0	2.3 - 10.4 ^d

Table 18: Average Daily Dosage (mg/kg/day) During the Stabilization Period by Target Dosage Group (All Randomized Subjects; Protocol YP)

Target Dosage Group ^a	Mean	Standard Deviation	Median	Range ^b
Placebo (N=43)				
125 (N=12)	118.8	22.63	125.0	54.9-149.7 ^c
175 (N=13)	174.4	2.31	175.0	166.7-175.0
225 (N=8)	222.4	3.82	223.0	208.2-225.0
400 (N=10)	399.7	0.87	400.0	397.3-400.0
Topiramate (N=41)				
125 (N=15)	119.9	11.00	125.0	89.4-127.2 ^c
175 (N=7)	171.4	9.45	175.0	150.0-175.0
225 (N=10)	211.9	27.59	223.0	150.0-225.0
400 (N=9)	361.7	85.22	400.0	150.5-400.0

^a Results based on administration of "25 mg" and "100 mg" placebo tablets that matched topiramate tablets.

^b One subject assigned to receive placebo 125 mg/day (Subject 524) and one subject assigned to receive topiramate 125 mg/day (Subject 526) exceeded their assigned target daily dosage once during the study.

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Table 19: Duration of Double-Blind Therapy
(All Randomized Subjects; Protocol YP)

Double-Blind Therapy (Days)	Placebo (N=45)		Topiramate (N=41)		Total (N=86)	
	No.	%	No.	%	No.	%
≤105	2	4.4	2	9.8	4	4.8
106-112	11	24.4	10	24.4	21	24.4
113-119	13	28.9	17	41.5	30	34.9
120-126	7	15.6	4	9.8	11	12.8
127-133	8	17.8	3	7.3	11	12.8
≥134	4	8.9	5	12.2	9	10.5
Mean (SD)	115.5 (23.60)		118.5 (11.41)		116.9 (18.76)	
Median	118.0		114.0		115.0	
Range	14-147		93-148		14-148	

Table 21: Subjects With Serious Adverse Events
(All Randomized Subjects; Protocol YP)

Investigator/ Subject No.	Age (yr)	Sex	Preferred Term	Day of AE Onset ^a (Period) ^b		Final Dose (mg/day)	Severity ^d Relationship ^d	Outcome (Duration)
				Placebo	Topiramate			
Wyllie/113	5/F		Convulsions Aggravated	26 (T)	25	125	Marked Possible	Resolved (2 days)
Elson/74	9/M		Infection Viral	66 (S)	175	175	Mild Unlikely	Resolved (6 days)
Wyllie/116	5/M		Convulsions Aggravated	104 (S)	100	100	Marked Unlikely	Resolved (2 days)
Wyllie/117	11/M		Constipation	50 (T)	125	100	Marked Unlikely	Resolved (14 days)

o U.S. IND Safety reports were filed.
s refers to the double-blind phase.
denotes titration period and S denotes stabilization period.
used on the investigator's assessment at the time of occurrence of the adverse event.

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2: Subjects With Treatment-Emergent Adverse Events Resulting in a Dosage
(All Randomized Subjects; Protocol YP)

Investigator/ Subject No.	Age (yr)	Sex	Preferred Term	Day of AE Onset ^a	Dose at AE Onset ^b	Severity ^c Relationship ^d	Action Taken (Dosage)	Outcome (Duration)	Total Days of Therapy ^e
Elton/530	14	F	Coordination abnormal	57	225	Mild Possible	Reduced	Persisted ^f	141
Sol/75	5	F	Influenza-like symptoms	24	50	Moderate Possible	Reduced	Resolved (7 days)	110
Wyllie/116	6	M	Mood problems	37	100	Moderate Possible	Reduced	Resolved (31 days)	126
Wyllie/117	8	F	Parosmia	37	100	Moderate Possible	Reduced	Resolved (31 days)	126
			Delusion	52	125	Mild Possible	Reduced	Resolved (16 days)	126
			Nausea	18	50	Moderate Possible	Reduced	Resolved (4 days)	142
			Vomiting	19	25	Moderate Possible	Reduced	Resolved (3 days)	142
			Urinary incontinence	80	75	Marked Possible	Reduced	Resolved (49 days)	142
Topiramate									
Reits/542	8	F	Somnolence	80	75	Mild Possible	Reduced	Resolved (31 days)	136
Bourgeois/4	4	M	Urinary Incontinence	68	125	Mild Possible	Reduced	Resolved (11 days)	148
Duchowny/26	11	F	Somnolence	50	225	Mild Possible	Reduced	Resolved (50 days)	113
Edwards/661	12	F	Apathy	15	200	Mild Probable	Reduced	Resolved (49 days)	118
			Confusion	15	200	Mild Unlikely	Reduced	Resolved (49 days)	118
			Aggressive reaction	44	400	Mild Probable	Reduced	Resolved (20 days)	118
			Weight increase	44	400	Mild Probable	Reduced	Persisted ^f	118
Sachdev/581	5	F	Aggressive reaction	13	0 ^g	Moderate Possible	Stopped Temp.	Resolved (2 days)	130
			Emotional lability	13	0 ^g	Moderate Possible		Resolved (2 days)	130
Wyllie/115	13	M	Rash	47	300	Moderate Possible	Reduced	Resolved (5 days)	103

^a Dosage adjustment includes dosage reduction and temporary discontinuation of treatment.

^b Number of days from the beginning of the double-blind phase.

^c Dosage in mg/day.

^d Based on the investigator's assessment at the time of the occurrence of the event; for relationship, probable=probable/likely.

^e Open-label extension data were not available for this subject.

^f Event persisted into the open-label extension phase of the study and was ongoing as of the 30 June 1996 cutoff date for this submission.

^g The subject's parents voluntarily withheld the subject's morning dose of study medication due to the adverse events. The subject's total daily dose prior to Day 13 was 25 mg/day.

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Figure 1: Study Design for Fluvoxamine 150

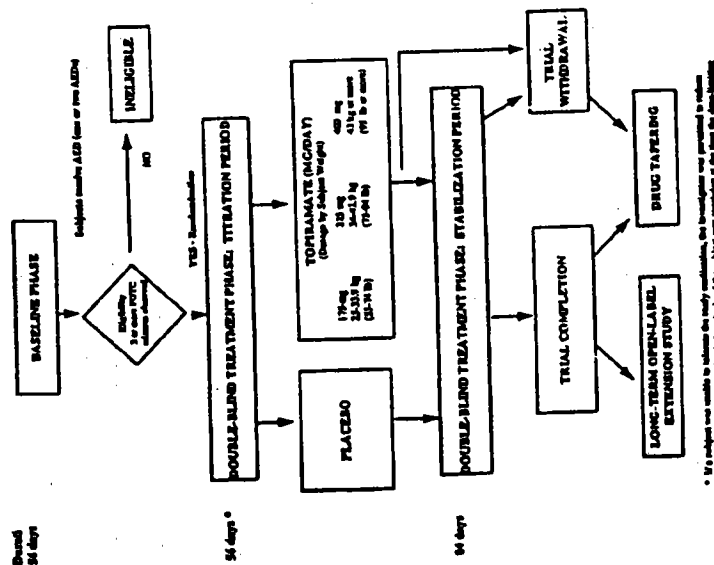


Figure 2: Completion and Withdrawal Summary

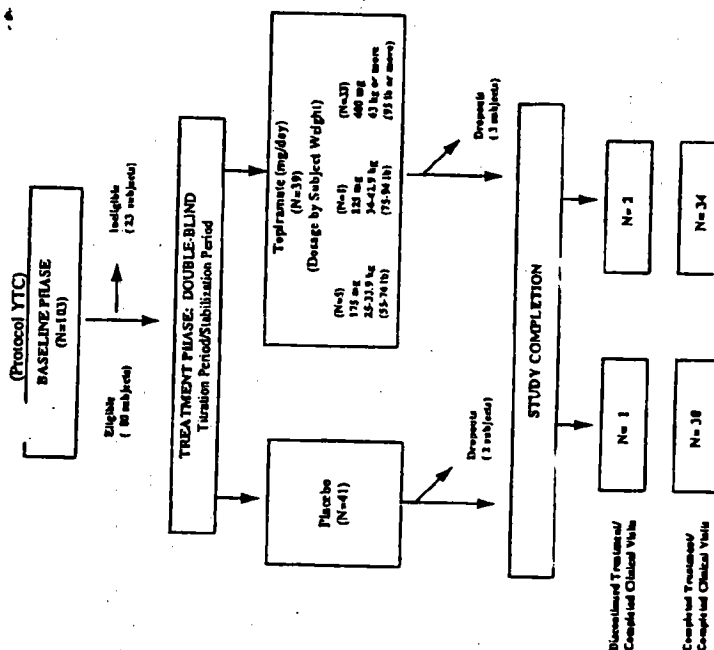


Figure 3: Mean Rank of Percent Seizure Rate Reduction by Center (All Randomized Subjects; Protocol YTC)

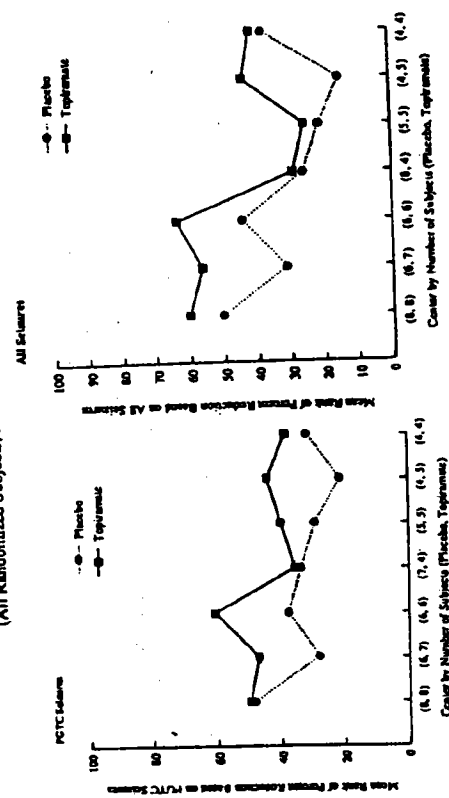


Figure 4: Cumulative Response Rate (All Randomized Subjects; Protocol YTC)

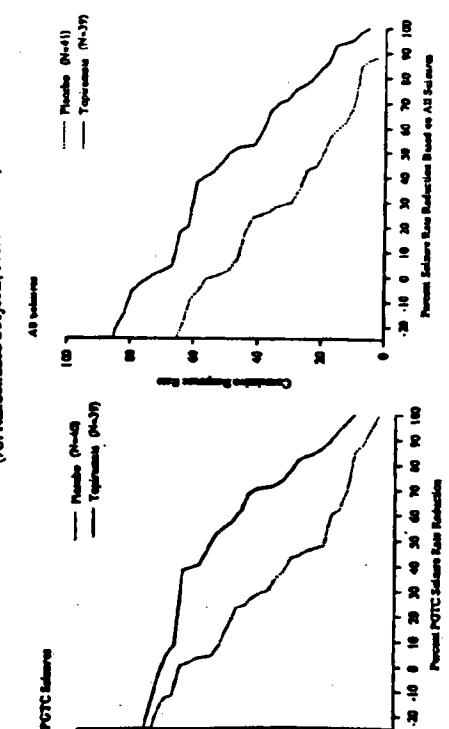


Table 1: Key Inclusion Criteria
(Protocol YTC)

- Four years of age or older, and if female, premenarchal or post-menopausal, or practicing an acceptable method of birth control.
- Weight of more than 25 kg.
- Primary generalized epilepsy including PGTC seizures with or without other seizure subtypes, with the exception of partial onset seizures.
- PGTC seizures treated with at least one, but no more than two, AED(s) and subject maintained on stable dosage regimen during the baseline phase.
- Three PGTC seizures during the 56-day baseline phase, with at least one PGTC seizure during each 28-day period.
- Electroencephalographic (EEG) or CCTV/EEG done prior to or during baseline phase with EEG features consistent with generalized epilepsy.
- CAT scan or MRI done prior to trial entry to exclude potentially progressive neurologic diseases.
- ECG during baseline phase without significant findings.

Table 2: Key Exclusion Criteria

Treatable cause of seizures (e.g., metabolic disturbance, toxic exposure, an active infection, or neoplasm) or progressive neurologic disorder.

Clinically diagnosed Lennox-Gastaut defined by age of onset of 1 to 8 years, multiple seizure types, mental retardation, and a history of an EEG with slow spike-waves (<3 counts per second) and/or multifocal abnormalities.

Documented history (within the past three months) of generalized tonic-clonic status epilepticus while complying with appropriate anticonvulsant therapy.

Seizures occurring only in clustered patterns (defined as numerous seizures occurring over a short period of time, i.e., < 30 min).

Significant history (within the past two years) of medical disease (e.g., cardiovascular, hepatic, renal, musculoskeletal, gastrointestinal, gynecologic, metabolic, or endocrine diseases) which may impair reliable participation in the trial or necessitate the use of medication not allowed by protocol.

History of alcohol or drug abuse.

History (within past six months) of a psychiatric or mood disorder requiring electroconvulsive therapy, major tranquilizers, or monoamine oxidase inhibitors. Tricyclic antidepressants could be used in low doses (e.g., amitriptyline at doses of 75 mg/day or less).

Schizophrenic or history of exhibiting psychotic symptomatology.

History of poor compliance as judged by the investigator.

Taking benzodiazepines on more than an occasional basis, unless used as one of the two concomitant AEDs.

History of suicide attempt.

Current malignancy or history of malignancy within past five years.

Treatment with an experimental drug or use of an experimental device within 60 days before admission.

Clinically significant ECG abnormalities.

History of nephrolithiasis.

Concurrent medications in past three months that included acetazolamide, zonisamide, triamterene, Vitamin C (in quantities greater than two grams per day), chronic use of antacids, or calcium supplements.

Inability to take medication or maintain a seizure calendar, independently or with assistance.

Table 3: Topiramate Dosing Schedule
(Protocol YTC)

Subject's Weight	Study Day					Target Dosage Range* (mg/kg/day)
	1 through 28	29 through 42	43 through 56	57 through 141		
25-33.9 kg (55-74 lb)	(2) 25 mg tabs PM	(2) 25 mg tab AM (2) 25 mg tab PM	(3) 25 mg tab AM (3) 25 mg tab PM	175 mg/day MAX (3) 25 mg tab AM (1) 100 mg tab PM		5.2 to 7.0
34-42.9 kg (75-94 lb)	(2) 25 mg tabs PM	(2) 25 mg tab AM (2) 25 mg tab PM	(3) 25 mg tab AM (3) 25 mg tab PM	225 mg/day MAX (1) 100 mg tab AM (1) 100 mg + (1) 25 mg tab PM		5.2 to 6.6
≥43 kg (≥95 lb)	(2) 25 mg tabs PM	(3) 25 mg tab AM (3) 25 mg tab PM	(1) 100 mg tab + (2) 25 mg tab AM (1) 100 mg tab + (2) 25 mg tab PM	400 mg/day MAX (2) 100 mg tab AM (2) 100 mg PM		5.9.3

* Theoretical dosage range based on protocol-defined daily topiramate target dosages.

Table 4: Schedule of Key Trial Procedures
(Protocol YTC)

Procedures	Baseline		Titration			Double-Blind	
	Visit 1 (Day)	Visit 2 (-29)	3 (1)	4 (29)	5 (43)	6,7,8 (57,85,113)	9 (141)*
Baseline procedures							
Medical history	X	X	X*				
Seizure history	X	X	X				
Inclusion/exclusion criteria	X	X	X				
Pregnancy test†							X
Efficacy Assessments							
Complete Seizure Diaries			X	X	X		X
Subject's Global Evaluations							X
Safety Assessments							X
Adverse Events							X
Clinical Laboratory Tests		X	X	X	X		X
Neurological Examination		X	X	X	X		X
Physical Examination		X	X	X	X		X
Vital Signs and Weight		X	X	X	X		X
ECG							X
Subject's Global Evaluations		X					X
Pharmacokinetic Assessments							X
Topiramate Plasma Concentrations		X	X	X	X		X
AED(s) Plasma Concentrations		X	X	X	X		X
Administrative							
Dispense Diary		X	X	X	X		X
Dispense Study Medication			X	X	X		X
Collect and Count Unused Study Medication			X	X	X		X

* Medical history was updated on Study Day 1 to record adverse events which occurred during baseline.

† Serum/urine pregnancy testing was performed before administration of study drug. Following Study Day 1, pregnancy testing was performed at the discretion of the investigator.

* Clinical lab testing performed on Study Days 57 and 85 only.

* On Study Day 141, subject was evaluated for admission to the open-label extension phase of the study, or was terminated.

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

	Placebo (N=41)	Topiramate (N=39)	Total (N=80)
Age (yr)	13 (32)	8 (21)	21 (26)
16; No. (%)	28 (68)	31 (79)	59 (74)
16; No. (%)	25.6	26.8	26.2
Weight (kg)	13.38	12.82	13.04
16; No. (%)	26.0	25.0	25.5
16; No. (%)	3.0 to 50.0	5.0 to 39.0	3.0 to 59.0
Height (kg)	6 (15)	5 (13)	11 (14)
16; No. (%)	2 (5)	1 (3)	3 (4)
16; No. (%)	33 (80)	33 (85)	66 (83)
can	61.3	71.8	66.5
can	21.06	28.52	27.14
can	62.0	72.0	64.0
can	17 to 129	22 to 143	17 to 143
Height (cm)	38	35	73
can	139.1	166.1	162.4
can	19.44	17.21	18.61
can	161.0	168.0	166.0
can	101 to 196	117 to 193	101 to 196
Baseline Avg. Monthly Seizure Rate ¹			
16; No. (%)	40	39	79
16; No. (%)	15.8	20.3	18.0
16; No. (%)	47.23	51.51	49.12
16; No. (%)	4.5	5.0	5.0
16; No. (%)	0.7 to 299.9	1.0 to 297.7	0.7 to 299.9
Seizures			
can	2000.9	91.1	1069.9
can	12347	214.7	8039
can	17.5	15.3	16.0
can	1.6 to 791.09	1.0 to 1134.0	1.0 to 791.09

as per 28 days. Monthly rate based on prospective baseline data.

Table 7: Therapy Discontinuation and Completion Information
(All Randomized Subjects; Protocol YTC)

	Placebo (N=41)	Topiramate (N=39)	Total (N=80)
Discontinuation Reasons	N	N	N
Subject Choice	1	2	3
Limiting Adverse Event	1	2	3
Lost to Follow-up	1	2	3
Other ^a	0	0	0
Total Discontinued	3	5	8
Total Completed	38	34	72

^a Reasons specified as "other" include noncompliance for one subject and premature advancement to open-label extension phase due to pharmacist distribution error for one subject.

Table 6b: Demographics
(All Randomized Subjects; Protocol YTC)

	Placebo (N=41)	Topiramate (N=39)	Total (N=80)
Sex	No.	No.	No.
Male	21	24	45
Female	20	15	35
Race	No.	No.	No.
White	36	32	68
Black	5	6	11
Other	0	1 ^a	1
Background AED ^b	No.	No.	No.
Valproic acid	20	19	39
Phenytoin	13	12	25
Carbamazepine	9	11	20
Lamotrigine	10	6	16
Phenobarbital	3	8	11
Chlorazepate	6	5	11
Clonazepam	3	3	6
Diazepam	4	3	7
Levetiracetam	3	4	7
Primidone	6	0	6
Chlorhexidine gluconate	1	0	1
Phenobarbital	1	0	1
Phenytoin	3	1	4
Methyphenobarbital	2	2	4
Mephentermine	0	0	0
Methamphetamine	0	0	0
Methamphetamine	1	0	1
One Background AED	9	9	18
Two Background AEDs	22	19	41
More Than Two Background AEDs	10	11	21
Baseline Seizure Type ^c	No.	No.	No.
Tonic-Clonic	40 ^d	39	79
Absence	16	16	32
Partial	10	9	19
Myoclonic	8	8	16
Drift attack ^e	5	2	7
Atypical absence	4	2	6
Clonic	1	2	3
Other ^f	1	1	2
Tonic-Clonic Only	13	13	26
Tonic-Clonic and at least one other	27	26	53

^a Subject 146 was of Hispanic descent.
^b Individual subjects may have received more than one background AED.
^c Includes valproic acid.
^d Individual subjects may have had more than one seizure type. Baseline seizure types are based on prospectively collected seizure data.
^e Subject 161 did not experience a tonic-clonic seizure during either baseline or double-blind phase (see Section IV.E, Protocol Deviations).
^f Includes seizures described as violent myoclonic jerks, tonic seizures, or drops to the floor.
^g Subject 98 (placebo) experienced seizures of an unknown type that were categorized as "other."
^h Subject 71 (topiramate) experienced complex partial seizures that were categorized as "other."

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Table 10a: Treatment Effects for the Double-Blind Phase

Seizure Type/ Treatment	No.	%	p-value ^a
PGTC Seizures			
Placebo (N=40)	8	20	
Topiramate (N=39)	22	56	0.001
All Seizures			
Placebo (N=41)	7	17	
Topiramate (N=39)	18	46	0.003

^a Subjects with 50% or greater reduction from baseline.
^b Topiramate vs. placebo; Cochran-Mantel-Haenszel test stratified by center.

Table 10b: Distribution of Subjects by Percent Reduction in Average Monthly Seizure Rate for the Double-Blind Phase

Seizure Type/ Percent Reduction	Placebo		Topiramate	
	N	%	N	%
PGTC Seizures				
100	2	5	5	13
75	5	13	13	33
50	8	20	22	56
25	18	45	26	67
0	25	63	28	72
All Seizures				
100	0	0	2	5
75	3	7	10	26
50	7	17	18	46
25	16	39	23	59
0	21	51	28	72

Table 12: Changes in Plasma Concentrations of Concomitant AEDs From the Baseline Phase to the Double-Blind Phase (Randomized Subjects With Available Data: Protocol YTC)

Concomitant AED	Baseline		Mean Change (SD)		p-value ^a
	N	Mean (µg/mL)	N	Mean (µg/mL)	
Valproic Acid	20	94.2 (18.94)	20	0.4 (16.05)	0.694
Phenytoin	12	17.3 (7.59)	12	-0.5 (6.55)	0.04
Carbamazepine	9	9.6 (3.01)	9	0.7 (0.85)	0.009
Lamotrigine	11	6.5 (4.25)	9	0.6 (1.79)	0.581
Phenobarbital	7	29.9 (4.22)	7	1.1 (7.30)	0.294

^a One-way ANOVA comparing topiramate with placebo with respect to mean change from baseline.

Table 13: Percent Seizure Rate Reduction and Treatment Responders by Plasma Topiramate Concentration Stratum (All Available Plasma Samples During Stabilization; Protocol YTC)

Seizure Type/ Plasma Topiramate Stratum	N	Median Percent Reduction	No. Responders
PGTC Seizures			
<5.04 µg/mL	12	39.5	5
5.04 to <8.46 µg/mL	12	60.8	7
8.46 to <12.88 µg/mL	11	51.5	6
All Seizures			
<5.04 µg/mL	12	2.9	4
5.04 to <8.46 µg/mL	12	59.0	7
8.46 to <12.88 µg/mL	11	51.5	7

Table 9: Percent Reduction From Baseline in Average Monthly Seizure Rate for the Double-Blind Phase

Seizure Type/ Treatment Group	Median	25 th to 75 th Percentile
PGTC Seizures		
Placebo (N=40)	9.0	-31.9 to 46.7
Topiramate (N=39)	56.7	-27.0 to 84.1
All Seizures		
Placebo (N=41)	0.9	-48.3 to 33.0
Topiramate (N=39)	42.1	-2.6 to 76.9

^a Negative numbers denote an increase in seizure rate.
^b Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.

^c Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.

^d Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.

^e Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.

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ⁱ Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.

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^l Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.

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^v Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.

^w Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.

^x Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.

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^z Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.

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^{dk} Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.

^{dl} Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.

^{dm} Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.

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

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

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

^b Topiramate vs. placebo; two factor (treatment and center) ANOVA on ranks.

^c Topiramate vs. placebo; Cochran-Mantel-Haenszel test.

^d Percent of subjects who had minimal, moderate, or marked improvement in seizure severity.

^e Topiramate vs. placebo; Wilcoxon-rank sum test stratified by center.

^f Topiramate vs. placebo; Wilcoxon-rank sum test unstratified.

Table 15a: Daily Dosage of Study Medication: Double-Blind Phase (All Randomized Subjects; Protocol YTC)

Treatment	Mean	Standard Deviation	Median	Range
Average Daily Dosage ^a (mg/kg/day)				
Placebo (N=41) ^b	4.4	1.54	4.3	0.6 - 7.3
Topiramate (N=39)	3.6	1.18	3.7	1.3 - 6.3

Maximum Daily Dosage^c (mg/kg/day)

Placebo (N=41) ^b	6.1	1.99	6.3	0.6 - 9.3
Topiramate (N=39)	5.3	1.52	5.3	2.1 - 8.5

^a Subject's average dosage (mg/kg per day) over entire double-blind phase.

^b Results based on administration of "25 mg" and "100 mg" placebo tablets that matched topiramate tablets.

^c Subject's maximum dosage (mg/kg per day) over the entire double-blind phase.

Table 15b: Daily Dosage of Study Medication: Stabilization Period (All Randomized Subjects; Protocol YTC)

Treatment	Mean	Standard Deviation	Median	Range
Average Daily Dosage ^a (mg/kg/day)				
Placebo (N=39) ^b	6.1	1.67	5.9	3.0 - 9.1
Topiramate (N=38)	5.0	1.55	5.1	1.7 - 8.5
Maximum Daily Dosage ^c (mg/kg/day)				
Placebo (N=39) ^b	6.3	1.71	6.3	3.1 - 9.3
Topiramate (N=38)	5.3	1.46	5.3	2.1 - 8.5

^a Subject's average dosage (mg/kg per day) over the stabilization period.

^b Results based on administration of "25 mg" and "100 mg" placebo tablets that matched topiramate tablets.

^c Subject's maximum dosage (mg/kg per day) over the stabilization period.

Table 16: Average Daily Dosage (mg/day) During the Stabilization Period by Target Dosage Group (All Randomized Subjects; Protocol YTC)

(All Randomized Subjects; Protocol YTC)					
Treatment Group	Target dosage (mg/day)	Mean	Standard Deviation	Median	Range
Placebo (N=39) ^a					
175 (N=6)		169.3	11.37	174.0	146 - 175
225 (N=2)		203.8	29.94	203.8	183 - 225
400 (N=31)		379.6	33.46	398.8	298 - 400

Topiramate (N=38)

175 (N=4)	174.2	1.00	174.3	173 - 175
225 (N=1)	225.0	--	225.0	--
400 (N=33)	355.2	69.41	393.8	156 - 400

^a Results based on administration of "25 mg" and "100 mg" placebo tablets that matched topiramate tablets.

Table 17: Duration of Double-Blind Therapy (All Randomized Subjects; Protocol YTC)

Double-Blind Therapy (Days)	Placebo (N=41)		Topiramate (N=39)		Total (N=80)	
	No.	%	No.	%	No.	%
1 to 133	5	12	6	15	11	14
134 to 140	11	27	8	21	19	24
141 to 147	12	29	13	33	25	31
148 to 154	8	20	7	18	15	19
≥155	5	12	5	13	10	13
Mean (SD)	138.8 (29.30)		139.9 (25.42)		139.3 (27.31)	
Median	141.0		142.0		141.5	
Range	1 to 176		48 to 197		1 to 197	

Table 20: Subjects Who Discontinued Study Medication Due to Limiting Adverse Events^a (All Randomized Subjects; Protocol YTC)

Investigator/Subject No.	Age (yr)	Sex	Preferred Term	Day of Onset ^b (Period) ^c	AE Onset (mg/day)	Final Dosage (mg/day)	Total Days of Therapy ^d	Severity ^e Relationship ^f	Outcome (Duration)
Pedley/105	38 M		Thrombocytopenia	9 (T)	50	50	43 (184)	Mild Possible Moderate Possible	Resolved (41 days) Resolved (42 days)
Wyllie/128	25 M		Anorexia	8 (T)	50	50	86 (129)	Mild Possible Mild Possible	Resolved (107 days) Resolved (84 days)
			Weight decrease	31 (T)	50	50			

^a Does not include one topiramate-treated subject (Subject 4) who stopped study medication after experiencing grand mal convulsions reported as a serious adverse event (see Section IV H.3.b.3 for further details). These convulsions were attributed to lack of compliance with the study medication and background AED regimen; therefore, noncompliance was specified as the reason for discontinuation.

^b Number of days from the beginning of the double-blind phase.

^c T denotes titration period.

^d Number of days from beginning of double-blind phase until time of study medication discontinuation; total number of days in the trial is indicated in parentheses.

^e Based on investigator assessment at the time of occurrence of event.

Key: AE = adverse event

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Figure 1: Study Design for Protocol YTC-E

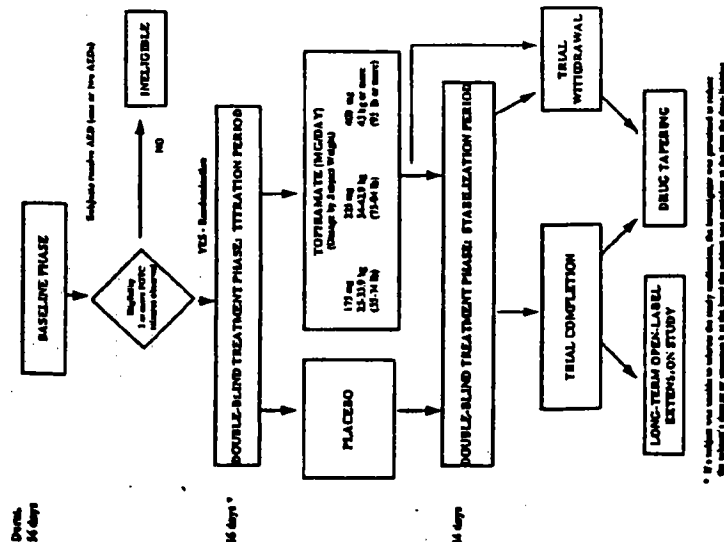
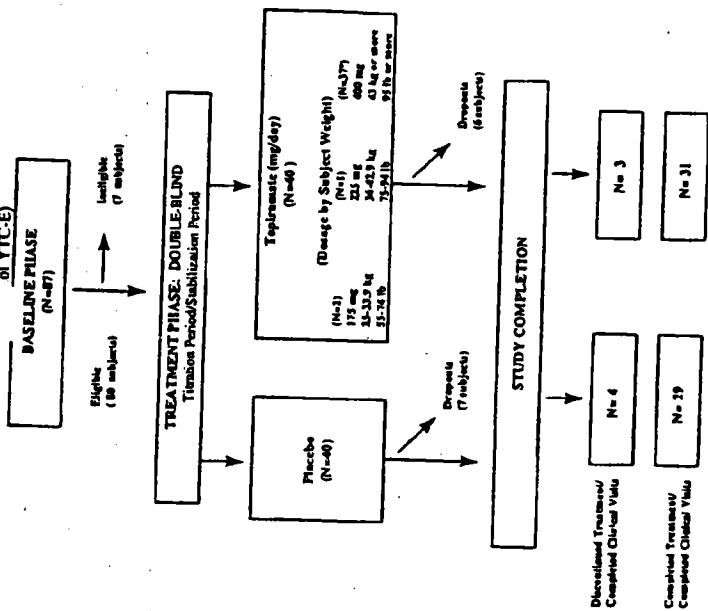


Figure 2: Study in and Withdrawal Summary of YTC-E



* Includes Subjects 317 (22.3 kg), 325 (41.4 kg) and 337 (42.3 kg) who received 400 mg/day topiramate dose instead of their target dose by baseline weight

Figure 4: Cumulative Response Rate (All Randomized Subjects; Protocol YTC-E)

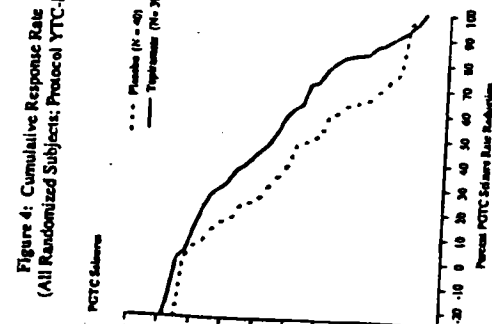
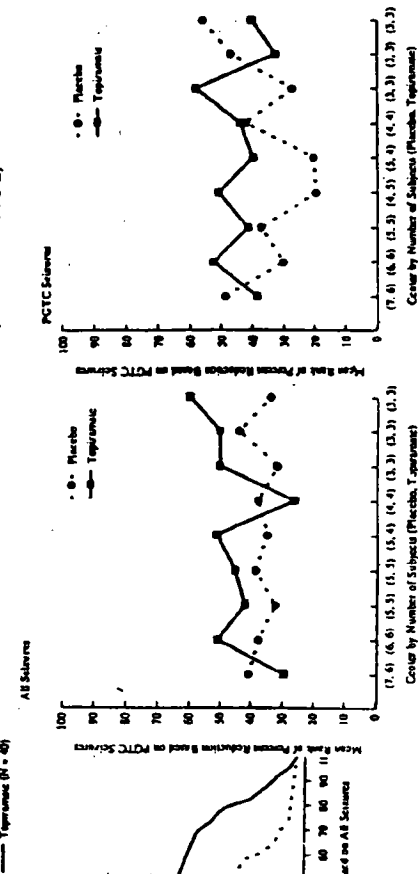


Figure 3: Mean Rank of Percent Seizure Rate Reduction by Analysis Center (All Randomized Subjects; Protocol YTC-E)



• Four years of age or older, and if female, premenarcheal or post-menopausal, or practicing an acceptable method of birth control.

- Four years of age or older, and if female, premenarcheal or post-menopausal, or practicing an acceptable method of birth control.
- Weight of more than 25 kg.
- Primary generalized epilepsies including PGTC seizures with or without other seizure subtypes, with the exception of partial onset seizures.
- PGTC seizures treated with at least one, but no more than two, AED(s) and subject maintained on stable dosage regimen during the baseline phase.
- Three PGTC seizures during the 56-day baseline phase, with at least one PGTC seizure during each 28-day period.
- Electroencephalographic (EEG) or CCTV/VEEG done prior to or during baseline phase with EEG features consistent with generalized epilepsy.
- CAT scan or MRI done prior to trial entry to exclude potentially progressive neurologic disease.
- ECG during baseline phase without significant findings.

Table 2: Key Exclusion Criteria

- Treatable cause of seizures (e.g., metabolic disturbance, toxic exposure, an active infection, or neoplasm) or progressive neurologic disorder.

- Treatable cause of seizures (e.g., metabolic disturbance, toxic exposure, an active infection, or neoplasm) or progressive neurologic disorder.
- Clinically diagnosed Lennox-Gastaut defined by age of onset of 1 to 8 years, multiple seizure types, mental retardation, and a history of an EEG with slow spike-waves (<3 counts per second) and/or multifocal abnormalities.
- Documented history (within the past three months) of generalized tonic-clonic status epilepticus while complying with appropriate anticonvulsant therapy.
- Seizures occurring only in clustered patterns (defined as numerous seizures occurring over a short period of time, i.e., < 30 min).
- Significant history (within the past two years) of medical disease (e.g., cardiovascular, hepatic, renal, musculoskeletal, gynecologic, gastrointestinal, metabolic, or endocrine diseases) which may impair reliable participation in the trial or necessitate the use of medication not allowed by protocol.
- History of alcohol or drug abuse.
- History (within past six months) of a psychiatric or mood disorder requiring electroconvulsive therapy, major tranquilizers, or monoamine oxidase inhibitors. Tricyclic antidepressants could be used in low doses (e.g., amitriptyline at doses of 75 mg/day or less).
- Schizophrenia or history of exhibiting psychotic symptomatology.
- History of poor compliance as judged by the investigator.
- Taking benzodiazepines on more than an occasional basis, unless used as one of the two concomitant AEDs.
- History of suicide attempt.
- Current malignancy or history of malignancy within past five years.
- Treatment with an experimental drug or use of an experimental device within 60 days before admission.
- Clinically significant ECG abnormalities.
- History of nephrolithiasis.
- Concurrent medications in past three months that included acetazolamide, zonisamide, triamterene, Vitamin C (ascorbic acid) (in quantities greater than two grams per day), chronic use of antacids, or calcium supplements.
- Inability to take medication or maintain a seizure calendar, independently or with assistance.

Subject's		Study Day				Target Dosage Range ^a (mg/kg/day)
Weight 25-33.9 kg (55-74 lb)	1 through 28	29 through 42	43 through 56	57 through 141		
	(2) 25 mg tabs PM	(2) 25 mg tab AM (2) 25 mg tab PM	(3)25 mg tab AM (3)25 mg tab PM	175 mg/day MAX (3)25 mg tab AM (1) 100 mg tab PM		5.2 to 7.0
34-42.9 kg (75-94 lb)	(2) 25 mg tabs PM	(2) 25 mg tab AM (2) 25 mg tab PM	(3)25 mg tab AM (3)25 mg tab PM	225 mg/day MAX (1)100 mg tab AM (1) 100 mg + (1) 25 mg tab PM		5.2 to 6.6
24.1 kg (295 lb)	(2) 25 mg tabs PM	(3)25 mg tab AM (3)25 mg tab PM	(1)100 mg tab + (2) 25 mg tab AM; (1)100 mg tab +	400 mg/day MAX (2)100 mg tab AM (2) 100 mg PM		\$9.3

Procedures	Double-Blind								
	Baseline						Titration		
	Visit (Day)	1 (-56)	2 (-29)	3 (1)	4 (29)	5 (43)	6,7,8 (57,85,113)	9 (141) ^a	
Baseline procedures									
Medical history	X	X	X						
Seizure history	X	X	X						
Inclusion/exclusion criteria	X	X	X						
Pregnancy test ^b									
Efficacy Assessments									
Complete Seizure Diaries									
Subject's Global Evaluations									
Safety Assessments									
Adverse Events									
Clinical Laboratory Tests									
Neurological Examination									
Physical Examination									
Vital Signs and Weight									
ECG									
Subject's Global Evaluations									
Pharmacokinetic Assessments									
Topiramate Plasma Concentrations									
AED(s) Plasma Concentrations									
Administrative									
Dispense Diary									
Dispense Study Medication									
Collect and Count United Study Medicines									

Targettop 1980 Annual Average Target Power:

Medical history: was updated on Study Day 1 to record adverse events which occurred during baseline

Serum/plasma pregnancy testing was performed before administration of study drug. Following Study Day 1, pregnancy testing was performed at the discretion of the investigator.

† Clinical lab testing performed on Study Days 57 and 85 only.

^d On Study Day 141, subject was evaluated for admission to the open-label extension phase of the study, or was terminated.

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

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

^a Rate per 28 days. Monthly rate based on prospective baseline data

Table 7: Treatment Discontinuation and Completion Information
(All Randomized Subjects; Protocol YTC-E)

	Placebo (N=40)	Topiramate (N=40)	Total (N=80)
Discontinuation Reason	N	%	N %
Limiting Adverse Event	7 ^a	18	5 13
Subject Choice	0	0	2 5
Investigator's Discretion	1	3	0 0
Other ^b	3	8	2 5
Total Discontinued	11 ^a	28	9 22
Total Completed	29	72	31 78
Total	40	100	80 100

^a Includes subject 209 who died suddenly during the trial.
^b Reasons associated with "Other" are detailed in Table 8.

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

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

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

Table 8: Subjects Who Prematurely Discontinued Study Treatment (Co. JTC-E)
(All Randomized Subjects; Protocol YTC-E)

Investigator/ Subject Number	Age	Sex	Duration (Days) of Double-Blind Treatment	Dosage at Discontinuation (mg/day)	Duration (Days) of Double-Blind Participation ^a	Reason for Discontinuation
idwick/5 ^b	28	F	81	75	152	Investigator's Discretion ^c
stuart/26	29	M	76	50	76	Limiting Adverse Event: convulsions, aggravated
alexander/40	34	M	27	50	27	Other: personal reasons
fan/41	26	M	108	100	129	Limiting Adverse Event: apathy; fatigue
hinger/43	27	F	134	400	134	Other ^d
idwick/60	17	M	83	50	110	Limiting Adverse Event: aggressive reaction; convulsions, aggravated; diplopia; dizziness; personality disorder; somnolence
idwick/62	33	F	14	50	15	Other: subject had a history of attempted suicide ^e
wford/65 ^b	23	M	133	300	149	Limiting Adverse Event: aggressive reaction; ataxia; ^f confusion; ^g convulsions, aggravated; ^h injury; ⁱ increased sweating
idwick/75 ^b	18	M	4	50	141	Limiting Adverse Event: aggressive reaction; agitation; anxiety; confusion; paranoia; personality disorder
m205 ^b	33	M	69	150	148	Limiting Adverse Event: nausea; ^j vomiting ^k
sy209	46	F	152 ^l	400	152	Limiting Adverse Event: sudden death ^m
die/16 ^b	42	M	120	200	149	Subject Choice
die/19	29	F	57	300	57	Limiting Adverse Event: vision abnormal ⁿ

^a Number of days from the beginning of the double-blind phase until withdrawal from, or completion of, trial.
^b These subjects prematurely discontinued study treatment but completed all nine protocol-specified clinical visits (140 days).

^c Further information is not available.
^d This deviation from protocol was discovered by the investigator after 14 days of therapy and the subject was prematurely discontinued from the trial.

^e These adverse events were considered serious by the investigator (see Table 19).
^f or subject 205, the reason specified on the study completion page of the case report form for premature discontinuation of the trial was "Subject Choice" but the adverse event page of the case report form indicated that study treatment was discontinued because of nausea and vomiting (see Table 20).

^g Due to extended time intervals between some clinical visits, the scheduled final (ninth) clinical visit for Subject 09 had not occurred even though she had received double-blind (placebo) treatment for more than 140 days.

Table 8: Subjects Who Prematurely Discontinued Study Treatment (Co. JTC-E)
(All Randomized Subjects; Protocol YTC-E)

Investigator/ Subject Number	Age	Sex	Duration (Days) of Double-Blind Treatment	Dosage at Discontinuation (mg/day)	Duration (Days) of Double-Blind Participation ^a	Reason for Discontinuation
Beght/27	32	M	60	400	60	Limiting Adverse Event: gait abnormal; somnolence
Ben-Menachem/ 31	28	F	24	50	27	Limiting Adverse Event: aggressive reaction; ^b agitation; ^c insomnia ^d
Blankenhorn/39 ^c	60	M	169 ^d	100	211	Other: subject did not have PGT seizures at baseline
Ben-Menachem/ 87	34	M	28	50	36	Limiting Adverse Event: ataxia; convulsions, aggravated; language problems (motor aphasia)
Rosenfeld/236	34	F	65	300	71	Other: subject stopped taking all treatments and did not return to clinic
Sperling/242 ^c	38	F	83	50	134	Limiting Adverse Event: ^d paranoid reaction
Sperling/245	39	F	69	50	107	Subject Choice

^a Number of days from the beginning of the double-blind phase until withdrawal from, or completion of, study.
^b These adverse events were considered serious by the investigator (see Table 19).

^c These subjects prematurely discontinued study treatment but completed all nine protocol-specified clinical visits (=140 days).

^d The study completion page of the case report form for this subject shows that the subject completed the study according to protocol. However, the adverse event page of the case report form indicates that the subject prematurely discontinued study treatment for a marked paranoid reaction (see Table 20).

Table 9: Percent Reduction From Baseline in Average Monthly Seizure Rate During the Double-Blind Phase
(All Randomized Subjects; Protocol YTC-E)

Seizure Type/ Treatment Group	Median	25th to 75th Percentile
PGTC Seizures		
Placebo (N=40)	33.2	1.4 to 64.5
Topiramate (N=39)	57.1	21.0 to 83.4
p-value		0.124 ^b
All Seizures		
Placebo (N=40)	12.1	-16.1 to 40.7
Topiramate (N=40)	26.0	-7.0 to 78.2
p-value		0.212 ^b

^a Negative numbers denote an increase in seizure rate.

^b Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.

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Table 10a: Treatment Responders For the Double-Blind Phase
(All Randomized Subjects; Protocol YTC-E)

Seizure Type/ Treatment	Treatment Responders ^a			p-value ^b
	N	%		
PGTC Seizures				
Placebo (N=40)	14	35		
Topiramate (N=39)	21	54		0.102
All Seizures				
Placebo (N=40)	8	20		
Topiramate (N=40)	16	40		0.061

^a Subjects with 50% or greater reduction from baseline
^b Topiramate vs. placebo; Cochran-Mantel-Haenszel test stratified by center

Table 10b: Distribution of Subjects by Percent Reduction in Average Monthly Seizure Rate for the Double-Blind Phase
(All Randomized Subjects; Protocol YTC-E)

Seizure Type/ Percent Reduction	Treatment Group			
	Placebo		Topiramate	
PGTC Seizures	N	%	N	%
100	4	10	3	8
75	6	15	14	36
50	14	35	21	54
25	23	58	29	74
0	30	75	31	79
2-25	31	78	34	87
All Seizures				
100	1	3	1	3
75	2	5	12	30
50	8	20	16	40
25	16	40	21	53
0	22	55	27	68
2-25	33	83	33	83

Table 11: Subject's Global Evaluation of Improvement in Seizure Severity
(All Randomized Subjects; Protocol YTC-E)

Improvement Rating	Placebo			Topiramate		
	(Score)	N	%	N	%	
Worse	(0)	3	8	4	10	
None	(1)	20	50	14	35	
Minimal	(2)	8	20	0	0	
Moderate	(3)	5	13	6	15	
Marked	(4)	0	0	13	33	
Not Assessed		4	10	3	8	
p-value						0.026 ^a 0.024 ^b

^a Wilcoxon Rank Sum test stratified by center
^b Wilcoxon Rank Sum test unstratified by center

Table 12: Change in Plasma Concentrations of Concomitant AEDs
From the Baseline Phase to the Double-Blind Phase
(Randomized Subjects With Available Data; Protocol YTC-E)

Concomitant AED	Placebo			Topiramate			p-value ^c
	N	Baseline Mean (SD) (µg/mL)	Change (SD) (µg/mL)	N	Baseline Mean (SD) (µg/mL)	Change (SD) (µg/mL)	
Lamotrigine	15	16.5 (35.48)	0.5 (1.87)	13	6.2 (4.00)	13 ^a -0.19 (0.81)	0.214
Carbamazepine	14	8.6 (2.55)	0.5 (1.24)	11	11.0 (7.45)	11 -0.4 (1.52)	0.146
Valproic acid	13	72.3 (28.10)	6.0 (13.40)	12	148.8 (190.25)	8 -26.4 (85.28)	0.189
Phenytoin	8	32.3 (31.17)	-0.5 (5.62)	7	26.7 (28.02)	7 2.7 (6.18)	0.309

^a One-way ANOVA comparing topiramate with placebo with respect to mean change from baseline

Table 15a: Daily Dosage of Study Treatment: Double-Blind Phase
(All Randomized Subjects; Protocol YTC-E)

Treatment	Mean	Standard Deviation	Median	Range
Average Daily Dosage^a (mg/kg/day)				
Placebo (N=40) ^b	3.2	1.34	3.3	0.5 - 5.7
Topiramate (N=40)	3.7	2.17	3.6	0.6 - 10.7 ^c
Maximum Daily Dosage^d (mg/kg/day)				
Placebo (N=40) ^b	4.6	1.70	4.8	0.5 - 7.9
Topiramate (N=40)	5.5	3.27	5.2	0.6 - 14.2 ^c

^a Subject's average dosage (mg/kg/day) over entire double-blind phase.
^b Results based on administration of "25 mg" and "100 mg" placebo tablets that matched topiramate tablets.
^c Five subjects (Subjects 14, 24, 217, 222, and 257) in the topiramate group received greater than the protocol-specified doses based on their weights. See Section IV.E for a description of these protocol deviations.
^d Subject's maximum dosage (mg/kg/day) during the entire double-blind phase.

Table 15b: Daily Dosage of Study Treatment: Stabilization Period
(All Randomized Subjects; Protocol YTC-E)

Treatment	Mean	Standard Deviation	Median	Range
Average Daily Dosage^a (mg/kg/day)				
Placebo (N=37) ^b	4.5	1.68	4.9	0.9 - 7.6
Topiramate (N=38)	5.2	2.78	5.1	0.8 - 14.0 ^c
Maximum Daily Dosage^d (mg/kg/day)				
Placebo (N=37) ^b	4.8	1.52	4.9	1.5 - 7.9
Topiramate (N=38)	5.8	3.16	5.3	0.8 - 14.2 ^c

^a Subject's average dosage (mg/kg/day) during stabilization.
^b Results based on administration of "25 mg" and "100 mg" placebo tablets that matched topiramate tablets.
^c Five subjects (Subjects 14, 24, 217, 222, and 257) in the topiramate group received greater than the protocol-specified doses based on their weights. See Section IV.E for a description of these protocol deviations.
^d Subject's maximum dosage (mg/kg/day) during the entire double-blind phase.

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Table 13: Percent Seizure Rate Reduction and Treatment Responders by Plasma Topiramate Concentration Stratum (All Available Plasma Samples During Stabilization; Protocol YTC-E)

Seizure Type/ Plasma Topiramate Stratum	Median Reduction		Treatment Responders	
	N	%	N	%
PGTC Seizures				
<0.01 µg/mL	9	25.1	4	44
≥0.01 to <0.67 µg/mL	11	68.5	8	73
≥0.67 µg/mL	11	35.3	4	36
All seizures				
<0.01 µg/mL	10	24.6	4	40
≥0.01 to <0.67 µg/mL	11	50.0	6	55
≥0.67 µg/mL	11	40.0	5	45

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

Efficacy Assessment	Treatment Group		p-value
	Placebo (N=40)	Topiramate (N=40)	
PGTC Seizures			
Primary Variable			
N	40	39	
Median percent reduction from baseline in average monthly seizure rate	33.2	57.1	0.124 ^a 0.078 ^b
Secondary Variable			
N	40	39	
Percent Treatment Responders ^c	35	54	0.102 ^d 0.016 ^e
All Seizures			
Secondary Variables			
Median percent reduction from baseline in average monthly seizure rate	12.1	26.0	0.212 ^f
Percent treatment responders ^g	20	40	0.061 ^h

Subjects' global evaluation of improvement in seizure severityⁱ

Topiramate vs. placebo; two factor (treatment and center) ANOVA on ranks
Topiramate vs. placebo; two factor (treatment and center) ANCOVA on ranks with baseline PCTC seizure rate as covariate.

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

Topiramate vs. placebo; Cochran-Mantel-Haenszel test
Topiramate vs. placebo; Logistic regression including treatment, center, and baseline PCTC seizure rate as terms in the model.

Percent of subjects who had minimal, moderate, or marked improvement in seizure severity.

Topiramate vs. placebo; Wilcoxon Rank Sum test stratified by center

Topiramate vs. placebo; Wilcoxon Rank Sum test unstratified

Table 16: Average Daily Dosage (mg/day) During the Stabilization Period by Target Dosage Group (All Randomized Subjects; Protocol YTC-E)

Treatment Group/ Target dosage (mg/day)	Mean	Standard Deviation	Median	Range
Placebo (N=37) ^a	174.7	---	174.7	174.7 - 174.7
175 (N=1)	337.0	98.74	388.9	60.0 - 400.0
400 (N=36)				
Topiramate (N=38)				
175 (N=2)	174.9	0.21	174.9	174.7 - 175.0
225 (N=1)	224.1	---	224.1	224.1 - 224.1
400 (N=35) ^b	338.9	103.80	388.5	50.0 - 475.3 ^c

^a Results based on administration of "25 mg" and "100 mg" placebo tablets that matched topiramate tablets.

^b Three subjects (subjects 217, 222, and 257) in the topiramate group whose weights were <43 kg were assigned a 400 mg/day target dosage. See Section IV.E for a description of these protocol deviations.

^c Two topiramate-treated subjects (Subjects 14 and 24) took daily doses >400 mg for a portion of the double-blind phase. See Section IV.E for a description of these protocol deviations.

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Table 17: Duration of Double-Blind Treatment (All Randomized Subjects; Protocol YTC-E)

Double-Blind Treatment (Days)	Placebo (N=40)		Topiramate (N=40)		Total (N=80)	
	No.	%	No.	%	No.	%
1 to 28	3	8	2	5	5	6
29 to 56	0	0	0	0	0	0
57 to 84	4	10	5	13	9	11
85 to 112	1	3	0	0	1	1
113 to 133	1	3	2	5	3	4
134 to 140	6	15	6	15	12	15
141 to 147	13	32	15	38	28	35
148 to 154	7	18	5	12	12	15
≥155	5	12	5	12	10	12
Mean (SD)	128.4 (39.97)		129.3 (36.90)		128.8 (38.22)	
Median	141.0		141.0		141.0	
Range	4 - 176		24 - 169		4 - 176	

Table 19 : Subjects With Serious Adverse Events*
(All Randomized Subjects; Protocol YTC-E)

Investigator/ Subject No. ^a	Age (yr)	Sex	Preferred Term	Day of AE Onset ^b (Period) ^c	Dose at AE Onset ^b (mg/day)	Total Days of Therapy	Final Dose (mg/day)	Severity ^d Relation- ship ^e	Outcome (Duration)
Placebo									
Chadwick/3	38	M	Pain	41 (T)	150	142	100	Marked	Resolved (2 days)
			Pain	70 (S)	400			Unlikely	Marked (2 days)
Chadwick/8	31	F	Convulsions, aggravated	27 (T)	50	141	400	Unlikely	Marked (2 days)
			Convulsions, aggravated	43 (T)	225			Marked	Resolved (2 days)
Crawford/23	22	M	Convulsions, aggravated	114 (S)	400	154	400	Unlikely	Marked (2 days)
Ben- Menachem/32	46	F	Injury	99 (S)	400	155	400	Possible	Marked (2 days)
								Unlikely	Resolved (57 days)
Crawford/65	23	M	Injury	112 (S)	300	133	300	Marked	Resolved (31 days)
			Convulsions, aggravated	112 (S)	300			Marked	Resolved (1 day)
								Possible	
			Alexia	126 (S)	300			Moderate	Resolved (17 days)
			Confusion	128 (S)	300			Possible	Resolved (15 days)
Chadwick/75	18	M	Convulsions, aggravated	14 (T)	Unknown	4	50	Marked	Resolved (2 days)
			Psychosis	86 (T)	Unknown			Unlikely	
			Convulsions, aggravated	86 (T)	Unknown			Marked	Resolved (9 days)
								Marked	Resolved (3 days)
3ilom/205	33	M	Nausea	69 (S)	150	69	150	Marked	Resolved (2 days)
			Vomiting	69 (S)	150			Possible	Marked (2 days)
			Hematemesis	69 (S)	150			Marked	Resolved (2 days)
zroy/209	46	F	Sudden death	152 (S)	400	152	400	Mild	Resolved (2 days)
								Unlikely	
								Marked	...
								Unlikely	...

No U.S. IND safety reports were filed.
Number of days from the beginning of the double-blind phase.
(T) denotes titration period and (S) denotes stabilization period.
Based on investigator's assessment at time of occurrence of the adverse event; for relationship, probable = probable/likely.
These subjects prematurely discontinued study treatment but completed all clinical visits (see Tables 8 and 20).
An encoding error was found for this date of onset. The case report form correctly identified the date of onset as Day 86 (Sept. 24, 1996) but the database captured the day of onset as Day 66 (Sept. 4, 1996). The database has not been changed. Text and tables reflect the correct date.
This subject prematurely discontinued study treatment and was withdrawn from study (see Tables 8 and 20).

Table 19: Subjects With Serious Adverse Events* (Continued)
(All Randomized Subjects; Protocol YTC-E)

Investigator/ Subject No. ^a	Age (yr)	Sex	Preferred Term	Day of AE Onset ^b (Period) ^c	Dose at AE Onset ^b (mg/day)	Total Days of Therapy	Final Dose (mg/day)	Severity ^d Relation- ship ^e	Outcome (Duration)
Topiramate									
Crawford/14	25	F	Somnolence*	57 (S)	800	141	400	Moderate	Resolved ^f (=100 days)
			Dizziness*	57 (S)	800			Probable	Marked (25 days)
			Overdose*	57 (S)	800			Marked	Resolved (25 days)
								Certain	Marked (1 day)
Brodie/19*	29	F	Vision abnormal	49 (T)	300	57	300	Marked	Resolved (11 days)
Ben- Menachem/31*	28	F	Aggressive reaction	3 (T)	50	24	50	Possible	Marked (25 days)
			Agitation	3 (T)	50			Probable	Marked (25 days)
			Insomnia	3 (T)	50			Marked	Resolved (25 days)
Chadwick/59	37	F	Abscess	100 (S)	400	153	400	Probable	Marked (25 days)
								Marked	Resolved (25 days)
								Unlikely	Marked (25 days)

* No U.S. IND safety reports were filed.
Number of days from the beginning of the double-blind phase.
(T) denotes titration period and (S) denotes stabilization period.
Based on investigator's assessment at time of occurrence of the adverse event; for relationship, probable = probable/likely.
These events required dose adjustment (see Table 21). Subject 14 mistakenly took 800 mg/day for 16 days. The overdose was encoded as "therapeutic response increased."
Based on follow-up information received on April 15, 1997, after closure of the database for this trial. This treatment-emergent adverse event was not considered serious by the investigator, but is included in this table because the subjects was hospitalized for drainage of the infected subcutaneous cyst.
These subjects prematurely discontinued study treatment and were withdrawn from study (see Tables 8 and 20).

Table 22: Subjects' Global Evaluation of Improvement in Mental Status
(All Randomized Subjects; Protocol YTC-E)

(All Randomized Subjects, 1:1000:1:2:2:2:2)																	
Score: Description:	Not Reported No.	(%)	(0) Worse		(1) None		(2) Minimal		(3) Moderate		(4) Marked						
			No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)					
Level of Alertness																	
Placebo (N=40)	4	(10)	3	(8)	25	(63)	6	(15)	1	(3)	1	(3)					
Topiramate (N=40)	3	(8)	5	(13)	23	(58)	3	(8)	5	(13)	1	(3)					
Level of Interaction With the Environment																	
Placebo (N=40)	4	(10)	2	(5)	27	(68)	4	(10)	3	(8)	0	(0)					
Topiramate (N=40)	3	(8)	4	(10)	22	(55)	5	(13)	4	(10)	2	(5)					
Ability to Perform Activities of Daily Living																	
Placebo (N=40)	4	(10)	4	(10)	27	(68)	1	(3)	4	(10)	0	(0)					
Topiramate (N=40)	3	(8)	5	(13)	22	(55)	2	(5)	6	(15)	2	(5)					
Responsiveness to Verbal Requests																	
Placebo (N=40)	4	(10)	2	(5)	27	(68)	5	(13)	1	(3)	1	(3)					
Topiramate (N=40)	3	(8)	6	(15)	21	(53)	6	(15)	2	(5)	2	(5)					

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Table 20

**Who Discontinued Study Treatment Due to Limiting Adverse Events
(All Randomized Subjects; Protocol YTC-E)**

Table 21 cts With Treatment-Emergent Adverse Events Resulting in a Dose Adjustment*
(All Randomized Subjects; Protocol YTC-E)

Investigator/ Subject No.	Age/ Sex	Preferred Term	Day of AE Onset ^a (Period) ^c	Dose at AE Onset (mg/day)	Severity/ Relation- ship ^d	Action Regarding Dose	Outcome (Duration)	Total Days of Therapy ^e
Placebo								
hadwick/3	38/ M	Ataxia	111 (S)	400	Moderate Possible	Reduced	Resolved (5 days)	141
rawford/11	19/ M	Diplopia	111 (S)	400	Moderate Possible	Reduced	Resolved (5 days)	154
		Dizziness	45 (T)	300	Moderate Probable	Stopped Reduced	Resolved (17 days)	
		Fatigue	45 (T)	300	Moderate Probable	Stopped Reduced	Resolved (17 days)	
		Insomnia	40 (T)	125	Moderate Probable	Reduced	Resolved ^f (=108 days)	
cra- lenachem/29	17/ F	Nervousness	40 (T)	125	Moderate Probable	Reduced	Resolved (29 days)	148
		Ataxia	123 (S)	400	Mild Probable	Reduced	Resolved (9 days)	145
perling/241	28/ F	Vertigo	123 (S)	400	Mild Probable	Reduced	Resolved (8 days)	169
Topiramate								
hadwick/6	39/ M	Dizziness	23 (T)	50	Moderate Possible	Reduced	Resolved (115 days)	141
rawford/14	25/ F	Nausea	23 (T)	50	Moderate Possible	Reduced	Resolved (115 days)	140
		Dizziness	57 (S)	800 ^g	Marked Probable	Reduced	Resolved (25 days)	
		Somnolence ^h	57 (S)	800 ^g	Moderate Possible	Reduced	Resolved (25 days)	
		Confusion	57 (S)	1200 ^g	Marked Certain	Reduced	Resolved (5 days)	
cra- lenachem/33	32/ F	Somnolence	57 (S)	1200 ^g	Certain	Reduced	Resolved (5 days)	126
		Fatigue	4 (T)	50	Moderate Probable	Reduced	Resolved (32 days)	
		Nervousness	4 (T)	50	Moderate Probable	Reduced	Resolved (32 days)	
		Nausea	32 (T)	150	Mild Possible	Reduced	Resolved (6 days)	
iron/201	36/ F	Vomiting	32 (T)	150	Mild Possible	Reduced	Resolved (6 days)	143
		Headache	16 (T)	50	Mild Unlikely	Reduced	Resolved (1 day)	
		Somnolence	59 (S)	400	Mild Possible	Reduced	Resolved (1 day)	
		Somnolence	59 (S)	400	Mild Possible	Reduced	Persisted ^f	

Dose adjustments may have included reduction, temporary discontinuation of treatment, or both.
Number of days from beginning of double-blind phase
(T) denotes duration period and (S) denotes stabilization period
Based on the investigator's assessment at time of occurrence of the adverse event; for relationship, probable-probable/likely
Based on follow-up information received on April 15, 1997 after closure of the database for this trial.
These adverse events were considered serious (see Table 19).
The investigator noted that this subject "took 800 mg rather than the 400 mg prescribed" for 16 days.
The investigator noted that the 1200 mg was "taken in error" for 4 days.

**Table 23: Incidence of Selected Treatment-Emergent
Markedly Abnormal Laboratory Analyte Values
(All Randomized Subjects; Protocol YTC-E)**

Topiramate Versus Placebo, Pooled T1C-E					
Laboratory Analyte	Markedly Abnormal Value ^a	Placebo (N=39) ^b		Topiramate (N=40)	
		No.	%	No.	%
<u>Liver Function Tests</u>					
SGOT	High	0	0	0	0
SGPT	High	0	0	1	3
Alkaline Phosphatase	High	0	0	0	0
Total Bilirubin	High	2	5	0	0
<u>Renal Function Tests</u>					
Creatinine	High	0	0	0	0
BUN	High	2	5	1	3
<u>Hematology Tests</u>					
Hemoglobin	Low	0	0	1	3
Hematocrit	Low	1	3	0	0
Platelet Count	Low	0	0	0	0
RBC Count	High	0	0	0	0
WBC Count	Low	0	0	0	0
Neutrophils	High	0	0	0	0
Lymphocytes	Low	0	0	0	0
Monocytes	High	0	0	0	0
Eosinophils	High	1	3	0	0
Basophils	High	2	5	1	3

^a Markedly abnormal criteria varied by age (see Attachment 9.3.1).
^b One subject did not have laboratory data.

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Figure 2: Study Completion and Withdrawal Summary
(All Subjects: Protocols YTC and YTC-E)

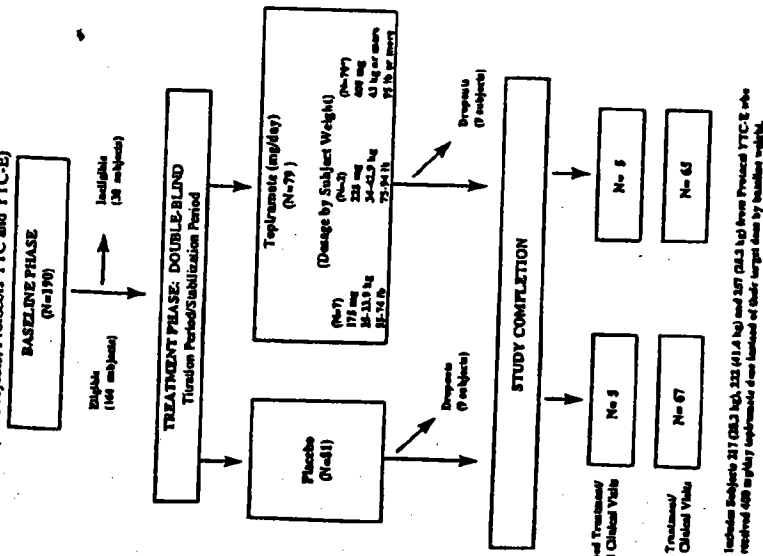


Table 1: Placebo-Controlled Trials With Topiramate in Subjects With Primary Generalized Tonic-Clonic Seizures

Protocol No. (Investigator's Ref. #)	Country (Study Site)	Study Design	Target Daily Dose (mg/day)	Number of Subjects Entered in Each Group	Sex (M/F) Ratio	Age (yr) Mean Range
YTC Multicenter (19)	USA, Brazil Compliance (5 May 94)	Double-blind, placebo-controlled, adjunctive therapy; M/F: 24 years of age with unprovoked primary generalized tonic-clonic seizures	Topiramate 175 mg 225 mg 400 mg Placebo	39 5 33 41 6 2 33	32W/68H 24/15	26.8 5 to 59 8/91
YTC-E Multicenter (20)	Europe and USA Compliance (15 Sep 94)	Double-blind, placebo-controlled, adjunctive therapy; M/F: 24 years of age with unprovoked primary generalized tonic-clonic seizures	Topiramate 175 mg 225 mg 400 mg Placebo	40 2 37 40 1 0 39	17/23 39W/18 40W	29.2 7 to 60 29.1 12 to 46 2/28

W = White; B = Black; H = Hispanic

Table 4: Therapy Discontinuation and Completion Information
(All Randomized Subjects: Protocols YTC and YTC-E)

Reason	Protocol YTC (All randomized subjects, protocol YTC and YTC-E)						Protocol YTC-E (All randomized subjects, protocol YTC and YTC-E)					
	Placebo (N=41)			Topiramate (N=39)			Placebo (N=40)			Topiramate (N=40)		
	N	%	N	%	N	%	N	%	N	%	N	%
Limiting Adverse Event	1	2	1	3	7	18	5	13	8	10	6	15
Subject Choice	1	2	2	5	0	0	2	5	1	1	4	10
Lost to Follow-up*	1	2	0	0	1*	3	0	0	2	2	0	0
Other ^b	0	0	2	5	3	8	2	5	3	4	4	10
Total Discontinued	3	7	5	13	11	28	9	23	14	17	14	35
Total Completed	38	93	34	87	29	72	31	78	67	83	65	85

* In Protocol YTC-E, Subject 5 prematurely discontinued study medication and was categorized as investigator's discretion.

^b Protocol YTC: Subject 4 (noncompliance) and Subject 32 (prematurely advanced to open-label phase due to pharmacy error).

Protocol YTC-E: Subjects 40 (subject discontinued study treatment for personal reasons), 43 (details not available), and 62 (patient had a history of attempted suicide in the placebo group and Subjects 39 (no PCTC seizures during baseline) and 216 (subject stopped taking all treatments and did not return to clinic) in the placebo group.

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Age, Weight, Height, and Average Monthly Seizure Rate
Controlled Subjects: YTC and YTC-B1

		C				Protocol YTC-8				YYOYTC-8 Combined			
		Placebo (N=11)	Topiramate (N=39)	Placebo (N=40)	Topiramate (N=40)	Placebo (N=41)	Topiramate (N=39)	Placebo (N=41)	Topiramate (N=39)				
No. (%)	13 (23)	8 (21)	2 (5)	9 (23)	15 (39)	17 (22)							
No. (%)	28 (60)	31 (79)	36 (95)	31 (77)	66 (81)	62 (78)							
	25.6	26.8	29.1	29.2	27.3	28.0							
	12.38	12.82	8.69	12.44	11.37	12.60							
	26.0	25.0	29.0	30.0	28.0	29.0							
	3 to 50	3 to 39	12 to 46	7 to 60	3 to 50	5 to 60							
(n)	6 (15)	5 (13)	1 (3)	4 (10)	7 (9)	9 (11)							
No. (%)	2 (5)	1 (3)	0 (0)	2 (5)	2 (3)	3 (4)							
No. (%)	33 (80)	33 (85)	39 (97)	34 (85)	72 (89)	67 (85)							
	61.3	71.8	78.7	71.3	69.9	71.5							
	25.06	28.52	19.34	23.63	23.93	25.99							
	62.0	72.0	77.9	73.6	71.4	73.5							
	17 to 129	22 to 143	33 to 146	25 to 123	17 to 146	22 to 143							
(cm)	38	35	33	37	71	72							
	139.1	166.1	170.3	166.6	164.3	166.3							
	19.44	17.21	8.83	17.15	16.29	17.04							
	161.0	160.0	170.0	168.0	166.4	168.0							
	101 to 196	117 to 193	155 to 188	119 to 200	101 to 196	117 to 200							
Average Monthly Seizure Rate ^a													
Seizures	40	39	40	39	80	78							
	15.8	20.3	6.5	15.5	11.1	17.9							
	47.23	51.51	8.68	28.62	34.06	41.47							
	4.5	5.0	3.0	5.0	3.5	5.0							
	0.7 to 299.9	1.0 to 297.7	0.5 to 34.1	0.5 to 139.5	0.5 to 299.9	0.5 to 297.7							
Seizures	2000.9	911.1	422.3	604.5	1221.4	351.0							
	12347	214.7	1799	2480	8856	2058							
	17.5	15.3	15.0	25.7	16.5	18.0							
	1.6 to 79109	1.0 to 1134.0	1.0 to 10676.0	1.5 to 18232.0	1.0 to 79109.0	1.0 to 18232.0							

^a 23 days. Monthly rate based on prospective baseline data.

21 days. Monthly rates based on prospective base-line data.

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Table 2b: Demographic and Baseline Characteristics: Sex, Race, and AED, and Seizure Type
(All Randomized Subjects: Protocols YTC and YTC-E)

	Practical YTC				Protective YTC				YTC/OTC Combined			
	Placebo (N=11)		Tetracycline (N=19)		Placebo (N=19)		Tetracycline (N=40)		Placebo (N=11)		Tetracycline (N=19)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Sex												
Male	31	51	34	62	21	52	17	43	42	52	41	52
Female	20	49	15	38	19	48	23	57	39	48	38	48
Race												
White	36	88	32	82	40	100	39	97	76	94	71	90
Black	5	12	6	15	0	0	1	3	5	6	7	9
Other	0	0	1	3	0	0	0	0	0	0	1	1
Background AFD*												
Vaginal acid	20	49	19	49	23	58	22	55	43	53	41	52
Carbamazepine	9	22	1	28	14	35	11	28	23	28	22	28
Lamotrigine	10	24	6	15	16	40	13	33	26	32	19	24
Phenytoin	13	32	12	31	8	20	7	18	21	26	19	24
Phenobarbital	3	7	8	21	1	3	3	13	4	5	13	16
Carbamazepine	3	7	4	10	2	5	3	13	5	6	9	11
Carbamazepine	6	15	6	15	2	5	1	3	8	10	7	9
Carbamazepine	3	7	5	13	4	10	4	10	7	9	9	11
Carbamazepine	0	0	0	0	1	3	4	10	1	1	4	5
Carbamazepine	4	10	3	8	0	0	1	3	4	5	4	5
Carbamazepine	3	7	1	3	1	3	3	8	4	5	4	5
Carbamazepine	1	2	3	8	0	0	0	0	1	1	3	4
Carbamazepine	2	5	2	5	0	0	0	0	2	2	2	3
Carbamazepine	2	5	0	0	0	0	0	0	2	2	2	3
Carbamazepine	0	0	1	3	0	0	0	0	0	0	1	1
Carbamazepine	0	0	0	0	1	3	1	3	1	1	1	1
Carbamazepine	1	2	0	0	1	3	0	0	2	2	2	3
Carbamazepine	6	15	0	0	2	5	0	0	8	10	0	0
Two Background AFD	9	22	9	23	11	27	9	23	20	25	18	23
Two Background AFDs	22	54	19	49	22	55	23	57	44	54	42	53
Two Background AFDs	10	24	11	28	7	18	8	20	17	21	19	24
Isotonic Saline Type*												
Tonic-Clonic	40*	98	39	100	40	100	39*	98	80*	99	70*	99
Absence	16	39	16	41	19	48	14	35	35	43	30	38
Myoclonic	8	20	8	21	10	25	13	33	18	22	21	27
Tonic	10	24	9	23	5	13	6	15	15	18	13	19
Atypical absence	4	10	2	5	3	7	18	6	7	3	4	
Drop attack	5	12	2	5	3	8	1	3	8	10	3	4
Other*	1	2	1	3	2	5	2	5	3	4	2	3
Clonic	1	2	1	3	0	0	1	3	1	1	2	3
Tonic-clonic only	13	32	13	33	9	23	9	23	22	27	22	28
Tonic-clonic and at least one other generalized seizure type	27	66	26	67	31	77	30	75	58	73	56	71

* Individual subjects may have received more than one background AFD

Tonic-clonic only
Tonic-clonic and at least
one other generalized

Individual subjects may have received valproic acid sodium (Depakene®) as baseline or the double-blind placebo (YTC-E, Subject 23) (topiramate) or "other" (YTC-E, Subject 23) (topiramate) information for Subjects 60 and

072

Table 5a: Daily Dosage of Study Medication During the Double-Blind Phase
(All Randomized Subjects; Protocols YTC and YTC-E)

Treatment Group	Protocol YTC			Protocol YTC-E			YTC/YTC-E Combined		
	N	Median	Range	N	Median	Range	N	Median	Range
Placebo	41	4.3	0.6 to 7.3	40	3.3	0.5 to 5.7	81	3.7	0.5 to 7.3
Topiramate	39	3.7	1.3 to 6.3	40	3.6	0.6 to 10.7	79	3.7	0.6 to 10.7
Topiramate	41	6.3	0.6 to 9.3	40	4.8	0.5 to 7.9	81	5.3	0.5 to 9.3
Topiramate	39	5.3	2.1 to 8.3	40	5.2	0.6 to 14.2	79	5.3	0.6 to 14.2

Topiramate dosage (mg/kg per day) over the entire double-blind phase.
 Topiramate dosage (mg/kg per day) over the entire double-blind phase.
 Topiramate dosage (mg/kg per day) over the entire double-blind phase.
 Topiramate dosage (mg/kg per day) over the entire double-blind phase.
 Topiramate dosage (mg/kg per day) over the entire double-blind phase.

Table 5b: Daily Dosage of Study Medication During the Stabilization Period
(All Randomized Subjects; Protocols YTC and YTC-E)

Treatment Group	Protocol YTC			Protocol YTC-E			YTC/YTC-E Combined		
	N	Median	Range	N	Median	Range	N	Median	Range
Placebo	39	5.9	3.0 to 9.1	37	4.9	0.9 to 7.6	76	5.3	0.9 to 9.1
Topiramate	38	5.1	1.7 to 8.5	38	5.1	0.8 to 14.0	76	5.1	0.8 to 14.0
Topiramate	39	6.3	2.1 to 9.3	37	4.9	1.5 to 7.9	76	5.4	1.5 to 9.3
Topiramate	38	5.3	2.1 to 8.5	38	5.3	0.8 to 14.2	76	5.3	0.8 to 14.2

Topiramate dosage (mg/kg per day) over the stabilization period.
 Topiramate dosage (mg/kg per day) over the stabilization period.
 Topiramate dosage (mg/kg per day) over the stabilization period.
 Topiramate dosage (mg/kg per day) over the stabilization period.
 Topiramate dosage (mg/kg per day) over the stabilization period.

Table 3: Numbers Enrolled in Baseline Phase and Randomized to Double-Blind Treatment
(Protocols YTC and YTC-E)

Treatment Group	Protocol YTC			Protocol YTC-E			YTC/YTC-E Combined		
	N	Median	Range	N	Median	Range	N	Median	Range
Placebo	41	4.3	0.6 to 7.3	40	3.3	0.5 to 5.7	81	3.7	0.5 to 7.3
Topiramate	39	3.7	1.3 to 6.3	40	3.6	0.6 to 10.7	79	3.7	0.6 to 10.7
Topiramate	41	6.3	0.6 to 9.3	40	4.8	0.5 to 7.9	81	5.3	0.5 to 9.3
Topiramate	39	5.3	2.1 to 8.3	40	5.2	0.6 to 14.2	79	5.3	0.6 to 14.2

Table 6: Average Daily Dose (mg/day) During the Stabilization Period
(All Randomized Subjects; Protocols YTC and YTC-E)

Treatment Group	Protocol YTC			Protocol YTC-E			YTC/YTC-E Combined		
	N	Median	Range	N	Median	Range	N	Median	Range
Placebo	6	174.0	146.2 to 175.0	1	174.7	--	7	174.7	146.2 to 175.0
Topiramate	2	203.8	182.7 to 225.0	0	--	--	2	203.8	182.7 to 225.0
Topiramate	31	398.8	298.2 to 400.0	36	388.9	60.0 to 400.0	67	392.4	60.0 to 400.0
Topiramate	4	174.3	173.0 to 175.0	2	174.9	174.7 to 175.0	6	174.9	173.0 to 175.0
Topiramate	1	223.0	--	1	224.1	--	2	224.1	224.1 to 224.1
Topiramate	33	393.8	155.7 to 400.0	35	388.5	50.0 to 475.3	68	389.8	50.0 to 475.3

Topiramate dosage (mg/day) over the stabilization period.
 Topiramate dosage (mg/day) over the stabilization period.
 Topiramate dosage (mg/day) over the stabilization period.
 Topiramate dosage (mg/day) over the stabilization period.
 Topiramate dosage (mg/day) over the stabilization period.

Table 7: Duration of Therapy
(All Randomized Subjects; Protocols YTC and YTC-E)

Treatment Group	Protocol YTC			Protocol YTC-E			YTC/YTC-E Combined		
	N	Median	Range	N	Median	Range	N	Median	Range
Placebo	5	12	6 to 15	9	23	9 to 23	14	17	13 to 23
Topiramate	134	140	11 to 27	8	21	6 to 15	15	17	13 to 23
Topiramate	141	147	12 to 29	13	33	13 to 38	25	31	28 to 35
Topiramate	148	154	8 to 20	7	18	7 to 18	15	19	15 to 23
Topiramate	2155	5	12 to 13	5	13	5 to 13	10	12	10 to 13
Topiramate	138.8 (29.30)	139.9 (33.42)	128.4 (39.97)	129.3 (36.90)	133.6 (35.15)	134.5 (32.00)	141.0	141.0	141.0 to 141.0
Topiramate	110 to 176	48 to 197	4 to 176	24 to 169	1 to 176	24 to 197	24 to 197	24 to 197	24 to 197

Topiramate dosage (mg/day) over the stabilization period.
 Topiramate dosage (mg/day) over the stabilization period.
 Topiramate dosage (mg/day) over the stabilization period.
 Topiramate dosage (mg/day) over the stabilization period.
 Topiramate dosage (mg/day) over the stabilization period.

Table 9: Treatment Responders* for the Double-Blind Phase Based on PGTC Seizures
(All Randomized Subjects With PGTC Seizures; Protocols YTC and YTC-E)

Treatment Group	Protocol YTC			Protocol YTC-E			YTC/YTC-E Combined		
	N	Median	Range	N	Median	Range	N	Median	Range
Placebo	40	8	20	40	14	35	80	22	28
Topiramate	39	22	56	39	21	54	78	43	53
Topiramate	39	22	56	39	21	54	78	43	53
Topiramate	39	22	56	39	21	54	78	43	53
Topiramate	39	22	56	39	21	54	78	43	53

Topiramate dosage (mg/day) over the stabilization period.
 Topiramate dosage (mg/day) over the stabilization period.
 Topiramate dosage (mg/day) over the stabilization period.
 Topiramate dosage (mg/day) over the stabilization period.
 Topiramate dosage (mg/day) over the stabilization period.

* Subjects with 50% or greater reduction from baseline.
 * Topiramate vs. placebo; Cochran-Mantel-Haenszel test stratified by treatment and center.
 * Topiramate vs. placebo; Cochran-Mantel-Haenszel test stratified by treatment and protocol.
 * Topiramate vs. placebo; logistic regression with terms for treatment, center, and baseline PGTC seizure rate.
 * Topiramate vs. placebo; logistic regression with terms for treatment, protocol, and baseline PGTC seizure rate.

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Table 10: Distribution of Percent Reduction in Average Monthly PGTC Seizure Rate for the Double-Blind Phase*
(All Randomized Subjects With PGTC Seizures; Protocols YTC and YTC-E)

Percent Reduction	Protocol YTC (N=40)		Protocol YTC-E (N=39)		YTC/YTC-E Combined (N=79)	
	Placebo	Topiramate	Placebo	Topiramate	Placebo	Topiramate
100	5	13	10	8	8	10
≥75	13	23	15	36	14	35
≥50	20	36	35	54	28	55
≥25	45	67	58	74	51	71
0	63	72	75	79	69	76
≥-25	73	74	78	87	75	81

* Tabulated numbers are percent of subjects in treatment group

Table 11: Percent Reduction From Baseline in Average Monthly PGTC Seizure Rate
During the Double-Blind Phase* - Completer Analysis
(All Subjects With PGTC Seizures Who Completed Double-Blind Therapy; Protocols YTC and YTC-E)

Percent Reduction	Protocol YTC (N=39)		Protocol YTC-E (N=40)		YTC/YTC-E Combined (N=79)	
	Placebo	Topiramate	Placebo	Topiramate	Placebo	Topiramate
100	5	13	10	8	8	10
≥75	13	23	15	36	14	35
≥50	20	36	35	54	28	55
≥25	45	67	58	74	51	71
0	63	72	75	79	69	76
≥-25	73	74	78	87	75	81

* Tabulated numbers are percent of subjects in treatment group

live numbers denote an increase in seizure rate.
* Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.
* Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.
* Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks with baseline PGTC seizure rate as a covariate.
* Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks with baseline PGTC seizure rate as a covariate.
* Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks with baseline PGTC seizure rate as a covariate.

Table 12: Treatment Responders* for the Double-Blind Phase
Based on PGTC Seizures - Completer Analysis
(All Subjects With PGTC Seizures Who Completed Double-Blind Therapy; Protocols YTC and YTC-E)

Treatment	Protocol YTC (N=39)		Protocol YTC-E (N=40)		YTC/YTC-E Combined (N=79)	
	N	%	N	%	N	%
Placebo	37	7	29	9	66	16
Topiramate	34	21	62	31	65	37
p-value	<0.001*		0.084*		<0.001*	

* Subjects with 50% or greater reduction from baseline.

* Topiramate vs. placebo; Cochran-Mantel-Haenszel test stratified by treatment and center.

* Topiramate vs. placebo; logistic regression with terms for treatment, center, and baseline PGTC seizure rate.

* Topiramate vs. placebo; logistic regression with terms for treatment, protocol, and baseline PGTC seizure rate.

Table 14: Percent Reduction From Baseline in Average Monthly Seizure Rate
During the Double-Blind Phase* Based on All Seizures
(All Randomized Subjects; Protocols YTC and YTC-E)

Treatment	Protocol YTC (N=40)		Protocol YTC-E (N=39)		YTC/YTC-E Combined (N=79)	
	N	Median	N	Median	N	Median
Placebo	41	0.9	48.5 to 35.0	40	12.1	-16.1 to 40.7
Topiramate	39	42.1	-2.6 to 76.9	40	26.0	-7.0 to 71.2
p-value	0.003*		0.003*		0.012*	

* Negative numbers denote an increase in seizure rate.

* Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.

* Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.

* Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.

Table 15: Treatment Responders* for the Double-Blind Phase Based on All Seizures
(All Randomized Subjects; Protocols YTC and YTC-E)

Treatment	Protocol YTC (N=40)		Protocol YTC-E (N=39)		YTC/YTC-E Combined (N=79)	
	N	%	N	%	N	%
Placebo	41	7	17	40	8	20
Topiramate	39	18	46	40	16	40
p-value	0.003*		0.003*		0.003*	

* Subjects with 50% or greater reduction from baseline.

* Topiramate vs. placebo; Cochran-Mantel-Haenszel test stratified by treatment and center.

Table 16: Distribution of Percent Reduction in Average Monthly Seizure Rate
for the Double-Blind Phase Based on All Seizures*
(All Randomized Subjects; Protocols YTC and YTC-E)

Percent Reduction	Protocol YTC (N=41)		Protocol YTC-E (N=40)		YTC/YTC-E Combined (N=81)	
	Placebo	Topiramate	Placebo	Topiramate	Placebo	Topiramate
100	0	5	3	3	1	4
≥75	7	26	5	30	6	28
≥50	17	46	20	40	19	43
≥25	39	59	40	53	40	56
0	51	72	55	68	53	70
≥-25	63	85	83	83	73	84

* Tabulated numbers are percent of subjects in treatment group.

Table 17: Median Percent Reduction From Baseline in
Average Monthly Seizure Rate by Seizure Type*
(All Randomized Subjects; Protocols YTC and YTC-E)

Seizure Type	Protocol YTC (N=41)		Protocol YTC-E (N=40)		YTC/YTC-E Combined (N=81)	
	Placebo	Topiramate	Placebo	Topiramate	Placebo	Topiramate
Absence	4.1	52.8	-16.1	-6.6	-10.9	-3.4
Myoclonic	-40.2	51.8	5.5	15.2	-15.3	39.5
Tonic	-1.0	28.0	-55.2	76.7	-20.9	49.3

* Efficacy summaries by seizure type are based on specific generalized seizure types experienced by subjects at any time during the trial.

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7 : Global Evaluation of Improvement in Seizure Severity
(All Randomized Subjects; Protocols YTC and YTC-E)

Improvement Rating (Score)	Protocol YTC						Protocol YTC-E						Overall	
	Placebo (N=41)			Topiramate (N=39)			Placebo (N=40)			Topiramate (N=40)			Placebo (N=81)	
	N	%	N	N	%	N	N	%	N	%	N	%	N	%
Worse (0)	4	10	3	8	4	10	3	8	4	10	3	8	7	9
None (1)	12	29	11	28	20	50	14	35	32	40	25	32	20	25
Minimal (2)	8	20	7	18	8	20	0	0	16	20	7	9	16	20
Moderate (3)	12	29	9	23	5	13	6	15	17	21	15	19	17	21
Marked (4)	3	7	8	21	0	0	13	33	3	4	21	27	3	4
Not Assessed	2	5	1	3	4	10	3	8	6	7	4	5	6	7
p-value	0.490 ^a			0.026 ^a			0.024 ^b			0.020 ^a			0.017 ^b	

^a Wilcoxon rank-sum test stratified by center.

^b Wilcoxon rank-sum test unstratified.

8 : Global Evaluation of Improvement in Seizure Severity - Completer Analysis
(All Subjects Who Completed Double-Blind Therapy; Protocols YTC and YTC-E)

Improvement Rating (Score)	Protocol YTC						Protocol YTC-E						YTC/YTC-E Combined	
	Placebo (N=38)			Topiramate (N=34)			Placebo (N=29)			Topiramate (N=31)			Placebo (N=67)	
	N	%	N	N	%	N	N	%	N	%	N	%	N	%
Worse (0)	4	11	3	9	3	10	2	6	7	10	5	8	7	10
None (1)	12	32	8	24	14	48	11	35	26	39	19	29	26	39
Minimal (2)	8	21	7	21	7	24	0	0	15	22	7	11	15	22
Moderate (3)	11	29	8	24	4	14	5	16	15	22	13	20	15	22
Marked (4)	3	8	8	24	0	0	12	39	3	4	20	31	3	4
Not Assessed	0	0	0	0	1	3	1	3	1	1	1	2	1	1
p-value	0.259 ^a			0.212 ^b			0.009 ^a			0.009 ^b			0.005 ^a	

^a Wilcoxon rank-sum test stratified by center.

^b Wilcoxon rank-sum test unstratified.

Table 20: Subgroup Summary: Efficacy Variables by Sex, Race, and Age
(All Randomized Subjects; Protocols YTC and YTC-E)

Subgroup Category	PGTC Seizures						All Seizures					
	No. of Subjects			Median % Seizure Rate Reduction			No. of Subjects			Median % Seizure Rate Reduction		
	PL	TPM	PL	PL	TPM	PL	PL	TPM	PL	PL	TPM	PL
Sex												
Male	42	40	15.1	58.7	21	55	42	41	-0.6	37.6	14	44
Female	38	38	28.4	54.4	34	55	39	38	25.3	33.4	23	42
Race												
White	75	70	29.5	54.3	29	54	76	71	12.1	37.6	20	44
Non-White	5	8	-12.5	70.9	0	63	5	8	-405.3	30.0	0	38
Age												
≤16 years	14	17	3.6	40.1	21	47	15	17	0.9	26.7	7	29
>16 years	66	61	29.3	57.1	29	57	66	62	12.1	43.5	21	47

^a Defined as ≥50% reduction in seizure rate relative to baseline.

Table 21: Subgroup Summary: Efficacy Variables by Protocol and Region
(All Randomized Subjects; Protocols YTC and YTC-E)

Region	Protocol YTC						Protocol YTC-E						Protocols YTC and YTC-E Combined					
	No. of Subjects			Median % Seizure Rate Reduction			No. of Subjects			Median % Seizure Rate Reduction			No. of Subjects			Median % Seizure Rate Reduction		
	PL	TPM	PL	PL	TPM	PL	PL	TPM	PL	PL	TPM	PL	PL	TPM	PL	PL	TPM	PL
PGTC Seizures																		
United States	40	39	9.0	56.7	20	56	15	16	37.9	48.5	40	50	55	55	23.6	56.7	25	55
Europe	NAP	NAP	..	..	..	..	25	23	31.4	60.0	32	57	25	23	31.4	60.0	32	57
All Seizures																		
United States	41	39	0.9	42.1	17	46	15	16	21.0	35.8	7	44	56	55	2.0	42.1	14	45
Europe	NAP	NAP	..	..	..	..	25	24	11.5	15.3	28	38	25	24	11.5	15.3	28	38

^a Defined as ≥50% reduction in seizure rate relative to baseline.

Key: PL = placebo; TPM = topiramate; NAP = not applicable

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