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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)	15 (33)	17 (41)	17 (41)	32 (37)	
1-7; No. (%)	20 (44)	13 (32)	13 (32)	33 (38)	
8-11; No. (%)	10 (22)	11 (27)	11 (27)	21 (24)	
2-12; No. (%)	9.0	8.8	8.8	8.9	
Mean	3.35	3.64	3.64	3.47	
SD	2-16	2-16	2-16	2-16	
Median					
Range					
Weight (kg)	13 (29)	15 (37)	15 (37)	28 (33)	
15-24.9 kg	13 (29)	7 (17)	7 (17)	20 (23)	
25-33.9 kg	9 (20)	10 (24)	10 (24)	19 (22)	
34-42.9 kg	10 (22)	9 (22)	9 (22)	19 (22)	
24-3 kg	35.1	34.7	34.7	34.9	
Mean	16.32	15.79	15.79	15.98	
SD	32.0	30.0	30.0	31.5	
Median	15.0-90.0	15.0-76.0	15.0-76.0	15.0-90.0	
Range					
Height (cm)	45	38	38	83	
N	132.6	131.8	131.8	132.2	
Mean	19.05	23.90	23.90	21.27	
SD	134.0	131.0	131.0	134.0	
Median	94.0-178.0	90.0-178.0	90.0-178.0	90.0-178.0	
Range					
Baseline Average Monthly Seizure Rate ^a					
Partial Onset Seizures	84.5	45.6	45.6	65.9	
Mean	190.1	56.18	56.18	143.5	
SD	19.0	21.5	21.5	21.3	
Median	2.0-1132.6	1.8-231.5	1.8-231.5	1.8-1132.6	
Range					
Secondarily Generalized Seizures	17	17	17	34	
N	41.1	16.4	16.4	28.8	
Mean	87.95	25.32	25.32	64.95	
SD	5.0	6.3	6.3	5.6	
Median	0.5-272.8	0.9-89.1	0.9-89.1	0.5-272.8	
Range					
All Seizures					
Mean	86.2	46.0	46.0	67.0	
SD	189.82	57.20	57.20	143.52	
Median	23.0	21.5	21.5	22.2	
Range	2.0-1132.6	1.8-284.0	1.8-284.0	1.8-1132.6	
Rate per 28 days					

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

	Placebo (N=45)		Topiramate (N=41)		Total (N=86)	
	N	%	N	%	N	%
Sex						
Male	25	56	22	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 ^b						
Carbamazepine	26	58	25	61	51	59
Valproic Acid	10	22	10	24	20	23
Phenytoin	9	20	6	15	15	17
Gabapentin	4	9	10	24	14	16
Lamotrigine	5	11	5	12	10	12
Diazepam	5	11	3	7	8	9
Clonazepam	4	9	3	7	7	8
Lorazepam	1	2	6	15	7	8
Primidone	5	11	2	5	7	8
Chlorzoxazone	2	4	3	7	5	6
Phenobarbital	4	9	1	2	5	6
Ethosuximide	0	0	2	5	2	2
Felbamate	1	2	1	2	2	2
Methsuximide	0	0	2	5	2	2
Acetazolamide	0	0	1	2	1	1
Ethotoin	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 ^c						
Complex Partial	37	82	31	76	68	79
Secondarily Generalized	17	38	17	42	34	40
Simple Partial	12	27	11	27	23	27
All Other Types	3	7	3	7	6	7

^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.

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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		Reason for Discontinuation
			Double-Blind Therapy (Days)	Double-Blind Participation (Days) ^a	
Wyllie/113	4	M	25	29	AE: rash
			Placebo		Subject choice: uncooperative
Edwards/662	10	M	100	28	
Wyllie/110*	5	M	93	119	Other: noncompliance
			Topiramate		

* 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 Partial Onset Seizures	Percent Seizure Rate Reduction ^a	
	Median	25th to 75th Percentile
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	-32.6 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 Partial Onset Seizures	Treatment Responders ^a		p-value ^b
	No.	%	
Placebo (N=45)	9	20	0.080
Topiramate (N=41)	16	39	
Secondarily Generalized Seizures			
Placebo (N=20)	6	30	0.127
Topiramate (N=20)	9	45	
All Seizures			
Placebo (N=45)	10	22	0.127
Topiramate (N=41)	16	39	

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

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

Seizure Type/ Partial Onset Seizures	Placebo (N=45)		Topiramate (N=41)	
	No.	%	No.	%
Percent Reduction	0	0	2	5
100	1	2	7	17
≥75	9	20	16	39
≥50	18	40	22	54
≥25	29	64	32	78
0	34	76	35	85
≥-25				
Secondarily Generalized Seizures ^a				
100	2	10	5	25
≥75	3	15	5	25
≥50	6	30	9	45
≥25	7	35	11	55
0	9	45	13	65
≥-25	12	60	15	75
All Seizures				
100	0	0	2	5
≥75	1	2	7	17
≥50	10	22	16	39
≥25	19	42	22	54
0	30	67	31	76
≥-25	35	78	35	85

^a 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)	
	No.	%	No.	%
Worse (0)	4	9	3	7
No Change (1)	26	58	14	34
Minimally (2)	7	16	8	20
Moderate (3)	3	7	4	10
Marked (4)	5	11	12	29
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 ^a	Placebo		Topiramate		p-value ^b
	Mean (SD) (µg/mL)	Change (SD) (µg/mL)	Mean (SD) (µg/mL)	Change (SD) (µg/mL)	
Carbamazepine	26	9.3 (2.49)	25	-0.3 (1.60)	0.428
Valproic Acid	12	75.6 (40.34)	10	-4.2 (16.28)	0.389
Lamotrigine	5	3.5 (1.36)	5	0.7 (0.96)	0.017
Phenytoin	9	12.8 (7.36)	9	-1.2 (3.66)	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 Stratification (All Available Plasma Samples During Stabilization; Protocol YP)

Seizure Type	N	Median Percent Reduction	Percent Responders
Plasma Stratum			%
Partial Onset Seizures	13	18.1	5
33.2 to <4	14	51.5	8
25.4	14	30.3	5
All Seizures	13	10.6	5
33.2 to <4	14	51.5	8
25.4	14	30.4	5

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

Efficacy Assessment	Placebo	Topiramate	p-value
Primary Variable			
Percent reduction from baseline in average monthly seizure rate for partial onset seizures	10.5	31.1	0.034 ^a
Secondary Variables			
Percent reduction from baseline in average monthly seizure rate for:			
All seizures	10.5	31.9	0.077 ^b
Generalized seizures	-10.6	31.6	
Percent treatment responders ^c :			
Partial onset seizures	20.0	39.0	0.040 ^d
All seizures	22.0	39.0	0.127 ^e
Parental global evaluation of improvement in seizure severity ^f	33	59	0.025 ^g
A treatment responder is defined as subject whose seizure rate was reduced 50% or more during the double-blind phase.			0.019 ^h

^aTPM vs. placebo; two factor (treatment and center) ANOVA on ranks.
^bTPM vs. placebo; Cochran-Mantel-Haenszel test.
^cPercent of subjects who had minimal, moderate, or marked improvement in seizure severity.
^dTPM vs. placebo; Wilcoxon rank-sum test stratified by center.
^eTPM vs. placebo; Wilcoxon rank-sum test unstratified.

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

Target Dosage (mg/kg per day)	Placebo (N=45)		Topiramate (N=41)		Total (N=86)	
	No.	(%)	No.	(%)	No.	(%)
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 (All Randomized Subjects; Protocol YP)

Treatment	Mean	Standard Deviation	Median	Range
Average Daily Dose ^a (mg/kg/day)				
Placebo ^b (N=43)	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 Dose ^c (mg/kg/day)				
Placebo ^b (N=43)	6.3	1.49	6.1	1.4-10.0 ^d
Topiramate (N=41)	6.3	1.20	6.0	3.9-10.4 ^e

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

Treatment	Mean	Standard Deviation	Median	Range
Average Daily Dose ^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 Dose ^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 ^e

^aSubject's average dosage (mg/kg per day) over the entire stabilization period.
^bResults based on administration of "25 mg" and "100 mg" placebo tablets that matched topiramate tablets.
^cSubject's maximum dosage (mg/kg per day) over the entire stabilization period.
^dSubject 524, a 20 kg boy assigned to receive placebo 125 mg/day, took 200 mg (10.0 mg/kg) placebo once during the study.
^eSubject 526, a 24 kg girl assigned to receive topiramate 125 mg/day, took 250 mg (10.4 mg/kg) topiramate once during the study.

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

Treatment Group/Target Dosage (mg/day)	Mean	Standard Deviation	Median	Range ^a
Placebo (N=43)				
125 (N=12)	118.8	22.63	125.0	54.9-149.7 ^b
175 (N=13)	174.4	2.31	175.0	166.7-175.0
225 (N=8)	222.4	3.82	225.0	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 ^b
175 (N=7)	171.4	9.45	175.0	150.0-175.0
225 (N=10)	211.9	27.59	225.0	150.0-225.0
400 (N=9)	361.7	85.22	400.0	150.5-400.0

^aResults based on administration of "25 mg" and "100 mg" placebo tablets that matched topiramate tablets.
^bOne 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)

Investigator/Subject No.	Double-Blind Therapy (Days)		Placebo (N=45)		Topiramate (N=41)		Total (N=86)	
	No.	%	No.	%	No.	%	No.	%
106-112	2	4.4	2	9.8	4	4.8		
113-119	11	24.4	10	24.4	21	24.4		
120-126	13	28.9	17	41.5	30	34.9		
127-133	7	15.6	4	9.8	11	12.8		
2134	8	17.8	3	7.3	11	12.8		
	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 ^b (Period) ^c	Dosage at AE Onset ^b (mg/day)	Total Days of Therapy ^d	Final Dosage (mg/day)	Severity ^e	Relationship ^f	Outcome (Duration)
101/113	5/F		Convulsions Aggravated	26 (T)	25	127	125	Marked Possible		Resolved (2 days)
110/174	9/M		Infection Viral	66 (S)	175	110	175	Mild-Moderate Unlikely		Resolved (6 days)
111/116	5/M		Convulsions Aggravated	104 (S)	100	126	100	Marked Unlikely		Resolved (2 days)
112/172	11/M		Constipation	50 (T)	125	127	100	Marked Unlikely		Resolved (14 days)

0 U.S. IND Safety reports were filed.
 1 refers to the double-blind phase.
 2 denotes titration period and S denotes stabilization period.
 3 based 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 ^b	Dosage at AE Onset ^b	Severity ^c	Relationship ^d	Action Taken (Dosage)	Outcome (Duration)	Total Days of Therapy ^e
106/112	14	F	Coordination abnormal	57	225	Mild	Possible	Reduced	Persisted ^f	141
107/75	5	F	Influenza-like symptoms	24	50	Moderate	Possible	Reduced	Resolved (7 days)	110
108/116	6	M	Mood problems	37	100	Moderate	Possible	Reduced	Resolved (31 days)	126
109/116	6	M	Parosmia	37	100	Moderate	Possible	Reduced	Resolved (31 days)	126
110/117	8	F	Delusion	52	125	Mild	Possible	Reduced	Resolved (16 days)	126
111/117	8	F	Nausea	18	50	Moderate	Possible	Reduced	Resolved (4 days)	142
112/117	8	F	Vomiting	19	25	Moderate	Possible	Reduced	Resolved (3 days)	142
113/117	8	F	Urinary incontinence	80	75	Marked	Possible	Reduced	Resolved (49 days)	142
114/117	8	F	Somnolence	80	75	Mild	Possible	Reduced	Resolved (31 days)	136
115/117	4	M	Urinary Incontinence	68	125	Mild	Possible	Reduced	Resolved (11 days)	148
116/117	11	F	Somnolence	50	225	Mild	Possible	Reduced	Resolved (50 days)	113
117/117	12	F	Apathy	15	200	Mild	Probable	Reduced	Resolved (49 days)	118
118/117	12	F	Confusion	15	200	Mild	Unlikely	Reduced	Resolved (49 days)	118
119/117	12	F	Aggressive reaction	44	400	Mild	Probable	Reduced	Resolved (20 days)	118
120/117	12	F	Weight increase	44	400	Mild	Probable	Reduced	Persisted ^f	118
121/117	12	F	Aggressive reaction	13	0 ^g	Moderate	Possible	Stopped Temp.	Resolved (2 days)	130
122/117	13	F	Emotional lability	13	0 ^g	Moderate	Possible	Resolved	Resolved (2 days)	130
123/117	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=probably/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 (Continued)

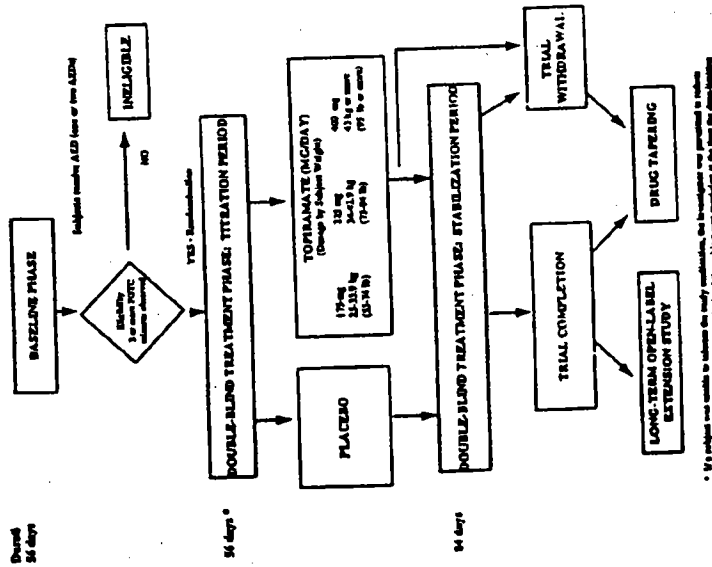


Figure 2: Completion and Withdrawal Summary

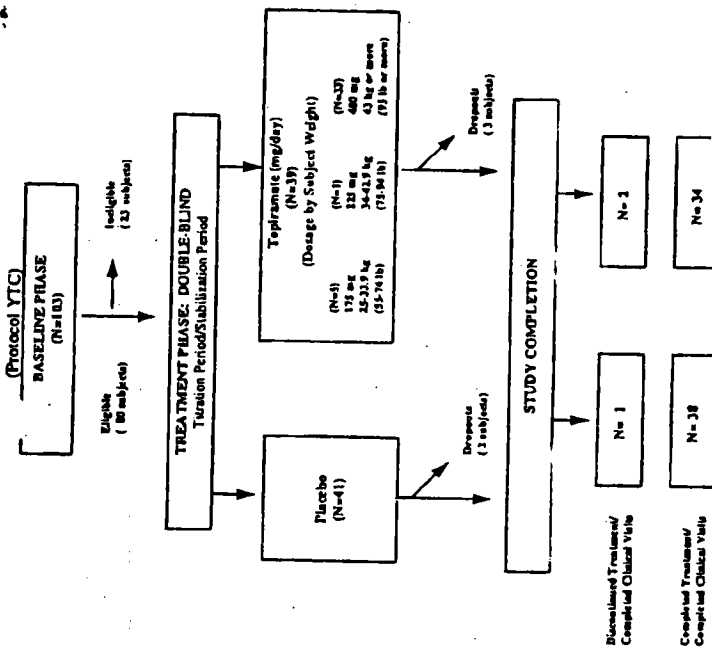


Figure 3: Mean Rank of Percent Seizure Rate Reduction by Center (All Randomized Subjects; Protocol YTC)

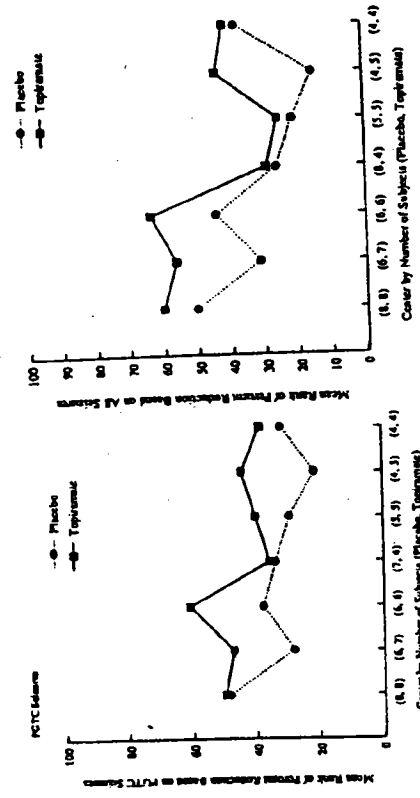


Figure 4: Cumulative Response Rate (All Randomized Subjects; Protocol YTC)

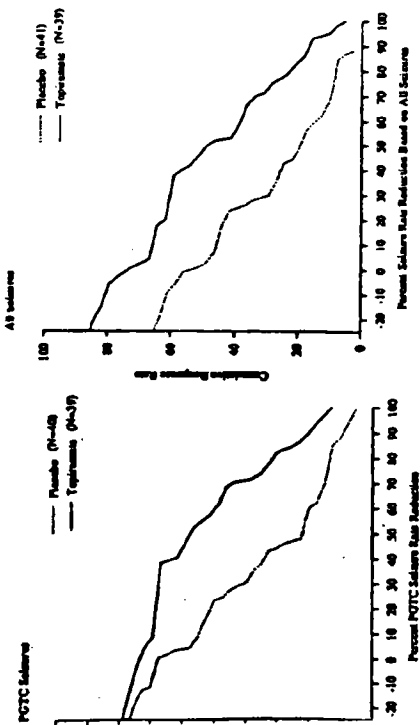


Table 1: Key Inclusion Criteria (Protocol YTC)

- Four years of age or older, and if female, premenarcheal 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 PM	400 mg/day MAX (2)100 mg tab AM (2) 100 mg PM	59.3

* 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		
	1 (Day)	2 (-56)	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 ^b							X	
Efficacy Assessments								
Complete Seizure Diaries			X	X	X	X	X	
Subject's Global Evaluations			X	X	X	X	X	
Safety Assessments								
Adverse Events			X	X	X	X	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	X	X	X	X	X	
Subject's Global Evaluations		X	X	X	X	X	X	
Pharmacokinetic Assessments								
Topiramate Plasma Concentrations		X	X	X	X	X	X	
AED(s) Plasma Concentrations		X	X	X	X	X	X	
Administrative								
Dispense Diary		X	X	X	X	X	X	
Dispense Study Medication		X	X	X	X	X	X	
Collect and Count Unused Study Medication		X	X	X	X	X	X	

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

^b 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.

^c 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: Title and Baseline Characteristics: Age, Weight, Height, and Average Monthly Seizure Rate
(All Randomized Subjects; Protocol YTC)

	Placebo (N=41)	Topiramate (N=39)	Total (N=80)
Age (yr)			
5-16; No. (%)	13 (32)	8 (21)	21 (26)
>16; No. (%)	28 (68)	31 (79)	59 (74)
Sex			
Male	25 (61)	26 (67)	51 (64)
Female	16 (39)	15 (38)	31 (39)
Race			
White	33 (80)	33 (85)	66 (83)
Black	6 (15)	5 (13)	11 (14)
Other	2 (5)	1 (3)	3 (4)
Weight (kg)			
5-33.9; No. (%)	6 (15)	5 (13)	11 (14)
34-42.9; No. (%)	2 (5)	1 (3)	3 (4)
43-50; No. (%)	33 (80)	33 (85)	66 (83)
Weight (lb)			
11-75	61 (15)	71 (18)	66 (83)
76-93	25 (61)	28 (72)	27 (34)
94-110	62 (15)	72 (18)	64 (80)
>110	17 (41)	22 (56)	17 (21)
Height (cm)			
101-119	38	35	73
120-137	139 (34)	166 (42)	162 (20)
138-154	19 (46)	17 (43)	18 (23)
>155	16 (39)	16 (41)	18 (23)
Age			
101 to 195	117 to 193	117 to 193	101 to 196
Seizure AVE Monthly Seizure Rate ¹			
0.7 to 299.9	1.0 to 297.7	0.7 to 299.9	
2000.9	91.1	1069.9	
12347	214.7	8839	
17.5	15.3	16.0	
1.6 to 791.09	1.0 to 1134.0	1.0 to 791.09	

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

Discontinuation Reason	Placebo (N=41)		Topiramate (N=39)		Total (N=80)
	N	%	N	%	
Subject Choice	1	2	3	8	4
Limiting Adverse Event	1	2	1	3	2
Lost to Follow-up	1	2	0	0	1
Other ^a	0	0	2	5	2
Total Discontinued	3	7	6	16	10
Total Completed	38	93	34	87	72

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

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

	Placebo (N=41)		Topiramate (N=39)		Total (N=80)
	No.	%	No.	%	
Sex					
Male	31	51	24	62	45 (56)
Female	10	24	15	38	25 (31)
Race					
White	36	88	32	82	68 (85)
Black	3	7	6	15	9 (11)
Other	2	5	1	3	3 (4)
Background AED ^a					
Valproic acid	20	49	19	49	39 (49)
Phenytoin	13	32	12	31	25 (31)
Carbamazepine	9	22	11	28	20 (25)
Lamotrigine	10	24	6	15	16 (20)
Phenobarbital	3	7	8	21	11 (14)
Chenopodium	6	15	6	15	12 (15)
Gabapentin	3	7	3	8	6 (8)
Diazepam	4	10	3	8	7 (9)
Levetiracetam	3	7	4	10	7 (9)
Primidone	6	15	0	0	6 (8)
Chenopodium diposium	1	2	3	8	4 (5)
Ethosuximide	3	7	1	3	4 (5)
Topiramate	2	5	2	5	4 (5)
Highly protein-bound	2	5	0	0	2 (3)
Metoprolol	0	0	1	3	1 (1)
Methamphetamine	1	2	0	0	1 (1)
One Background AED	9	22	9	23	18 (23)
Two Background AEDs	22	54	19	49	41 (51)
More Than Two Background AEDs	10	24	11	28	21 (26)
Baseline Seizure Type ^b					
Tonic-Clonic	40	98	39	100	79 (99)
Absence	16	39	16	41	32 (40)
Myoclonic	10	24	9	23	19 (24)
Drop attack	8	20	6	15	14 (18)
Atypical absence	5	12	2	5	7 (9)
Clonic	4	10	2	5	6 (8)
Other ^c	1	2	1	3	2 (3)
Tonic-Clonic Only	13	32	13	33	26 (33)
Tonic-Clonic and at least one other	27	66	26	67	53 (66)

^a Individual subjects may have received more than one background AED.

^b Individual subjects may have received more than one seizure type. Baseline seizure types are based on prospectively collected seizure data.

^c Subject 181 did not experience a POTC seizure during either baseline or double-blind phase (see Section IV.E, Protocol Deviations).

^d Includes seizures described as violent myoclonic jerks, atonic seizures, or drops to the floor.

^e Subject 92 (placebo) experienced seizures of an unknown type that were categorized as "other".

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

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Table 10a: Treatment Results for the Double-Blind Phase (All Randomized Subjects; Protocol YTC)

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

* Subjects with 50% or greater reduction from baseline.
† 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)

Seizure Type/ Percent Reduction	Placebo (N=40)		Topiramate (N=39)	
	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
2-25	29	73	29	74
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
2-25	26	63	33	85

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	Placebo		Topiramate		p-value*
	Mean (SD)	N	Mean (SD)	N	
Valproic Acid	20.9 (18.94)	20	0.4 (16.05)	20	0.096
Phenytoin	12.17 (7.59)	12	-0.5 (6.55)	15	0.404
Carbamazepine	9.6 (3.01)	9	0.7 (0.81)	13	0.009
Lamotrigine	11.65 (4.25)	9	0.6 (1.79)	6	0.381
Phenobarbital	7.29 (14.22)	7	1.1 (7.36)	9	0.294

* 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	42
	5.04 to <8.46 µg/mL	12	60.8	7	58
	≥8.46 µg/mL	11	51.5	6	55
All Seizures	<5.04 µg/mL	12	2.9	4	33
	5.04 to <8.46 µg/mL	12	59.0	7	58
	≥8.46 µg/mL	11	51.5	7	64

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

Investigator/Subject No.	Age	Sex	Duration (Days) of Double-Blind Therapy	Daily Dosage at Discontinuation (mg/day)	Duration (Days) of Double-Blind Participation*	Reason for Discontinuation	Percent Seizure Rate Reduction†	
							Median	25 th to 75 th Percentiles
Placebo								
Collins/98	50	F	119	400	119	Lost to follow-up		
Wiley/105	38	M	43	50	184	Limiting adverse event: granulocytopenia, thrombocytopenia		
Hyler/121	18	M	1	50	125	Subject choice: self abusive behavior, restlessness, insomnia		
Topiramate								
Bloom/4	21	F	129	100	149	Other: noncompliance		
Wang/52	8	M	79	175	79	Other: prematurely advanced to open-label phase due to pharmacist distribution error		
Uveller/67	6	M	48	25	48	Subject choice		
Hyler/122	25	M	86	100	129	Limiting adverse event: anorexia, weight decrease		
Wang/186	22	F	103	400	112	Subject choice		

* Number of days from the beginning of the double-blind phase until withdrawal from or completion of the trial.
† Discontinued therapy prematurely but completed the trial.

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

Seizure Type/ Treatment Group	Median	25 th to 75 th Percentiles	p-value*
PGTC Seizures			
Placebo (N=40)	9.0	-31.9 to 46.7	
Topiramate (N=39)	36.7	-27.0 to 84.1	0.019
All Seizures			
Placebo (N=41)	0.9	-48.5 to 35.0	
Topiramate (N=39)	42.1	-2.6 to 76.9	0.003

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

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

Improvement Rating (Score)	Placebo (N=41)		Topiramate (N=39)		p-value
	N	%	N	%	
None	4	10	3	8	
Mild	12	29	11	28	
Modest	8	20	7	18	
Marked	12	29	9	23	
Maximal	3	7	8	21	
p-value			0.490†		0.388†

* Two placebo-treated subjects and one topiramate-treated subject were not assessed for this efficacy variable at the final visit.
† Wilcoxon-Rank Sum test stratified by center.
‡ Wilcoxon-Rank Sum test unstratified by center.

Table 14: Summary of the Efficacy Results for the Double-Blind Phase

Efficacy Assoc. Primary Variable	Target Dose Group (All Randomized Subjects; Protocol YTC)		p-value
	Placebo	Topiramate	
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 responders ^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 ^e
			0.388 ^f

^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	Standard			Range
	Mean	Deviation	Median	
Average Daily Dosage ^a (mg/kg/day)	4.4	1.54	4.3	0.6 - 7.3
Placebo (N=41) ^b	3.6	1.18	3.7	1.3 - 6.3
Topiramate (N=39)				
Maximum Daily Dosage ^c (mg/kg/day)	6.1	1.99	6.3	0.6 - 9.3
Placebo (N=41) ^b	5.3	1.52	5.3	2.1 - 8.5
Topiramate (N=39)				

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

^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 Dose Group
(All Randomized Subjects; Protocol YTC)

Treatment Group Target dosage (mg/day)	Standard			Range
	Mean	Deviation	Median	
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/ 103	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	100	86 (129)	Mild Possible Mild Possible	Resolved (107 days) Resolved (84 days)

^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 parenthesis.

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

Key: AE = adverse event

Table 22: Subject Evaluation of Improvement in Mental Status Administered Subjects; Protocol YTC

Investigator/Subject No.	Age	Sex	Preferred Term	Day of Onset*	AE Onset (mg/day)	Not Improved		Improved		Total Days of Therapy
						No.	(%)	No.	(%)	
Level of Alertness						(1) None	(2) Minimal	(3) Moderate	(4) Marked	
Placibo (N=41)	2	(5)	0	(0)	23	(56)	7	(17)	8	(20)
Topiramate (N=39)	1	(3)	3	(8)	17	(44)	8	(21)	3	(8)
Level of Interference With the Environment										
Placibo (N=41)	2	(5)	3	(7)	24	(59)	6	(15)	5	(12)
Topiramate (N=39)	1	(3)	3	(8)	17	(44)	9	(23)	8	(21)
Ability to Perform Activities of Daily Living										
Placibo (N=41)	2	(5)	0	(0)	27	(66)	6	(15)	5	(12)
Topiramate (N=39)	1	(3)	1	(3)	21	(54)	9	(23)	7	(18)
Response to Verbal Requests										
Placibo (N=41)	2	(5)	1	(3)	24	(59)	9	(23)	5	(13)
Topiramate (N=39)	1	(3)	2	(5)	20	(51)	7	(18)	8	(21)

Table 21: Subjects With an Adverse Event Resulting in a Dosage Adjustment* (All Randomized Subjects; Protocol YTC)

Investigator/Subject No.	Age	Sex	Preferred Term	Day of Onset*	AE Onset (mg/day)	Severity Relationship ^b	Action Taken (Dosage)	Outcome (Duration)	Total Days of Therapy
33	8	F	Anxiety	69	225	Mild Possible	Reduced	Permitted ^c	154
			Gait abnormal	71	225	Mild Possible	Reduced	Resolved (14 days)	
			Personality disorder	58	225	Mild Possible	Reduced	Resolved (17 days)	
			Automatism	1	50	Moderate Possible	DST ^d	Resolved (6 days)	1 ^e
			Insomnia	1	50	Moderate Possible	DST ^d	Resolved (6 days)	
67	6	M	Insomnia	26	50	Mild Possible	Reduced	Permitted ^c	48
			Difficulty with memory	27	50	Mild Possible	Reduced	Permitted ^c	
94	44	F	Gait abnormal	81	400	Marked Probable	Reduced	Resolved (22 days)	197
			Nervousness	81	400	Moderate Probable	Reduced	Resolved (22 days)	
			Tremor	81	400	Moderate Probable	Reduced	Resolved (22 days)	
			Speech disorders and related speech problems	81	400	Marked Probable	Reduced	Resolved (22 days)	
155	59	M	Difficulty with memory	46	150	Moderate Possible	Reduced	Resolved (18 days)	147
			Somnolence	46	150	Moderate Possible	Reduced	Resolved (18 days)	
195	23	M	Stuper	3	50	Moderate Probable	Reduced	Resolved (22 days)	148
			Somnolence	34	150	Mild Probable	Reduced	Permitted ^c	
			Cognitive problems	80	300	Mild Possible	Reduced	Resolved (18 days)	
			Confusion	80	300	Mild Possible	Reduced	Resolved (18 days)	

* Dosage adjustments included dosage reductions or temporary discontinuation of treatment.
^b Number of days from the beginning of the double-blind phase.
^c Based on the investigator's assessment at the time of the occurrence of the adverse event.
^d Drug stopped temporarily due to adverse events, then resumed permanently due to subject choice.
^e Event persisted into open label extension phase and was ongoing at 30 June 1996 cut-off date for this report.
 Key: AE = adverse event; DST = drug stopped temporarily.

Table 23: Subjects With Serious Adverse Events* (All Randomized Subjects; Protocol YTC)

Investigator/Subject No.	Age	Sex	Term	Day of Onset (mg/day)	Total Days of Therapy (mg/day)	Severity Relationship ^b	Outcome (Duration)
1000	38	F	Allucinations	92 (5)	400	Moderate Possible	Resolved (53 days)
1001	33	M	Chest pain	151 (5)	400	Marked Possible	Resolved (2 days)
1002	21	F	Convulsions, grand mal	123 (5)	400	Moderate Possible	Resolved (2 days)
1003	44	F	Tremor	81 (5)	400	Moderate Possible	Resolved (22 days)
			Speech disorders and related speech problems	81 (5)	400	Marked Probable	Resolved (22 days)
			Gait abnormal	81 (5)	400	Marked Probable	Resolved (22 days)
			Nervousness	81 (5)	400	Moderate Probable	Resolved (22 days)
1004	6	M	Pneumonia	40 (7)	100	Moderate Probable	Resolved (22 days)
1005	33	M	Thrombocytopenia	9 (7)	50	Unlikely Moderate	Resolved (15 days)
			Microvision disorder	62 (5)	400	Unlikely Moderate	Resolved (12 days)
			Urinary incontinence	62 (5)	400	Possible Moderate	Resolved (46 days)
			Prostatic disorder	62 (5)	400	Possible Moderate	Resolved (46 days)
			Viral infections	69 (5)	400	Possible Moderate	Resolved (7 days)

* Serious adverse events were defined as those that were fatal or life-threatening, or required hospitalization for at least 24 hours.
^b U.S. FDA safety reports were filed.
^c Number of days from the beginning of the double-blind phase.
^d Serious adverse events were defined as those that were fatal or life-threatening, or required hospitalization for at least 24 hours.
^e All 6 previously discontinued study medications had completed all clinical visits.
^f AE = adverse event.

Table 24: Subjects With Recurrent Treatment-Emergent Markedly Abnormal Laboratory Values for Selected Analyses* (All Randomized Subjects; Protocol YTC)

Investigator/Subject No.	Age	Sex	Laboratory Analysis	Value	Day of Therapy	TFM Dose (mg/day)
1	19	M	WBC count ($\times 10^3$ cells/L)	3.8	28	0
			($< 2.1 \times 10^3$ cells/L)	3.3 L	1 (BL)	0
				2.6 L	29	150
				2.5 L	51	407
				2.6 L	75	400
				2.9 L	146 (Final)	400
66	29	M	Monocyte percentage (% WBC)	12.3 H	27	0
			(21.5%)	8.2	0	0
				13.0 H	29	90
				15.5 H	32	300
				15.6 H	46	300
				15.6 H	92	400
				12.0	149 (Final)	400
67	5	M	Lymphocyte percentage (% WBC)	62.0 H	-3	0
			($> 60\%$)	62.2 H	1 (BL)	50
				62.0 H	38	50
				62.0 H	62	175
				62.0 H	87	175
				62.0 H	148 (Final)	175
			Neutrophil percentage (% WBC)	32.0	-3	0
			($< 15\%$)	34.1	1 (BL)	50
				27.0	38	50
				28.0	62	175
				11.0 L	87	175
				7.0 L	148 (Final)	175

* Laboratory values were defined as markedly abnormal if they were outside the range of normal values for the analysis.
 BL = below normal; H = high; L = low.
 TFM = topiramate.
 Values were markedly abnormal.

Figure 1: Study Design for Protocol YTC-E

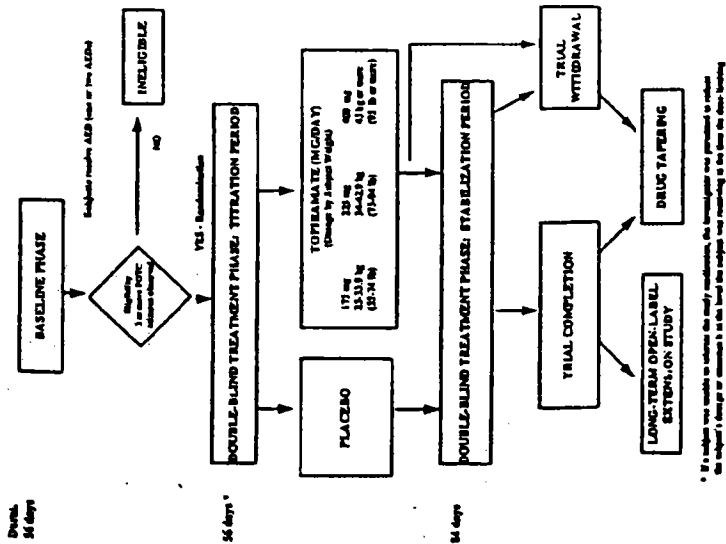


Figure 4: Cumulative Response Rate (All Randomized Subjects; Protocol YTC-E)

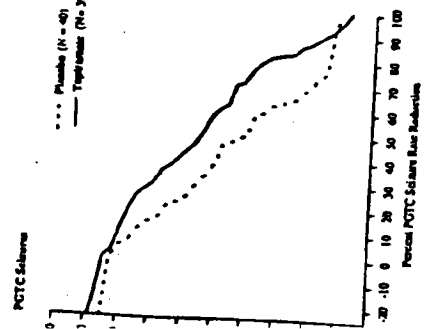


Figure 3: Mean Rank of Percent Seizure Rate Reduction by Analysis Center (All Randomized Subjects; Protocol YTC-E)

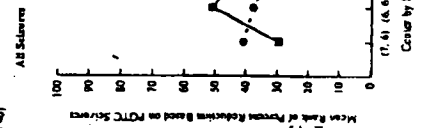


Figure 2: Study Design and Withdrawal Summary of YTC-E

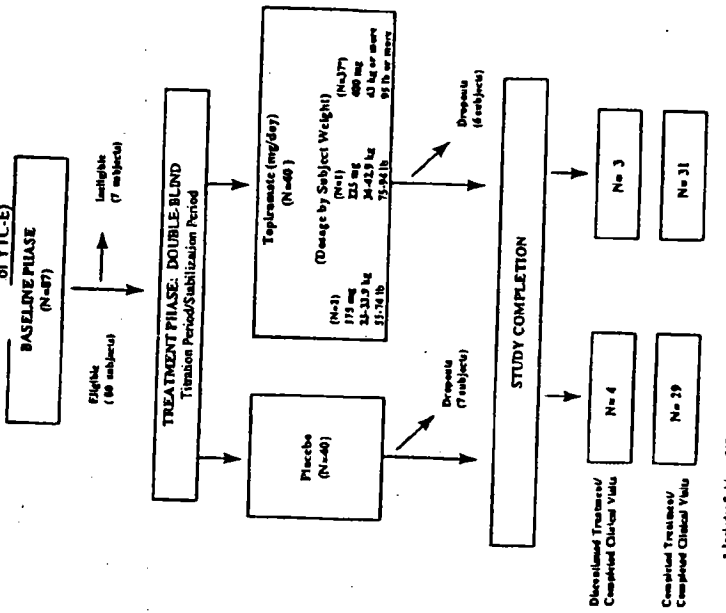
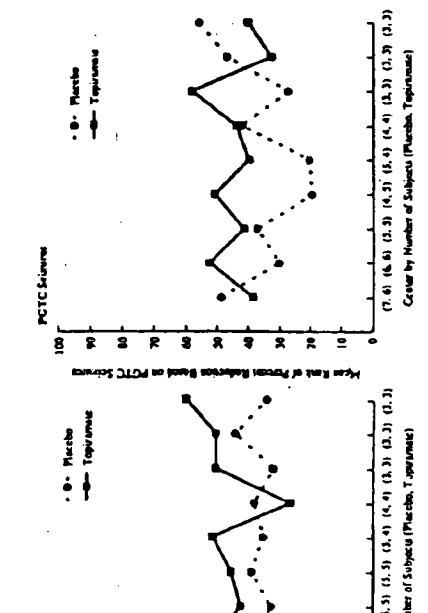


Figure 1: Study Design for Protocol YTC-E



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Table 1: Key Inclusion Criteria
(Protocol YTC-E)

- 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 CCT/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 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, 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).
- 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 (ascorbic acid) (in quantities greater than two grams per day), chronic use of antiacids, or calcium supplements.
- Inability to take medication or maintain a seizure calendar, independently or with assistance.

Table 3: Topiramate Dosing Schedule
(Protocol YTC-E)

Subject's Weight (55-74 lb)	Study Day					Target Dosage Range* (mg/kg/day)
	1 through 28 (2) 25 mg tabs PM	29 through 42 (2) 25 mg tab AM (2) 25 mg tab PM	43 through 56 (3) 25 mg tab AM (3) 25 mg tab PM	57 through 141 175 mg/day MAX (3) 25 mg tab AM (1) 100 mg tab PM		
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 + (1) 25 mg tab PM		5.2 to 6.6
243 kg (535 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		59.3

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

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

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

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

^b 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.

^c 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

Table 6b: Baseline Average Monthly Seizure Rate: PGTC Seizures

	Placebo (N=40)	Topiramate (N=40)	Total (N=80)
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

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

	Placebo (N=40)	Topiramate (N=40)	Total (N=80)
Discontinuation Reason			
Limiting Adverse Event	7	5	12
Subject Choice	0	2	2
Investigator's Discretion	1	0	1
Other ^a	3	8	11
Total Discontinued	11^a	9	20
Total Completed	29	31	60

^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: Sex, Background Antiepileptic Drug, and Baseline Seizure Type (All Randomized Subjects; Protocol YTC-E)

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

^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 (All Randomized Subjects; Protocol YTC-E)

Investigator/ Subject Number	Age	Sex	Duration (Days) of Double-Blind Treatment		Discontinuation of Double-Blind Treatment (mg/day)	Duration (Days) of Double-Blind Treatment	Reason for Discontinuation
			Placebo	Topiramate			
idwick/5 ^a	28	F	81	75	152	Investigator's Discretion ^c	
stuart/26	29	M	76	50	76	Limiting Adverse Event: convulsions, aggravated	
alcahorn/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 ^c	
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 ^a	
wford/65 ^b	23	M	133	300	149	Limiting Adverse Event: aggressive reaction; alaxia; ^c confusion; ^c convulsions, aggravated; ^c injury; ^c increased sweating	
dwick/75 ^b	18	M	4	50	141	Limiting Adverse Event: aggressive reaction; agitation; anxiety; confusion; parosmia; personality disorder	
in/205 ^b	33	M	69	150	148	Limiting Adverse Event: ^c nausea; ^c vomiting ^c	
oy/209	46	F	152 ^a	400	152	Limiting Adverse Event: sudden death ^a	
die/16 ^b	42	M	120	Topiramate 200	149	Subject Choice	
die/19	29	F	57	300	57	Limiting Adverse Event: vision abnormal ^a	

Number of days from the beginning of the double-blind phase until withdrawal from, or completion of, trial.
^a These subjects prematurely discontinued study treatment but completed all nine protocol-specified clinical visits (140 days).
^b Further information is not available.
^c This deviation from protocol was discovered by the investigator after 14 days of therapy and the subject was prematurely discontinued from the trial.
^d These adverse events were considered serious by the investigator (see Table 19).
^e On 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).
^f 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 9: Subjects Who Prematurely Discontinued Study Treatment (All Randomized Subjects; Protocol YTC-E)

Investigator/ Subject Number	Age	Sex	Duration (Days) of Double-Blind Treatment		Discontinuation of Double-Blind Treatment (mg/day)	Duration (Days) of Double-Blind Treatment	Reason for Discontinuation
			Topiramate	Placebo			
Beghi/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; ^b insomnia	
Blankenhorn/39 ^c	60	M	169 ^d	100	211	Other: subject did not have FGTC seizures at baseline	
Ben-Menachem/ 87	34	M	28	50	36	Limiting Adverse Event: alaxia; 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	

Number of days from the beginning of the double-blind phase until withdrawal from, or completion of, study.
^a These adverse events were considered serious by the investigator (see Table 19).
^b These subjects prematurely discontinued study treatment but completed all nine protocol-specified clinical visits (=140 days).
^c 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).
^d Negative numbers denote an increase in seizure rate.

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	Percent Seizure Rate Reduction ^a	
	Median	25th to 75th Percentile
FGTC 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
AU 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

Negative numbers denote an increase in seizure rate.
^a 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	0.102
Topiramate (N=39)	21	54	
All Seizures			
Placebo (N=40)	8	20	0.061
Topiramate (N=40)	16	40	

^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

^a Wilcoxon Rank Sum test stratified by center.

^b Wilcoxon Rank Sum test unstratified by center

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

Improvement Rating	Placebo		Topiramate		p-value
	N	%	N	%	
Worse	3	8	4	10	
None	20	50	14	35	
Minimal	8	20	0	0	
Modest	5	13	6	15	
Marked	0	0	13	33	
Not Assessed	4	10	3	8	

^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 ^a		
	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)	13	0.5 (1.87)	13	6.2 (4.00)	13	-0.19 (0.81)	0.214
Carbamazepine	14	8.6 (2.55)	13	0.5 (1.24)	11	11.0 (7.45)	11	-0.4 (1.52)	0.146
Valproic acid	13	72.3 (28.10)	13	6.0 (13.40)	12	148.8 (190.25)	8	-26.4 (85.28)	0.189
Phenytoin	8	32.3 (31.17)	8	-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

^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.

^e Subject's maximum dosage (mg/kg/day) during the entire double-blind phase.

^f Results based on administration of "25 mg" and "100 mg" placebo tablets that

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^g Five subjects (Subjects 14, 24, 217, 222, and 257) in the topiramate group received

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ⁱ Subject's maximum dosage (mg/kg/day) during the entire double-blind phase.

^j Results based on administration of "25 mg" and "100 mg" placebo tablets that

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^m Subject's maximum dosage (mg/kg/day) during the entire double-blind phase.

ⁿ Results based on administration of "25 mg" and "100 mg" placebo tablets that

matched topiramate tablets.

^o Five subjects (Subjects 14, 24, 217, 222, and 257) in the topiramate group received

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^u Subject's maximum dosage (mg/kg/day) during the entire double-blind phase.

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^x Subject's maximum dosage (mg/kg/day) during the entire double-blind phase.

^y Subject's maximum dosage (mg/kg/day) during the entire double-blind phase.

^z Results based on administration of "25 mg" and "100 mg" placebo tablets that

matched topiramate tablets.

^{aa} Five subjects (Subjects 14, 24, 217, 222, and 257) in the topiramate group received

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^{ab} Subject's maximum dosage (mg/kg/day) during the entire double-blind phase.

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^{bn} Results based on administration of "25 mg" and "100 mg" placebo tablets that

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^{bq} Subject's maximum dosage (mg/kg/day) during the entire double-blind phase.

^{br} Results based on administration of "25 mg" and "100 mg" placebo tablets that

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^{bv} Results based on administration of "25 mg" and "100 mg" placebo tablets that

matched topiramate tablets.

^{bw} Five subjects (Subjects 14, 24, 217, 222, and 257) in the topiramate group received

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^{ch} Results based on administration of "25 mg" and "100 mg" placebo tablets that

matched topiramate tablets.

^{ci} 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.

^{cj} Subject's maximum dosage (mg/kg/day) during the entire double-blind phase.

^{ck} Subject's maximum dosage (mg/kg/day) during the entire double-blind phase.

^{cl} Results based on administration of "25 mg" and "100 mg" placebo tablets that

matched topiramate tablets.

^{cm} 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.

^{cn} Subject's maximum dosage (mg/kg/day) during the entire double-blind phase.

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				
<5.01 µg/mL	9	25.1	4	44
≥5.01 to <9.67 µg/mL	11	68.5	8	73
≥9.67 µg/mL	11	35.3	4	36
All seizures				
<5.01 µg/mL	10	24.6	4	40
≥5.01 to <9.67 µg/mL	11	50.0	6	55
≥9.67 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
Secondary Variable			
N	40	39	
Percent Treatment Responders ^b	35	54	0.078 ^b
All Seizures			
Secondary Variables			
Median percent reduction from baseline in average monthly seizure rate	12.1	26.0	0.102 ^d
Percent treatment responders ^c	20	40	0.016 ^c

^a Subjects' global evaluation of improvement in seizure severity^d

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

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

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

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

^f Topiramate vs. placebo; Logistic regression including treatment, center, and baseline PGTC seizure rate as terms in the model.

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

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

ⁱ 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.

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.	%	
1 to 28	3	8	2	5	6
29 to 56	0	0	0	0	0
57 to 84	4	10	5	13	11
85 to 112	1	3	0	0	1
113 to 133	1	3	2	5	4
134 to 140	6	15	6	15	15
141 to 147	13	32	15	38	35
148 to 154	7	18	5	12	15
≥155	5	12	5	12	10
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* (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 (mg/day)	Final Dosage (mg/day)	Severity ^d Relation- ship ^e	Outcome (Duration)
Chadwick/3	38	M	Pain	41 (T)	150	142	100	Marked Unlikely	Resolved (2 days)
				Placebo					
				70 (S)	400			Marked Unlikely	Resolved (2 days)
Chadwick/8	31	F	Convulsions, aggravated	27 (T)	50	141	400	Marked Unlikely	Resolved (2 days)
Crawford/23	22	M	Convulsions, aggravated	43 (T)	225			Marked Unlikely	Resolved (2 days)
Ben- Menachem/32	46	F	Injury	114 (S)	400	154	400	Moderate Possible	Resolved (2 days)
				99 (S)	400	155	400	Marked Unlikely	Resolved (57 days)
Crawford/65	23	M	Injury	112 (S)	300	133	300	Marked Possible	Resolved (31 days)
			Convulsions, aggravated	112 (S)	300			Marked Possible	Resolved (1 day)
			Ataxia	126 (S)	300			Moderate Possible	Resolved (17 days)
			Confusion	128 (S)	300			Moderate Possible	Resolved (15 days)
Chadwick/75	18	M	Convulsions, aggravated	14 (T)	Unknown	4	50	Marked Unlikely	Resolved (2 days)
			Psychosis	86 (T)	Unknown			Marked Unlikely	Resolved (9 days)
			Convulsions, aggravated	86 (T)	Unknown			Marked Unlikely	Resolved (3 days)
Blom/205	33	M	Nausea	69 (S)	150	69	150	Marked Possible	Resolved (2 days)
			Vomiting	69 (S)	150			Marked Possible	Resolved (2 days)
			Hematemesis	69 (S)	150			Mild Unlikely	Resolved (2 days)
eroy/209	46	F	Sudden death	152 (S)	400	152	400	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 (mg/day)	Final Dosage (mg/day)	Severity ^d Relation- ship ^e	Outcome (Duration)
Crawford/14	25	F	Somnolence ^f	57 (S)	800	141	400	Moderate Probable	Resolved ^g (=100 days)
			Dizziness ^f	57 (S)	800			Marked Probable	Resolved (25 days)
			Overdose ^f	57 (S)	800			Marked Certain	Resolved (1 day)
Brodie/19 ^h	29	F	Vision abnormal	49 (T)	300	57	300	Marked Possible	Resolved (11 days)
Ben- Menachem/31 ⁱ	28	F	Aggressive reaction	3 (T)	50	24	50	Marked Probable	Resolved (25 days)
			Agitation	3 (T)	50			Marked Probable	Resolved (25 days)
			Insomnia	3 (T)	50			Marked Probable	Resolved (25 days)
Chadwick/59	37	F	Abscess	100 (S)	400	153	400	Marked Unlikely	Persisted ^j

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 subject was hospitalized for drainage of the infected sebaceous 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)

Description:	Score:			Improved		
	Not Reported No. (%)	Worse No. (%)	None No. (%)	Minimal No. (%)	Moderate No. (%)	Marked 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 21 cis 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 ^b (Period)	Dosage at AE Onset ^b (mg/day)	Severity/ Relation- ship ^a	Action Regarding Dose	Outcome (Duration)	Total Days of Therapy ^b
hadwick/3	38/ M	Axial	111 (S)	400 Placebo	Moderate	Reduced	Resolved (5 days)	141
newford/11	19/ M	Diplopia	111 (S)	400	Possible	Reduced	Resolved (5 days)	154
		Dizziness	45 (T)	300	Moderate	Stopped	Resolved (17 days)	
con- lenachem/29	17/ F	Fatigue	45 (T)	300	Probable	Stopped	Resolved (17 days)	148
		Insomnia	40 (T)	125	Probable	Reduced	Resolved ^c (17 days)	
perling/241	28/ F	Nervousness	40 (T)	125	Moderate	Reduced	Resolved ^c (108 days)	145
		Axial	123 (S)	400	Probable	Reduced	Resolved (29 days)	
hadwick/6	39/ M	Vertigo	123 (S)	400	Mild	Reduced	Resolved (9 days)	169
		Dizziness	23 (T)	50 Topiramate	Moderate	Reduced	Resolved (8 days)	
newford/14	25/ F	Nausea	23 (T)	50	Possible	Reduced	Resolved (115 days)	141
		Dizziness	57 (S)	800 ^d	Moderate	Reduced	Resolved (115 days)	
newford/24	25/ M	Somnolence ^e	57 (S)	800 ^d	Probable	Reduced	Resolved (25 days)	140
		Confusion	57 (S)	1200 ^b	Moderate	Reduced	Resolved (25 days)	
con- lenachem/33	32/ F	Somnolence	57 (S)	1200 ^b	Marked	Reduced	Resolved (5 days)	126
		Fatigue	4 (T)	50	Certain	Reduced	Resolved (5 days)	
iton/201	36/ F	Nervousness	4 (T)	50	Probable	Reduced	Resolved (32 days)	143
		Nausea	32 (T)	150	Moderate	Reduced	Resolved (32 days)	
osenfeld/234	25/ M	Vomiting	32 (T)	150	Mild	Reduced	Resolved (6 days)	146
		Headache	16 (T)	50	Possible	Reduced	Resolved (6 days)	
perling/244	32/ M	Somnolence	59 (S)	400	Unlikely	Reduced	Resolved (1 day)	136
					Mild	Reduced	Persisted ^d	
					Possibly			

Dosage adjustments may have included reductions, temporary discontinuation of treatment, or both.

(T) denotes time from beginning of double-blind phase.

(S) denotes time from beginning of double-blind phase.

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)**

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

^a Markedly abnormal criteria varied by age (see Attachment 9.3.1).

^b One subject did not have laboratory data.

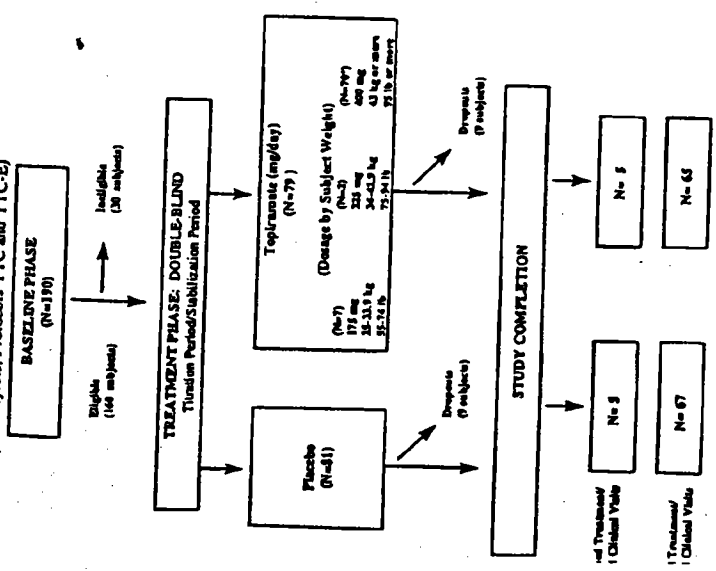
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Table 1: Placebo-Controlled Trials With Topiramate in Subjects With Primary Generalized Tonic-Clonic Seizures

Protocol No. Investigator(s) (Ref. No.)	Country Study Status (Start Date)	Study Design	Target Daily Dose (Duration)	Number of Subjects Entered in Each Group	Sex (M/F)	Age (yr) Mean Range
YTC Multicenter (19)	USA Costa Rica Complete (3 May 94)	Double-blind, placebo-controlled, adjunctive therapy; M/F: 34 years of age with uncontrolled primary generalized tonic-clonic seizures	Topiramate 175 mg 225 mg 400 mg (140 days)	39	24/15	26.8 5 to 59 6/1
YTC-E Multicenter (20)	Europe and USA Complete (15 Sep 94)	Double-blind, placebo-controlled, adjunctive therapy; M/F: 24 years of age with uncontrolled primary generalized tonic-clonic seizures	Topiramate 175 mg 225 mg 400 mg (140 days)	40	17/23	29.2 7 to 60 9/31

W = White; B = Black; H = Hispanic

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



Include Subjects 317 (28.2 kg), 323 (41.4 kg) and 327 (32.3 kg) from Protocol YTC-E who received 400 mg/day topiramate from baseline of their target dose by baseline weight.

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

Reason	Protocol YTC		Protocol YTC-E		YTC/YTC-E	
	Placebo (N=41)	Topiramate (N=77)	Placebo (N=40)	Topiramate (N=60)	Placebo (N=81)	Topiramate (N=137)
Limiting Adverse Event	1	3	7	18	8	21
Subject Choice	1	2	0	0	1	2
Lost to Follow-up*	1	0	1	0	2	0
Other*	0	0	3	8	3	8
Total Discontinued	3	5	11	26	14	29
Total Completed	38	93	29	72	67	108

* In Protocol YTC-E, Subject 5 prematurely discontinued study medication and was categorized as investigator's discretion. Protocol YTC: Subject 4 (noncompliance) and Subject 52 (prematurely advanced to open-label phase due to pharmacy error). Protocol YTC-E: Subject 40 (subject discontinued study treatment for personal reasons), 43 (details not available), and 62 (patient had a history of attempts in the placebo group and Subjects 39 (no PGTIC seizures during baseline) and 236 (subject stopped taking all treatments and did not return to clinic) in the to group.

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Table 2b: Difference in Baseline Characteristics: Sex, Race, and AED, and Seizure Type
Subjects: Protocols YTC and YTC-E

Sex	Protocol YTC		Protocol YTC-E		YTC/YTC-E Combined	
	No.	%	No.	%	No.	%
Male	31	51	24	62	21	32
Female	20	49	15	38	19	48
White	36	88	32	82	40	100
Black	5	12	6	15	0	0
Other	0	0	1	3	0	0

Background AED*	Protocol YTC		Protocol YTC-E		YTC/YTC-E Combined	
	No.	%	No.	%	No.	%
Valproic acid [†]	20	49	19	49	23	58
Carbamazepine	9	22	11	28	14	35
Lamotrigine	10	24	6	15	16	40
Phenytoin	13	32	12	31	8	20
Phenobarbital	3	7	8	21	1	3
Levetiracetam	3	7	4	10	2	5
Clemastine	6	15	6	15	2	5
Gabapentin	3	7	5	13	4	10
Clobazam	0	0	0	0	1	3
Diazepam	4	10	3	8	0	0
Ethosuximide	3	7	1	3	1	3
Chlorzoxazone dipotassium	1	2	3	8	0	0
Felbamate	2	5	2	5	0	0
Methylphenidate	2	5	0	0	0	0
Mephentermine	0	0	1	3	0	0
Vigabatrin	0	0	0	0	1	3
Mebutamide	1	2	0	0	1	3
Primidone	6	15	0	0	2	5

Seizure	Protocol YTC		Protocol YTC-E		YTC/YTC-E Combined	
	No.	%	No.	%	No.	%
One Background AED	9	22	9	23	11	27
Two Background AEDs	22	54	19	49	23	58
> Two Background AEDs	10	24	11	28	7	18

Baseline Seizure Type*	Protocol YTC		Protocol YTC-E		YTC/YTC-E Combined	
	No.	%	No.	%	No.	%
Absence	40 [†]	98	39	100	40	100
Myoclonic	16	39	16	41	19	48
Tonic	8	20	8	21	10	25
Atypical absence	10	24	9	23	5	13
Drop attack	4	10	2	5	3	8
Other [‡]	5	12	2	5	3	8
Clonic	1	2	1	3	2	5

Avg. Monthly Seizure Rate [§]	Protocol YTC		Protocol YTC-E		YTC/YTC-E Combined	
	No.	%	No.	%	No.	%
0.7 to 0.99	39	93	39	100	40	100
1.0 to 1.99	15.8	39	15.5	39	11.1	28
2.0 to 2.99	47.23	117	8.68	21.62	34.06	85.3
3.0 to 3.99	4.5	11	3.0	7.5	3.5	9
4.0 to 4.99	0.7	1.7	0.5	1.2	0.5	1.2
5.0 to 5.99	0.0	0.0	0.0	0.0	0.0	0.0
6.0 to 6.99	0.0	0.0	0.0	0.0	0.0	0.0
7.0 to 7.99	0.0	0.0	0.0	0.0	0.0	0.0
8.0 to 8.99	0.0	0.0	0.0	0.0	0.0	0.0
9.0 to 9.99	0.0	0.0	0.0	0.0	0.0	0.0
10.0 to 10.99	0.0	0.0	0.0	0.0	0.0	0.0
11.0 to 11.99	0.0	0.0	0.0	0.0	0.0	0.0
12.0 to 12.99	0.0	0.0	0.0	0.0	0.0	0.0
13.0 to 13.99	0.0	0.0	0.0	0.0	0.0	0.0
14.0 to 14.99	0.0	0.0	0.0	0.0	0.0	0.0
15.0 to 15.99	0.0	0.0	0.0	0.0	0.0	0.0
16.0 to 16.99	0.0	0.0	0.0	0.0	0.0	0.0
17.0 to 17.99	0.0	0.0	0.0	0.0	0.0	0.0
18.0 to 18.99	0.0	0.0	0.0	0.0	0.0	0.0
19.0 to 19.99	0.0	0.0	0.0	0.0	0.0	0.0
20.0 to 20.99	0.0	0.0	0.0	0.0	0.0	0.0
21.0 to 21.99	0.0	0.0	0.0	0.0	0.0	0.0
22.0 to 22.99	0.0	0.0	0.0	0.0	0.0	0.0
23.0 to 23.99	0.0	0.0	0.0	0.0	0.0	0.0
24.0 to 24.99	0.0	0.0	0.0	0.0	0.0	0.0
25.0 to 25.99	0.0	0.0	0.0	0.0	0.0	0.0
26.0 to 26.99	0.0	0.0	0.0	0.0	0.0	0.0
27.0 to 27.99	0.0	0.0	0.0	0.0	0.0	0.0
28.0 to 28.99	0.0	0.0	0.0	0.0	0.0	0.0
29.0 to 29.99	0.0	0.0	0.0	0.0	0.0	0.0
30.0 to 30.99	0.0	0.0	0.0	0.0	0.0	0.0
31.0 to 31.99	0.0	0.0	0.0	0.0	0.0	0.0
32.0 to 32.99	0.0	0.0	0.0	0.0	0.0	0.0
33.0 to 33.99	0.0	0.0	0.0	0.0	0.0	0.0
34.0 to 34.99	0.0	0.0	0.0	0.0	0.0	0.0
35.0 to 35.99	0.0	0.0	0.0	0.0	0.0	0.0
36.0 to 36.99	0.0	0.0	0.0	0.0	0.0	0.0
37.0 to 37.99	0.0	0.0	0.0	0.0	0.0	0.0
38.0 to 38.99	0.0	0.0	0.0	0.0	0.0	0.0
39.0 to 39.99	0.0	0.0	0.0	0.0	0.0	0.0
40.0 to 40.99	0.0	0.0	0.0	0.0	0.0	0.0
41.0 to 41.99	0.0	0.0	0.0	0.0	0.0	0.0
42.0 to 42.99	0.0	0.0	0.0	0.0	0.0	0.0
43.0 to 43.99	0.0	0.0	0.0	0.0	0.0	0.0
44.0 to 44.99	0.0	0.0	0.0	0.0	0.0	0.0
45.0 to 45.99	0.0	0.0	0.0	0.0	0.0	0.0
46.0 to 46.99	0.0	0.0	0.0	0.0	0.0	0.0
47.0 to 47.99	0.0	0.0	0.0	0.0	0.0	0.0
48.0 to 48.99	0.0	0.0	0.0	0.0	0.0	0.0
49.0 to 49.99	0.0	0.0	0.0	0.0	0.0	0.0
50.0 to 50.99	0.0	0.0	0.0	0.0	0.0	0.0

* Background AEDs were recorded at baseline and at least one other generalization.
[†] Includes valproic acid and sodium valproate.
[‡] Includes tonic-clonic, tonic-clonic and at least one other generalization.
[§] Individual subjects may have experienced more than one seizure type.
[¶] Subject 161 in Protocol YTC and Subject 39 in Protocol YTC-E did not experience a NCTC seizure during either the baseline or the double-blind phase.
^{‡‡} In Protocol YTC, Subject 98 (placebo) experienced seizures of an unknown type that were categorized as "other" and Subject 71 (topiramate) experienced complex partial seizures that were categorized as "other". In Protocol YTC-E, Subject 235 (topiramate) experienced complex partial seizures that were categorized as "other". Additional information for Subjects 60 and 225 (placebo) and Subject 235 (topiramate) was unavailable.

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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 ^a	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 ^b	79	3.7	0.6 to 10.7 ^b
Topiramate + Placebo	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 + Placebo	39	5.3	2.1 to 8.3	40	5.2	0.6 to 14.2 ^c	79	5.3	0.6 to 14.2 ^c

^a 50% average dosage (mg/kg) over the entire double-blind phase.
^b based on administration of "25 mg" and "100 mg" placebo tablets that matched topiramate tablets.
^c based on administration of "25 mg", "222, 257" and "100 mg" placebo tablets that matched topiramate tablets.
^d based on their baseline weight.
^e 50% maximum 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 ^a	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 ^b	76	5.1	0.8 to 14.0 ^b
Topiramate + Placebo	39	6.3	3.1 to 9.3	37	4.9	1.5 to 7.9	76	5.4	1.5 to 9.3
Topiramate + Placebo	38	5.3	2.1 to 8.5	38	5.3	0.8 to 14.2 ^c	76	5.3	0.8 to 14.2 ^c

^a 50% average dosage (mg/kg per day) over the stabilization period.
^b based on administration of "25 mg" and "100 mg" placebo tablets that matched topiramate tablets.
^c based on administration of "25 mg", "222, 257" and "100 mg" placebo tablets that matched topiramate tablets.
^d based on their baseline weight.
^e 50% maximum 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	Number Enrolled in Baseline Phase		Number Randomized to Double-Blind Study Drug	
	Placebo	Topiramate	Placebo	Topiramate
Overall	103	87	175	225
Topiramate	41	40	25 (33.9 kg)	34 (43.9 kg)
Topiramate + Placebo	81	81	7	2
Overall	190	190	325	400

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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 ^a	6	174.0	146.2 to 175.0	1	174.7	..	7	174.7	146.2 to 174.7
Topiramate	2	203.8	182.7 to 225.0	0	..	..	2	203.8	182.7 to 203.8
Topiramate + Placebo	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 + Placebo	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 + Placebo	1	225.0	..	1	224.1	..	2	224.5	224.1 to 225.0
Topiramate + Placebo	33	393.8	155.7 to 400.0	35 ^b	388.5	50.0 to 475.3 ^c	68	389.8 ^d	50.0 to 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, 257) in the topiramate group whose weights were <45 kg were assigned a 400 mg/day target dosage.
^c Two topiramate-treated subjects (Subjects 14 and 24) took daily doses >400 mg for a portion of the double-blind phase.

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 ^a	5	12	6 to 15	9	23	9 to 23	14	17	13 to 23
Topiramate	14	10	5 to 27	6	15	6 to 15	17	14	11 to 18
Topiramate + Placebo	12	29	13 to 33	13	15	3 to 25	25	21	21 to 33
Topiramate + Placebo	8	20	7 to 18	7	11	5 to 12	15	10	10 to 15
Topiramate + Placebo	5	13	5 to 13	5	12	5 to 12	10	12	10 to 13
Topiramate + Placebo	138.8 (28.30)	139.9 (25.42)	128.4 (39.97)	129.3 (36.90)	133.6 (25.15)	141.0	141.0	141.0	141.0
Topiramate + Placebo	141.0	141.0	141.0	141.0	141.0	141.0	141.0	141.0	141.0
Topiramate + Placebo	48 to 197	48 to 197	48 to 197	24 to 169	24 to 169	24 to 197	24 to 197	24 to 197	24 to 197

^a Overall mean (SD) duration of therapy was as follows: 139.3 (27.31) days for Protocol YTC; 128.8 (38.72) days Protocol YTC-E; and 134.1 (33.53) days for the combined total.

^b Subjects with 50% or greater reduction from baseline.

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

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

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

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

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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		Protocol YTC-E		N	Median	Percentile	YTC
	N	%	N	%				
Placebo	41	0.9	48.5 to 35.0	40	12.1	16.1 to 40.7	81	7.3
Topiramate	39	42.1	2.6 to 76.9	40	26.0	7.0 to 78.2	79	37.6
p-Value		0.003 ^b				0.212 ^c		

* Negative numbers denote an increase in seizure rate.
^b Topiramate vs. placebo; two-factor (treatment and protocol) ANOVA on ranks.
^c Topiramate vs. placebo; two-factor (treatment and protocol) 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 Group	Protocol YTC		Protocol YTC-E		N	No.	%	N	No.
	N	%	N	%					
Placebo	41	7	40	8	20	81	15		
Topiramate	39	18	46	16	40	79	34		
p-Value		0.003 ^b		0.061 ^b					

* 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		Protocol YTC-E		N	No.	%	N	No.
	N	%	N	%					
100	0	0	3	3	1	4			
275	7	26	5	30	6	28			
250	17	46	20	40	19	43			
225	39	59	40	53	40	56			
2-25	51	72	55	68	53	70			
	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		Protocol YTC-E		N	Median	Percentile	YTC
	N	%	N	%				
Absence	41	51.8	16.1	6.6	10.9	3.4		
Myoclonic	401.2	31.8	5.5	15.2	15.3	39.5		
Tonic	-1.0	28.0	-33.2	76.7	-20.9	49.3		

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

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		Protocol YTC-E		N	Median	Percentile	YTC
	N	%	N	%				
100	5	13	8	8	10	10		
275	13	33	14	36	35	55		
250	20	56	35	28	55	71		
225	45	67	58	74	69	76		
2-25	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		Protocol YTC-E		N	Median	Percentile	YTC
	N	%	N	%				
100	37	9.3	29	33.8	12.5 to 61.8	66	27.1	-12.5 to 49.8
275	34	64.2	31	60.0	21.0 to 86.8	65	60.7	10.9 to 85.6
p-Value		0.003 ^b		0.094 ^b				0.002 ^c

* 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 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		Protocol YTC-E		N	No.	%	N	No.
	N	%	N	%					
Placebo	37	7	29	9	31	66	16	24	
Topiramate	34	21	62	31	16	52	37	57	
p-Value		<0.001 ^b		0.084 ^b				<0.001 ^c	

* Topiramate vs. placebo; two-factor (treatment and center) ANOVA on ranks.
^b Topiramate vs. placebo; Cochran-Mantel-Haenszel test stratified by treatment and center.
^c Topiramate vs. placebo; logistic regression with terms for treatment, center, and baseline PGTC seizure rate.

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Table 19: 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				Overall					
	Placebo (N=41)		Topiramate (N=39)		Placebo (N=40)		Topiramate (N=79)		Placebo (N=81)		Topiramate (N=79)			
Worse (0)	N	%	N	%	N	%	N	%	N	%	N	%	N	%
None	4	10	3	8	4	10	7	9	7	9	7	9	7	9
Minimal (1)	12	29	11	28	20	50	14	35	32	40	25	32	32	40
Moderate (2)	8	20	7	18	8	20	0	0	16	20	7	9	17	21
Marked (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	0	0
p-value	0.490 ^a		0.388 ^b		0.026 ^a		0.024 ^b		0.020 ^a		0.017 ^b			

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	
Sex	PL	TPM	PL	TPM	PL	TPM	PL	TPM
Male	42	40	15.1	58.7	21	55	42	41
Female	38	38	28.4	54.4	34	55	39	38
Race								
White	75	70	29.5	54.3	29	54	76	71
Non-White	5	8	-12.5	70.9	0	63	5	8
Age								
≤16 years	14	17	3.6	40.1	21	47	15	17
>16 years	66	61	29.3	57.1	29	57	66	62
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		Percent Responders*	
PGTC Seizures	PL	TPM	PL	TPM	PL	TPM	PL	TPM	PL	TPM	PL	TPM	PL	TPM
United States	40	39	9.0	56.7	20	56	15	16	37.9	48.5	40	50	55	55
Europe	NAP	NAP	..	..	..	..	25	23	31.4	60.0	32	57	25	23
All Seizures														
United States	41	39	0.9	42.1	17	46	15	16	21.0	35.8	7	44	56	55
Europe	NAP	NAP	..	..	..	..	25	24	11.5	15.3	28	38	25	24
Defined as ≥50% reduction in seizure rate relative to baseline.														

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

Table 19: 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 (N=65)					
	Placebo (N=38)		Topiramate (N=34)		Placebo (N=39)		Topiramate (N=31)		Placebo (N=67)		Topiramate (N=65)			
Worse (0)	N	%	N	%	N	%	N	%	N	%	N	%	N	%
None	4	11	3	9	3	10	2	6	7	10	5	8	7	10
Minimal (1)	12	32	8	24	14	48	11	35	26	39	19	29	26	39
Moderate (2)	8	21	7	21	7	24	0	0	15	22	7	11	15	22
Marked (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	1	1	1
p-value	0.259 ^a		0.212 ^b		0.009 ^a		0.009 ^b		0.005 ^a		0.005 ^b			

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	
Sex	PL	TPM	PL	TPM	PL	TPM	PL	TPM
Male	42	41	-0.6	37.6	14	44	42	41
Female	38	38	25.3	33.4	23	42	39	38
Race								
White	75	71	12.1	37.6	20	44	76	71
Non-White	5	8	-405.3	30.0	0	38	5	8
Age								
≤16 years	14	17	0.9	26.7	7	29	15	17
>16 years	66	62	12.1	43.5	21	47	66	62
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		Percent Responders*	
PGTC Seizures	PL	TPM	PL	TPM	PL	TPM	PL	TPM	PL	TPM	PL	TPM	PL	TPM
United States	40	39	9.0	56.7	20	56	15	16	37.9	48.5	40	50	55	55
Europe	NAP	NAP	..	..	..	..	25	23	31.4	60.0	32	57	25	23
All Seizures														
United States	41	39	0.9	42.1	17	46	15	16	21.0	35.8	7	44	56	55
Europe	NAP	NAP	..	..	..	..	25	24	11.5	15.3	28	38	25	24
Defined as ≥50% reduction in seizure rate relative to baseline.														

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

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