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	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
Oriental	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
Clorazepate dipotassium	2	4	3	7	5	6
Phenobarbital	4	9	1	2	5	6
Ethosuximide	0	0	2	5	2	2
Felbamate	1	2	1	2	2	2
Methsuximide	0	0	2	5	2	2
Acetazolamide	0	0	1	2	1	1
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[b]						
Complex Partial	37	82	31	76	68	79
Secondarily Generalized	17	38	17	42	34	40
Simple Partial	12	27	11	27	23	27
All Other Types	3	7	3	7	6	7

[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)			
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)
25-33.9 kg	13 (29)	7 (17)	20 (23)
34-42.9 kg	9 (20)	10 (10)	19 (22)
≥43 kg	10 (22)	9 (22)	19 (22)
Mean	35.1	34.7	34.9
SD	16.32	15.79	15.98
Median	32.0	30.0	31.5
Range	15.0-90.0	15.0-76.0	15.0-90.0
Height (cm)			
N	45	38	83
Mean	132.6	131.8	132.2
SD	19.05	23.90	21.27
Median	134.0	133.0	134.0
Range	94.0-178.0	90.0-178.0	90.0-178.0
Baseline Average Monthly Seizure Rate:[b]			
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			
N	17	17	34
Mean	41.1	16.4	28.8
SD	87.95	25.32	64.95
Median	5.0	6.3	5.6
Range	0.5-272.8	0.9-89.1	0.5-272.8
All Seizures			
Mean	86.2	46.0	67.0
SD	189.82	57.20	143.52
Median	23.0	21.5	22.2
Range	2.0-1132.6	1.8-244.0	1.8-1132.6

[b] Rate per 28 days.

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

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

[a] 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	Percent Seizure Rate Reduction[a] Median	25th to 75th Percentile
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	-326.6 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	Treatment Responders[a] No.	%	p-value[b]
Partial Onset Seizures			
Placebo (N=45)	9	20	
Topiramate (N=41)	16	39	0.080
Secondarily Generalized Seizures			
Placebo (N=20)	6	30	
Topiramate (N=20)	9	45	
All Seizures			
Placebo (N=45)	10	22	
Topiramate (N=41)	16	39	0.127

[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/ Percent Reduction	Placebo (N=45) No.	%	Topiramate (N=41) No.	%
Partial Onset Seizures				
100	0	0	2	5
≥75	1	2	7	17
≥50	9	20	16	39
≥25	18	40	22	54
0	29	64	32	78
≥-25	34	76	35	85
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) No.	%	Topiramate (N=41) 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	Placebo N	Baseline Mean (SD) (µg/mL)		N	Mean Change (SD) (µg/mL)		Topiramate N	Baseline Mean (SD) (µg/mL)		N	Mean Change (SD) (µg/mL)		p-value[a]
Carbamazepine	26	9.3	(2.49)	25	-0.3	(1.60)	25	8.9	(2.46)	25	-0.8	(2.18)	0.428
Valproic Acid	12	75.6	(40.34)	10	-4.2	(16.28)	10	83.3	(34.78)	10	-11.5	(20.47)	0.389
Lamotrigine	5	3.5	(1.36)	5	0.7	(0.96)	5	7.8	(5.39)	5	-0.8	(0.49)	0.017
Phenytoin	9	12.8	(7.36)	9	-1.2	(3.66)	7	9.8	(6.70)	6	1.9	(2.96)	0.101

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

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

Seizure Type / Plasma Stratum (µg/mL)	N	Median Percent Reduction	Percent Responders No.	%
Partial Onset Seizures				
≤3.2	13	18.1	5	38
≥3.2 to <5.4	14	51.5	8	57
≥5.4	14	30.3	5	36
All Seizures				
≤3.2	13	10.6	5	38
≥3.2 to <5.4	14	51.5	8	57
≥5.4	14	30.4	5	36

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	33.1	0.034[b]
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[a]:			
Partial onset seizures	20.0	39.0	0.080[c]
All seizures	22.0	39.0	0.127[c]
Parental global evaluation of improvement in seizure severity[d]	33	59	0.025[e] 0.019[f]

[a] A treatment responder is defined as subject whose seizure rate was reduced 50% or more during the double-blind phase.
[b] TPM vs. placebo; two factor (treatment and center) ANOVA on ranks.
[c] TPM vs. placebo; Cochran-Mantel-Haenszel test.
[d] Percent of subjects who had minimal, moderate, or marked improvement in seizure severity.
[e] TPM vs. placebo; Wilcoxon rank-sum test stratified by center.
[f] TPM vs. placebo; Wilcoxon rank-sum test unstratified.

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

Target Dosage (mg/kg per day)	Placebo (N=45) No.	(%)	Topiramate (N=41) No.	(%)	Total (N=86) 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: Double-Blind Phase
(All Randomized ... 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[e]

[a] Subject's average dosage (mg/kg per day) over the 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.
[d] Subject 524, a 20 kg boy assigned to receive placebo 125 mg/day, took 200 mg (10.0 mg/kg) placebo once during the study.
[e] Subject 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 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[e]

[a] Subject's average dosage (mg/kg per day) over the entire stabilization period.
[b] Results based on administration of "25 mg" and "100 mg" placebo tablets that matched topiramate tablets.
[c] Subject's maximum (mg/kg per day) over the entire stabilization period.
[d] Subject 524, a 20 kg boy assigned to receive placebo 125 mg/day, took 200 mg (10.0 mg/kg) placebo once during the study.
[e] Subject 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/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)[b]				
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	5.82	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[c]
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

[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.

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

Double-Blind Therapy (Days)	Placebo (N=45) No.	%	Topiramate (N=41) No.	%	Total (N=86) 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)

vestigator/ bject No.[a]	Age (yr)/ Sex	Preferred Term	Day of AE Onset[b] (Period)[c]	Dosage at AE Onset (mg/day)	Total Days of Therapy[b]	Final Dosage (mg/day)	Severity[d] Relationship[d]	Outcome (Duration)
				Placebo				
ollins/13	5/F	Convulsions Aggravated	26 (T)	25	127	125	Marked Possible	Resolved (2 days)
lson/74	9/M	Infection Viral	66 (S)	175	110	175	Moderate Unlikely	Resolved (6 days)
yllie/116	5/M	Convulsions Aggravated	104 (S)	100	126	100	Marked Unlikely	Resolved (2 days)
				Topiramate				
urgeois/2	11/M	Constipation	50 (T)	125	127	100	Marked Unlikely	Resolved (14 days)

o U.S. IND Safety reports were filed.
efers to the double-blind phase.
denotes titration period and S denotes stabilization period.
ased 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 nent[a]
(All Randomized Subjects; Protocol YP)

Investigator/ Subject No.	Age Sex	Preferred Term	Day of AE Onset[b]	Dosage at AE Onset[c]	Severity[d] Relationship[d]	Action Taken (Dosage)	Outcome (Duration)	Total Days of Therapy[b]
				Placebo				
Elterman/ 530	14 F	Coordination abnormal	57	225	Mild Possible	Reduced	Persisted[e]	141
So/ 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
		Paroniria	37	100	Moderate Possible	Reduced	Resolved (31 days)	126
		Delusion	52	125	Mild Possible	Reduced	Resolved (16 days)	126
Wyllie/ 117	8 F	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				
Bettis/ 542	8 F	Somnolence	80	75	Mild Possible	Reduced	Resolved (31 days)	136
Bourgeoris/ 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
Sachdeo/ 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 Protocol YTC

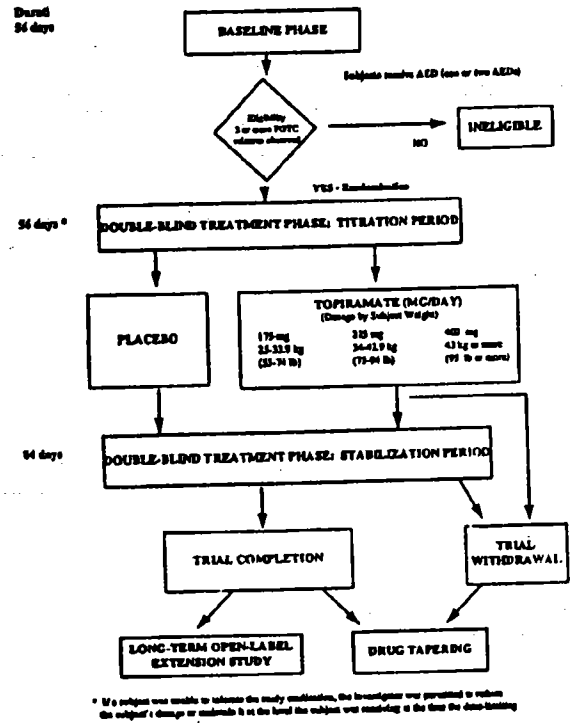

Figure 2: [illegible] Completion and Withdrawal Summary

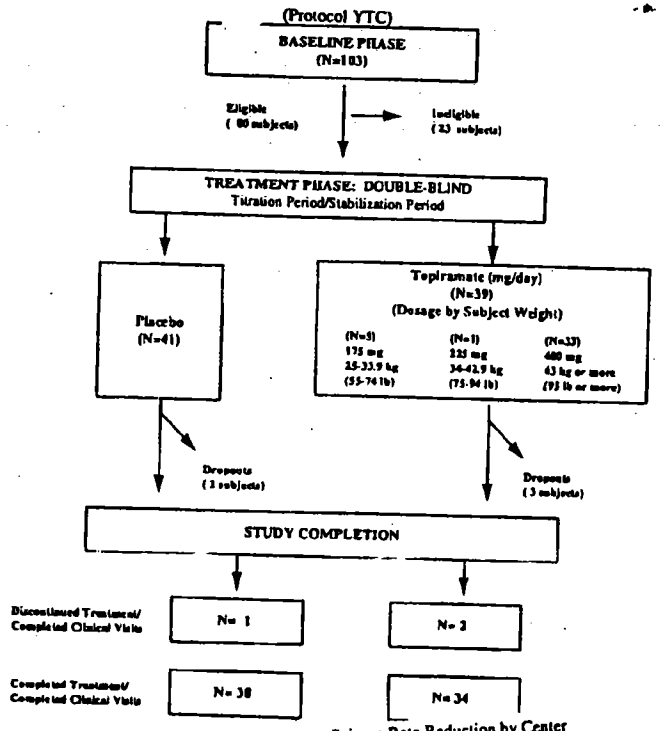

Figure 4: Cumulative Response Rate
(All Randomized Subjects; Protocol YTC)

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

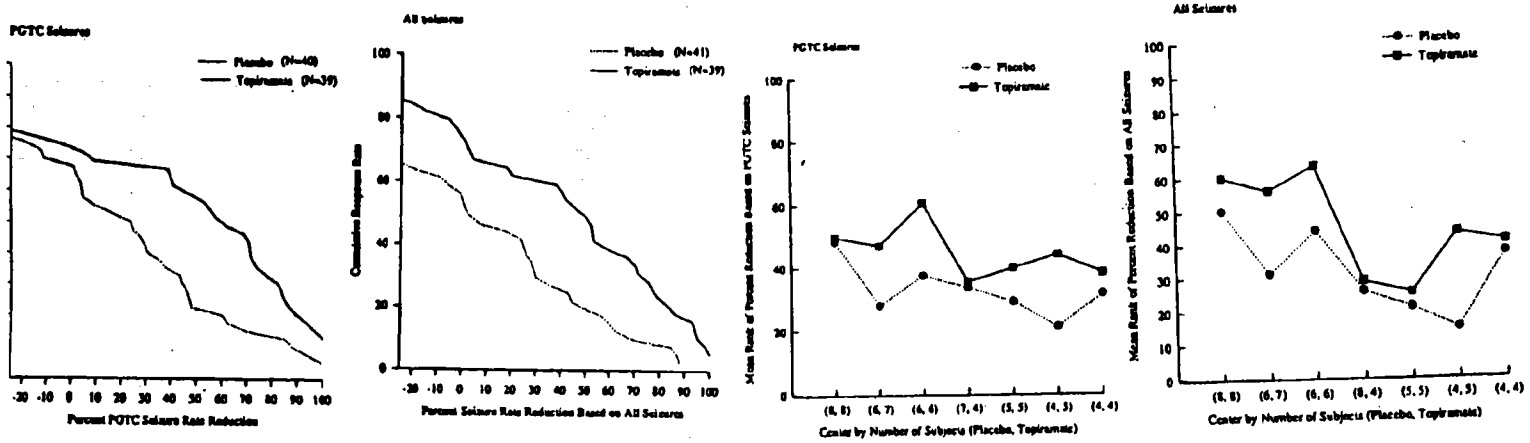

Table 1: Key Inclusion Criteria
(Protocol YTC)

- 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: 1 through 28	29 through 42	43 through 56	57 through 141	Target Dosage Range[a] (mg/kg/day)
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	≤9.3

[a] Theoretical dosage range based on protocol-defined daily topiramate target dosages.

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

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

[a] 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: [illegible] and Baseline Characteristics: Age, Weight, Height, and Average Monthly Seizure Rate
[illegible]l Randomized Subjects; Protocol YTC)

	Placebo (N=41)	Topiramate (N=39)	Total (N=80)
[illegible]ge (yr)			
[illegible]16; No. (%)	13 (32)	8 (21)	21 (26)
[illegible]16; No. (%)	28 (68)	31 (79)	59 (74)
[illegible]ean	25.6	26.8	26.2
[illegible]D	13.38	12.82	13.04
[illegible]edian	26.0	25.0	25.5
[illegible]ange	3.0 to 50.0	5.0 to 59.0	3.0 to 59.0
[illegible]Veight (kg)			
[illegible]3-33.9; No. (%)	6 (15)	5 (13)	11 (14)
[illegible]34-42.9; No. (%)	2 (5)	1 (3)	3 (4)
[illegible]43; No. (%)	33 (80)	33 (85)	66 (83)
[illegible]ean	61.3	71.8	66.5
[illegible])	25.06	28.52	27.14
[illegible]edian	62.0	72.0	64.0
[illegible]nge	17 to 129	22 to 143	17 to 143
[illegible]eight (cm)[a]			
[illegible]ean	38	35	73
[illegible])	139.1	166.1	162.4
[illegible]edian	19.44	17.21	18.61
[illegible]nge	161.0	168.0	166.0
[illegible]seline Avg. Monthly Seizure Rate[b]:	101 to 196	117 to 193	101 to 196
[illegible]TC Seizures			
[illegible]an	40	39	79
[illegible]	15.8	20.3	18.0
[illegible]edian	47.23	51.51	49.12
[illegible]nge	4.5	5.0	5.0
	0.7 to 299.9	1.0 to 297.7	0.7 to 299.9
[illegible] Seizures			
[illegible]an	2000.9	91.1	1069.9
	12347	214.7	8839
[illegible]dian	17.5	15.3	16.0
[illegible]ge	1.6 to 79109	1.0 to 1134.0	1.0 to 79109

[illegible]ate 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 Reason	N	%	N	%	N	%
Subject Choice	1	2	2	5	3	4
Limiting Adverse Event	1	2	1	3	2	3
Lost to Follow-up	1	2	0	0	1	1
Other[a]	0	0	2	5	2	3
Total Discontinued	3	7	5	13	8	10
Total Completed	38	93	34	87	72	90

[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: Demogr[illegible]d Baseline Characteristics: Sex, Race, Background AED, and Seizure Type
(All Randomized Subjects; Protocol YTC)

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

[a] Subject 146 was of Hispanic descent.
[b] Individual subjects may have received more than one background AED.
[c] Includes valproate disodium.
[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 PGTC seizure during either baseline or double-blind phase (see Section IV.E, Protocol Deviations).
[f] Includes seizures described as violent myoclonic jerks, atonic seizures, or drops to the floor.
[g] Subject 98 (placebo) experienced seizures of an unknown type that were categorized as "other". Subject 71 (topiramate) experienced complex partial seizures that were categorized as "other".

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Tal **jects Who Prematurely Discontinued Study Medication**
(All Randomized Subjects; Protocol YTC)

vestigator/ ubject No.	Age	Sex	Duration (Days) of Double-Blind Therapy	Daily Dosage at Discontinuation (mg/day)	Duration (Days) of Double-blind Participation[a]	Reason for Discontinuation
				Placebo		
Collins/98	50	F	119	400	119	Lost to follow-up
edley/105[b]	38	M	43	50	184	Limiting adverse event: granulocytopenia, thrombocytopenia
Wyllie/121	18	M	1	50	125	Subject choice: self abusive behavior, restlessness, insomnia
				Topiramate		
Biton/4[b]	21	F	129	100	149	Other: noncompliance
ourgeois/52	8	M	79	175	79	Other: prematurely advanced to open-label phase due to pharmacist distribution error
Livielle/67	6	M	48	25	48	Subject choice
Wyllie/128[b]	25	M	86	100	129	Limiting adverse event: anorexia, weight decrease
oderow/186	22	F	103	400	112	Subject choice

[a] Number of days from the beginning of the double-blind phase until withdrawal from or completion of the trial.
[b] 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	Percent Seizure Rate Reduction[a] Median	25th to 75th percentile
PGTC Seizures		
Placebo (N=40)	9.0	-31.9 to 46.7
Topiramate (N=39)	56.7	-27.0 to 84.1
p-value[b]	0.019	
All Seizures		
Placebo (N=41)	0.9	-48.5 to 35.0
Topiramate (N=39)	42.1	-2.6 to 76.9
p-value[b]	0.003	

[a] Negative numbers denote an increase in seizure rate.
[b] 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[a]) N	%	Topiramate (N=39[a]) N	%
Worse	(0)	4	10	3	8
None	(1)	12	29	11	28
Minimal	(2)	8	20	7	18
Moderate	(3)	12	29	9	23
Marked	(4)	3	7	8	21
p-Value		0.490[b]			
		0.388[c]			

[a] Two placebo-treated subjects and one topiramate-treated subject were not assessed for this efficacy variable at the final visit.
[b] Wilcoxon-Rank Sum test stratified by center.
[c] Wilcoxon-Rank Sum test unstratified by center.

Table 10a: Treatment **rs for the Double-Blind Phase**
(All Random **jects; Protocol YTC)**

Seizure Type/ Treatment	Treatment Responders[a] No.	%	p-value[b]
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
(All Randomized Subjects; Protocol YTC)

Seizure Type/ Percent Reduction	Treatment Group: Placebo N	%	Topiramate N	%
PGTC Seizures	(N=40)		(N=39)	
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
≥ -25	29	73	29	74
All Seizures	(N=41)		(N=39)	
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
≥ -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 N	Baseline Mean (SD) (μg/mL)	N	Mean Change (SD) (μg/mL)	Topiramate N	Baseline Mean (SD) (μg/mL)	N	Mean Change (SD) (μg/mL)	P-value[a]
Valproic Acid	20	94.2 (28.94)	20	0.4 (16.05)	20	96.4 (40.20)	19	-1.5 (14.11)	0.606
Phenytoin	12	17.3 (7.59)	12	-0.5 (6.55)	15	14.5 (8.63)	12	-2.5 (4.89)	0.404
Carbamazepine	9	9.6 (3.01)	9	0.7 (0.85)	13	8.9 (4.33)	11	-1.4 (2.01)	0.009
Lamotrigine	11	6.5 (4.25)	9	0.6 (1.79)	6	4.3 (2.09)	6	1.2 (2.03)	0.581
Phenobarbital	7	29.9 (14.22)	7	1.1 (7.36)	9	21.0 (11.83)	7	-3.4 (8.02)	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	Responders No.	%
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

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

Efficacy Asse	Placebo	Topiramate	p-value
Primary Variable			
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] Topirmate 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.

7 : Average Daily Dosage (mg/day) During the Stabilization Period by Target Dosage Group
(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) No.	%	Topiramate (N=39) No.	%	Total (N=80) 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 Dosage at AE Onset (mg/day)	Total Days of Therapy[d]	Final Dosage (mg/day)	Severity[e] Relationship[e]	Outcome (Duration)
				Placebo					
Pedley/ 105	38	M	Thrombocytopenia	9(T)	50	43 (184)	50	Mild Possible	Resolved (41 days)
			Granulocytopenia	16 (T)	50			Moderate Possible	Resolved (42 days)
				Topiramate					
Wyllie/ 128	25	M	Anorexia	8 (T)	50	86 (129)	100	Mild Possible	Resolved (107 days)
			Weight decrease	31 (T)	50			Mild Possible	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 23: Subjects With Serious Adverse Events[a]
(All Randomized Subjects; Protocol YTC)

Investigator/ Subject No.[b]	Age (yr)	Sex	Preferred Term	Day of AE Onset[c] (Period)[d]	Dosage at AE Onset (mg/day)	Total Days of Therapy[e]	Final Dosage (mg/day)	Severity[f] Relationship[g]	Outcome (Duration)
			Placebo						
[illegible]	38	F	Abscess	92 (S)	400	144	400	Moderate Possible	Resolved (53 days)
[illegible]/93	33	M	Chest pain	151 (S)	400	164	400	Marked Possible	Resolved (2 days)
			Topiramate						
[illegible]/4[h]	21	F	Convulsions, grand mal	123 (S)	400	129	100	Moderate Possible	Resolved (2 days)
[illegible]/94	44	F	Tremor	81 (S)	400	197	200	Moderate Probable	Resolved (22 days)
			Speech disorders and related speech problems	81 (S)	400			Marked Probable	Resolved (22 days)
			Gait abnormal	81 (S)	400			Marked Probable	Resolved (22 days)
			Nervousness	81 (S)	400			Moderate Probable	Resolved (22 days)
[illegible]/146	6	M	Pneumonia	40 (T)	100	141	175	Marked Unlikely	Resolved (15 days)
[illegible]/154	33	M	Thrombophlebitis	9 (T)	50	141	400	Moderate Unlikely	Resolved (12 days)
			Micturition disorder	62 (S)	400			Moderate Possible	Resolved (46 days)
			Urinary incontinence	62 (S)	400			Moderate Possible	Resolved (46 days)
			Prostatic disorder	62 (S)	400			Mild Possible	Resolved (46 days)
			Viral infection	69 (S)	400			Marked Unlikely	Resolved (7 days)

does not include one subject (198) who was hospitalized for elective skin graft surgery.
a U.S. IND safety reports were filed.
number of days from the beginning of the double-blind phase.
dosetus duration period and 3 dosetus stabilization period.
ased on investigator's assessment at the time of the occurrence of the adverse event; for relationship, probable = obable/likely
ubject 4 prematurely discontinued study medication but completed all clinical visits.
AE = adverse event

Table 24: Subjects With Recurrent Treatment-Emergent Markedly Abnormal Laboratory Values for Selected Analytes[a]
(All Randomized Subjects; Protocol YTC)

Investigator/ Subject No.	Age (years)	Sex	Laboratory Analyte (Markedly Abnormal Range)	Laboratory Analyte Value	Day of Therapy	TPM Dosage (mg/day)
			Topiramate			
/	19	M	WBC count (≥ 10^3 cells/μL) (≤ 2.8 x 10^3 cells/μL)	3.8	-28	0
				3.3 L	1 (BL)	50
				2.6 L*	29	150
				2.5 L*	55	401
				2.6 L*	75	400
				2.9 L	140 (Final)	400
[illegible]/	29	M	Monocyte percentage (% WBC) (≥15%)	12.3 H	-27	0
				9.2	1 (BL)	50
				13.0 H	29	150
				15.5 H*	52	300
				15.6 H*	66	300
				13.6 H	92	400
				12.0	149 (Final)	0
o/	5	M	Lymphocyte percentage (% WBC) (> 60%)	62.0 H*	-33	0
				59.2	1 (BL)	50
				63.0 H*	38	50
				67.0 H*	62	175
				79.0 H*	87	175
				85.0 H*	148 (Final)	175
			Neutrophil percentage (% WBC) (< 15%)	32.0	-33	0
				34.1	1 (BL)	50
				27.0	38	50
				26.0	62	175
				11.0 L*	87	175
				9.0 L*	148 (Final)	175

rent indicates at least two occurrences of a treatment-emergent marked abnormality at consecutive visits for selected es (see Table 23).
ies value was markedly abnormal.

Table 22: Su[illegible] Global Evaluation of Improvement in Mental Status
idomized Subjects; Protocol YTC)

(Score) Description	Not Reported No.	Not Reported (%)	(0) Worse No.	(0) Worse (%)	(1) None No.	(1) None (%)	Improved (2) Minimal No.	Improved (2) Minimal (%)	Improved (3) Moderate No.	Improved (3) Moderate (%)	Improved (4) Marked No.	Improved (4) Marked (%)
Level of Alertness												
Placebo (N=41)	2	(5)	0	(0)	23	(56)	7	(17)	8	(20)	1	(2)
Topiramate (N=39)	1	(3)	3	(8)	17	(44)	8	(21)	7	(18)	3	(8)
Level of Interaction With the Environment												
Placebo (N=41)	2	(5)	3	(7)	24	(59)	6	(15)	5	(12)	1	(2)
Topiramate (N=39)	1	(3)	2	(5)	17	(44)	9	(23)	8	(21)	2	(5)
Ability to Perform Activities of Daily Living												
Placebo (N=41)	2	(5)	0	(0)	27	(66)	6	(15)	5	(12)	1	(2)
Topiramate (N=39)	1	(3)	1	(3)	21	(54)	9	(23)	7	(18)	0	(0)
Responsiveness to Verbal Requests												
Placebo (N=41)	2	(5)	1	(2)	24	(59)	9	(22)	5	(12)	0	(0)
Topiramate (N=39)	1	(3)	2	(5)	20	(51)	7	(18)	8	(21)	1	(3)

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

Investigator/ Subject No.	Age Sex	Preferred Term	Day of AE Onset[b]	Dosage at AE Onset (mg/day)	Severity[c] Relationship[d]	Action Taken (Dosage)	Outcome (Duration)	Total Days of Therapy[b]
				Placebo				
So/ 33	B F	Anxiety	69	225	Mild Possible	Reduced	Persisted[e]	154
		Gait abnormal	71	225	Mild Possible	Reduced	Resolved (14 days)	
		Personality disorder	58	225	Mild Possible	Reduced	Resolved (17 days)	
Wyllie/ 121	18 M	Automatism	1	50	Moderate Possible	DST[f]	Resolved (6 days)	1[g]
		Insomnia	1	50	Moderate Possible	DST[f]	Resolved (6 days)	
				Topiramate				
Riviello/ 67	6 M	Insomnia	26	50	Mild Possible	Reduced	Persisted[e]	48
		Difficulty with memory	27	50	Mild Possible	Reduced	Persisted[e]	
Schaul/ 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)	
Montouris/ 155	59 M	Difficulty with memory	46	150	Moderate Possible	Reduced	Resolved (18 days)	147
		Somnolence	46	150	Moderate Possible	Reduced	Resolved (18 days)	
Leroy/ 195	23 M	Stupor	3	50	Moderate Probable	Reduced	Resolved (22 days)	148
		Somnolence	54	150	Mild Possible	Reduced	Persisted[e]	
		Cognitive problems	80	300	Mild Possible	Reduced	Resolved (48 days)	
		Confusion	80	300	Mild Possible	Reduced	Resolved (48 days)	

Dosage adjustments included dosage reduction or temporary discontinuation of treatment.
Number of days from the beginning of the double-blind phase.
Based on the investigator's assessment at the time of the occurrence of the adverse event.
Event persisted as of the last double-blind visit for this subject. The subject withdrew from the trial by choice and was lost to follow-up.
Drug stopped temporarily due to adverse events, then stopped permanently due to subject choice.
Event persisted into open label extension phase and was ongoing as of 30 June 1996 cut-off date for this report.
Key: AE = adverse event; DST = drug stopped temporarily

Figure 1: Study Design for Protocol YTC-E

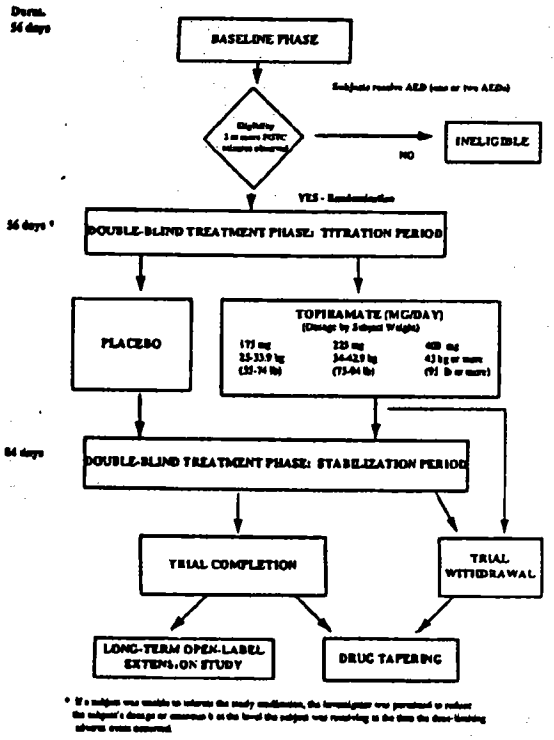

Figure 2: Study ... and Withdrawal Summary of YTC-E)

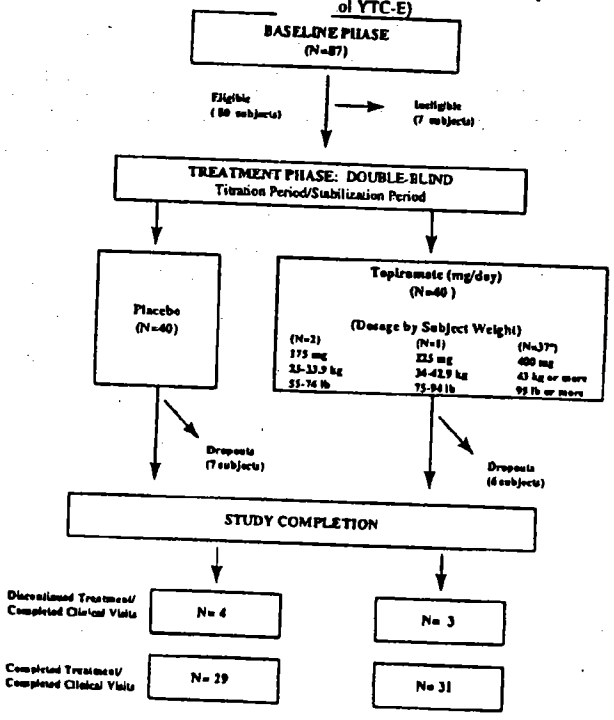

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Figure 4: Cumulative Response Rate (All Randomized Subjects; Protocol YTC-E)

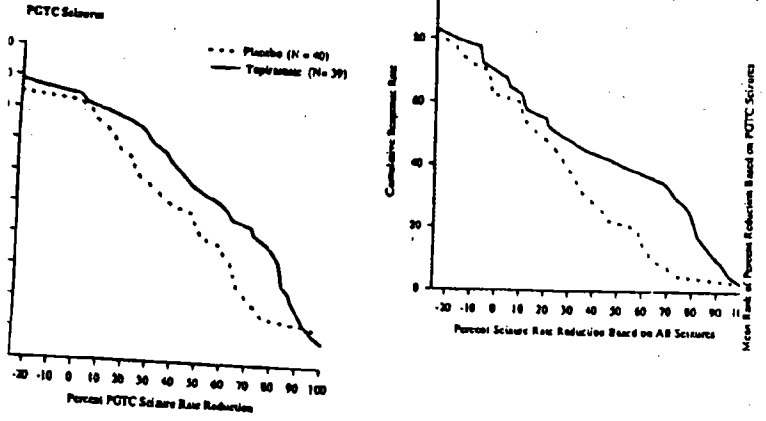

Figure 3: Mean Rank of Percent Seizure Rate Reduction by Analysis Center: (All Randomized Subjects; Protocol YTC-E)

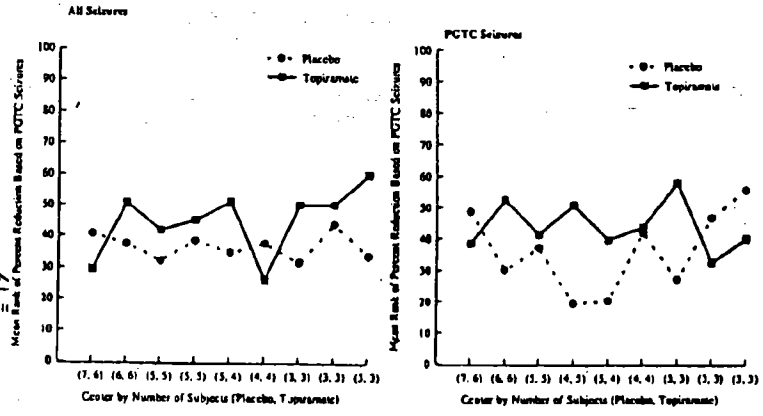

Table 1: Key Inclusion Criteria
(Protocol YTC-E)

- 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 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, 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 antacids, 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	Study Day: 1 through 28	29 through 42	43 through 56	57 through 141	Target Dosage Range[a] (mg/kg/day)
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	≤9.3

[a] Theoretical dosage range based on protocol-defined daily topiramate target dosages.

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

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

[a] 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
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	%	N	%
Limiting Adverse Event	7[a]	18	5	13	12	15
Subject Choice	0	0	2	5	2	3
Investigator's Discretion	1	3	0	0	1	1
Other[b]	3	8	2	5	5	6
Total Discontinued	11[a]	28	9	22	20	25
Total Completed	29	72	31	78	60	75

[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:
Age, 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	38	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.

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

...vestigator/ ...ject Number	Age	Sex	Duration (Days) of Double-Blind Treatment	Dosage at Discontinuation (mg/day)	Duration (Days) of Double-Blind Participation[a]	Reason for Discontinuation
				Placebo		
...dwick/5[b]	28	F	81	75	152	Investigator's Discretion[c]
...sinari/26	29	M	76	50	76	Limiting Adverse Event: convulsions, aggravated
...nkenhorn/40	34	M	27	50	27	Other: personal reasons
...fan/41	26	M	108	100	129	Limiting Adverse Events: apathy; fatigue
...hinger/43	27	F	134	400	134	Other[c]
...dwick/60	17	M	83	50	110	Limiting Adverse Events: aggressive reaction; convulsions, aggravated; diplopia; dizziness; personality disorder; somnolence
...dwick/62	33	F	14	50	15	Other: subject had a history of attempted suicide[d]
...wford/65[b]	23	M	133	300	149	Limiting Adverse Events: aggressive reaction; ataxia;[e] confusion;[e] convulsions, aggravated;[e] injury;[e] increased sweating
...dwick/75[b]	18	M	4	50	141	Limiting Adverse Events: aggressive reaction; agitation; anxiety; confusion; paroniria; personality disorder
...n/205[b]	33	M	69	150	148	Limiting Adverse Event:[f] nausea;[e] vomiting[e]
...y/209	46	F	152[g]	400	152	Limiting Adverse Events: sudden death[e]
				Topiramate		
...die/16[b]	42	M	120	200	149	Subject Choice
...die/19	29	F	57	300	57	Limiting Adverse Event: vision abnormal[e]

...umber of days from the beginning of the double-blind phase until withdrawal from, or completion of, trial.
...hese subjects prematurely discontinued study treatment but completed all nine protocol-specified clinical visits ...140 days).
...urther information is not available.
...his deviation from protocol was discovered by the investigator after 14 days of therapy and the subject was ...rematurely discontinued from the trial.
...hese adverse events were considered serious by the investigator (see Table 19).
...or subject 205, the reason specified on the study completion page of the case report form for premature ...iscontinuation of the trial was "Subject Choice" but the adverse event page of the case report form indicated that ...tudy treatment was discontinued because of nausea and vomiting (see Table 20).
...ue 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...d) (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
				Topiramate (Continued)		
Beghi/27	32	M	60	400	60	Limiting Adverse Events: gait abnormal; somnolence
Ben-Menachem/ 31	28	F	24	50	27	Limiting Adverse Events: aggressive reaction;[b] agitation;[b] insomnia[b]
Blankenhorn/39[c]	60	M	169[d]	100	211	Other: subject did not have PGTC seizures at baseline
Ben-Menachem/ 87	34	M	28	50	36	Limiting Adverse Events: 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	Percent Seizure Rate Reduction[a] 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.

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

Seizure Type/ Treatment	Treatment Responders[a] N	%	p-value[b]
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)

	Treatment Group			
	Placebo		Topiramate	
Seizure Type/ Percent Reduction	N	%	N	%
PGTC Seizures	(N=40)		(N=39)	
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
≥ -25	31	78	34	87
All Seizures	(N=40)		(N=40)	
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
≥ -25	33	83	33	83

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

Improvement Rating	(Score)	Placebo (N=40) N	%	Topiramate (N=40) 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)

	Placebo				Topiramate				
Concomitant AED	N	Baseline Mean (SD) (µg/mL)	N	Mean Change (SD) (µg/mL)	N	Baseline Mean (SD) (µg/mL)	N	Mean Change (SD) (µg/mL)	p-value[a]
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]
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) dur[illegible]

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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	N	Median Reduction	N	Treatment Responders %
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: Placebo (N=40)	Topiramate (N=40)	p-value
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[a]
Percent treatment responders[c]	20	40	0.061[d]
Subjects' global evaluation of improvement in seizure severity[f]	33	48	0.026[g] 0.024[h]

[a] Topiramate vs. placebo; two factor (treatment and center) ANOVA on ranks
[b] Topiramate vs. placebo; two factor (treatment and center) ANCOVA on ranks with baseline PGTC seizure rate as covariate.
[c] A treatment responder is defined as a subject whose seizure rate was reduced 50% or more during the double-blind phase.
[d] Topiramate vs. placebo; Cochran-Mantel-Haenszel test
[e] Topiramate vs. placebo; Logistic regression including treatment, center, and baseline PGTC seizure rate as terms in the model.
[f] Percent of subjects who had minimal, moderate, or marked improvement in seizure severity.
[g] Topiramate vs. placebo; Wilcoxon Rank Sum test stratified by center
[h] 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]				
175 (N=1)	174.7	---	174.7	174.7 - 174.7
400 (N=36)	337.0	98.74	388.9	60.0 - 400.0
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) No.	%	Topiramate (N=40) No.	%	Total (N=80) 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[a]
(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 (mg/day)	Total Days of Therapy	Final Dosage (mg/day)	Severity[d] Relation-ship[d]	Outcome (Duration)
Placebo									
Chadwick/3	38	M	Pain	41 (T)	150	142	100	Marked Unlikely	Resolved (2 days)
			Pain	70 (S)	400			Marked Unlikely	Resolved (2 days)
Chadwick/8	31	F	Convulsions, aggravated	27 (T)	50	141	400	Marked Unlikely	Resolved (2 days)
			Convulsions, aggravated	43 (T)	225			Marked Unlikely	Resolved (2 days)
Crawford/23	22	M	Convulsions, aggravated	114 (S)	400	154	400	Moderate Possible	Resolved (2 days)
Ben-Menachem/32	46	F	Injury	99 (S)	400	155	400	Marked Unlikely	Resolved (57 days)
Crawford/65[e]	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[e]	18	M	Convulsions, aggravated	14 (T)	Unknown	4	50	Marked Unlikely	Resolved (2 days)
			Psychosis	86(T)[f]	Unknown			Marked Unlikely	Resolved (9 days)
			Convulsions, aggravated	86 (T)	Unknown			Marked Unlikely	Resolved (3 days)
Hilton/205[g]	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)
Leroy/209[g]	46	F	Sudden death	152 (S)	400	152	400	Marked Unlikely	--- ---

[a] No U.S. IND safety reports were filed.
[b] Number of days from the beginning of the double-blind phase
[c] (T) denotes titration period and (S) denotes stabilization period.
[d] Based on investigator's assessment at time of occurrence of the adverse event; for relationship, probable = probable/likely.
[e] These subjects prematurely discontinued study treatment but completed all clinical visits (see Tables 8 and 20).
[f] 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.
[g] This subject prematurely discontinued study treatment and was withdrawn from study (see Tables 8 and 20).

Table 19: Subjects With Serious Adverse Events[a] (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 (mg/day)	Total Days of Therapy	Final Dosage (mg/day)	Severity[d] Relation-ship[d]	Outcome (Duration)
Topiramate									
Crawford/14	25	F	Somnolence[e]	57 (S)	800	141	400	Moderate Probable	Resolved[f] (=100 days)
			Dizziness[e]	57 (S)	800			Marked Probable	Resolved (25 days)
			Overdose[e]	57 (S)	800			Marked Certain	Resolved (1 day)
Brodie/19[g]	29	F	Vision abnormal	49 (T)	300	57	300	Marked Possible	Resolved (11 days)
Ben-Menachem/31[g]	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[f]

[a] No U.S. IND safety reports were filed.
[b] Number of days from the beginning of the double-blind phase
[c] (T) denotes titration period and (S) denotes stabilization period.
[d] Based on investigator's assessment at time of occurrence of the adverse event; for relationship, probable = probable/likely.
[e] 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."
[f] 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 sebaceous cyst.
[g] 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)

Score: Description:	Not Reported		(0) Worse		(1) None		Improved (2) Minimal		(3) Moderate		(4) Marked	
	No.	(%)	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)

Table 20 Who Discontinued Study Treatment Due to Limiting Adverse Events (All Randomized Subjects; Protocol YTC-E)

Investigator/ Subject No.	Age (yr)	Sex	Preferred Term	Day of AE Onset [a] (Period)[b]	Dosage at AE Onset (mg/day)	Total Days of Treatment[c]	Final Dosage (mg/day)	Severity[d]/ Relation-ship[d]	Outcome (Duration)
				Placebo					
'assinari/26	29	M	Convulsions, aggravated	60 (S)	100	76 (76)	50	Mild Possible	Resolved (28 days)
'ielan/41	26	M	Apathy	53 (T)	300	108 (129)	100	Moderate Possible	Resolved (63 days)
			Fatigue	53 (T)	300			Moderate Probable	Resolved (63 days)
hadwick/60	17	M	Aggressive reaction	43 (T)	300	83 (110)	50	Moderate Possible	Resolved (67 days)
			Convulsions, aggravated	50 (T)	150			Moderate Possible	Persisted[e]
			Dizziness	71 (T)	100			Moderate Possible	Persisted[e]
			Somnolence	71 (S)	100			Moderate Possible	Persisted[e]
wford/65	23	M	Aggressive reaction	112 (S)	300	133 (149)	300	Mild Possible	Resolved (31 days)
			Convulsions, aggravated[f]	112 (S)	300			Marked Possible	Resolved (1 day)
			Injury[g]	112 (S)	300			Marked Possible	Resolved (31 days)
			Ataxia[g]	126 (S)	300			Moderate Possible	Resolved (17 days)
			Confusion[g]	128 (S)	300			Moderate Possible	Resolved (15 days)
			Sweating, increased	128 (S)	300			Mild Unlikely	Resolved (15 days)

umber of days from the beginning of the double-blind phase
T) denotes titration period and (S) denotes stabilization period.
umber of days from the beginning of the double blind phase until time of discontinuation of study treatment; total number of days in e study is indicated in parenthesis (see Table 8).
ased on investigator's assessment at time of occurrence of the adverse event; for relationship, probable=probable/likely.
ese adverse events were considered serious (see Table 19).
ased on follow-up information received on April 15, 1997 after closure of the database for this trial.

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Table 20: S to Discontinued Study Treatment Due to Limiting Adverse Events (Continued) (All Randomized Subjects; Protocol YTC-E)

Investigator/ Subject No.	Age (yr)	Sex	Preferred Term	Day of AE Onset [a] (Period)[b]	Dosage at AE Onset (mg/day)	Total Days of Treatment[c]	Final Dose (mg/day)	Severity[d] Relation-ship[d]	Outcome (Duration)
				Placebo (continued)					
Chadwick/75	18	M	Aggressive reaction	1 (T)	50	4 (141)	50	Marked Unlikely	Resolved (62 days)
			Paranoria	1 (T)	50			Marked Unlikely	Resolved (6 days)
			Agitation	2 (T)	50			Marked Unlikely	Resolved (6 days)
			Anxiety	2 (T)	50			Marked Unlikely	Resolved (6 days)
			Confusion	2 (T)	50			Marked Unlikely	Resolved (6 days)
			Personality disorder	2 (T)	50			Marked Unlikely	Resolved (6 days)
Biton/205[h]	33	M	Nausea[i]	69 (S)	150	69 (148)	150	Marked Possible	Resolved (2 days)
			Vomiting[i]	69 (S)	150			Marked Possible	Resolved (2 days)
Leroy/209	46	F	Sudden death[j]	152 (S)	400	152 (152)	400	Marked Unlikely	—
				Topiramate					
Brodie/19	29	F	Vision abnormal[f]	49 (T)	300	57 (57)	300	Marked Possible	Resolved (11 days)
Beghi/27	32	M	Gait abnormal	57 (S)	400	60 (60)	400	Moderate Possible	Resolved (5 days)
			Somnolence	57 (S)	400			Moderate Possible	Resolved (5 days)
Ben-Menachem/31	28	F	Aggressive reaction[f]	3 (T)	50	24 (27)	50	Marked Probable	Resolved (25 days)
			Agitation[f]	3 (T)	50			Marked Probable	Resolved (25 days)
			Insomnia[f]	3 (T)	50			Marked Probable	Resolved (25 days)
Ben-Menachem/87	34	M	Ataxia	1 (T)	50	28 (36)	50	Marked Probable	Resolved (34 days)
			Convulsions, aggravated	2 (T)	50			Marked Certain	Resolved (33 days)
			Language problems	4 (T)	50			Marked Certain	Resolved (31 days)
Sperling/242[k]	38	F	Paranoid reaction	71 (S)	300	83 (134)	50	Marked Probable	Resolved (12 days)

[a] Number of days from the beginning of the double-blind phase
[b] (T) denotes titration period and (S) denotes stabilization period.
[c] Number of days from the beginning of the double blind phase until time of discontinuation of study treatment; total number of days in the study is indicated in parenthesis (see Table 8).
[d] Based on investigator's assessment at time of occurrence of the adverse event; for relationship, probable=probable/likely.
[e] For this subject, the reason specified on the study completion page of the case report form is "Subject Choice" (see Table 8); however, the adverse event page of the case report form indicates that the subject prematurely discontinued study treatment for marked nausea/vomiting.
[f] These adverse events were considered serious (see Table 19).
[g] 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 8).

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

Investigator/ Subject No.	Age/ Sex	Preferred Term	Day of AE Onset[b] (Period)[c]	Dosage at AE Onset (mg/day)	Severity[d]/ Relation-ship[d]	Action Regarding Dose	Outcome (Duration)	Total Days of Therapy[b]
				Placebo				
hadwick/3	38/ M	Ataxia	111 (S)	400	Moderate Possible	Reduced	Resolved (5 days)	141
		Diplopia	111 (S)	400	Moderate Possible	Reduced	Resolved (5 days)	
rawford/11	19/ M	Dizziness	45 (T)	300	Moderate Probable	Stopped Reduced	Resolved (17 days)	154
		Fatigue	45 (T)	300	Moderate Probable	Stopped Reduced	Resolved (17 days)	
en-lenachem/29	17/ F	Insomnia	40 (T)	125	Moderate Probable	Reduced	Resolved[e] (=108 days)	148
		Nervousness	40 (T)	125	Moderate Probable	Reduced	Resolved (29 days)	
perling/241	28/ F	Ataxia	123 (S)	400	Mild Probable	Reduced	Resolved (9 days)	145
		Vertigo	123 (S)	400	Mild Probable	Reduced	Resolved (8 days)	
				Topiramate				
hadwick/6	39/ M	Dizziness	23 (T)	50	Moderate Possible	Reduced	Resolved (115 days)	169
		Nausea	23 (T)	50	Moderate Possible	Reduced	Resolved (115 days)	
rawford/14	25/ F	Dizziness[f]	57 (S)	800[g]	Marked Probable	Reduced	Resolved (25 days)	141
		Somnolence[f]	57 (S)	800[g]	Moderate Possible	Reduced	Resolved (25 days)	
rawford/24	25/ M	Confusion	57 (S)	1200[h]	Marked Certain	Reduced	Resolved (5 days)	140
		Somnolence	57 (S)	1200[h]	Marked Certain	Reduced	Resolved (5 days)	
en-lenachem/33	32/ F	Fatigue	4 (T)	50	Moderate Probable	Reduced	Resolved (32 days)	126
		Nervousness	4 (T)	50	Moderate Probable	Reduced	Resolved (32 days)	
iton/201	36/ F	Nausea	32 (T)	150	Mild Possible	Reduced	Resolved (6 days)	143
		Vomiting	32 (T)	150	Mild Possible	Reduced	Resolved (6 days)	
osenfeld/234	25/ M	Headache	16 (T)	50	Mild Unlikely	Reduced	Resolved (1 day)	146
perling/244	32/ M	Somnolence	59 (S)	400	Mild Possibly	Reduced	Persisted[e]	136

Dosage adjustments may have included reduction, temporary discontinuation of treatment, or both.
Number of days from beginning of double-blind phase
(T) denotes titration 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)

Laboratory Analyte	Markedly Abnormal Value[a]	Placebo (N=39)[b] No.	Placebo (N=39)[b] %	Topiramate (N=40) No.	Topiramate (N=40) %
Liver Function Tests					
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
Renal Function Tests					
Creatinine	High	0	0	0	0
BUN	High	2	5	1	3
Hematology Tests					
Hemoglobin	Low	0	0	1	3
Hematocrit	Low	1	3	0	0
Platelet Count	Low	0	0	0	0
	High	0	0	0	0
RBC Count	Low	0	0	0	0
	High	0	0	0	0
WBC Count	Low	0	0	0	0
	High	1	3	0	0
Neutrophils	Low	0	0	0	0
	High	0	0	0	0
Lymphocytes	Low	0	0	0	0
	High	0	0	0	0
Monocytes	High	1	3	0	0
Eosinophils	High	2	5	1	3
Basophils	High	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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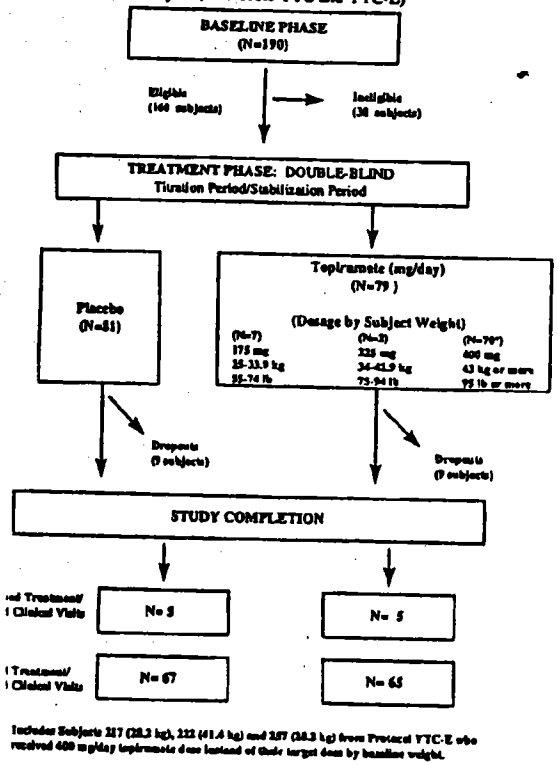
Figure 2: Study Completion and Withdrawal Summary
(All Subjects; Protocols YTC and YTC-E)



Includes Subjects 217 (28.2 kg), 222 (41.4 kg) and 257 (38.3 kg) from Protocol YTC-E who received 400 mg/day topiramate dose instead of their target dose by baseline weight.

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 Dosages (Duration)	Number of Subjects Entered in Each Group	Sex (M/F) Race[a]	Age (yr) Mean Range ≤16/>16
YTC Multicenter [19]	USA Costa Rica Complete (5 May 94)	Double-blind, placebo-controlled, adjunctive therapy; M/F; ≥4 years of age with uncontrolled primary generalized tonic-clonic seizures	Topiramate	39	24/15 32W/6B/1H	26.8 5 to 59 8/31
			175 mg	5		
			225 mg	1		
			400 mg	33		
			Placebo	41	21/20 36W/5B	25.6 3 to 50 13/28
			175 mg	6		
			225 mg	2		
			400 mg	33		
			(140 days)			
YTC-E Multicenter [20]	Europe and USA Complete (15 Sep 94)	Double-blind, placebo-controlled, adjunctive therapy; M/F; ≥4 years of age with uncontrolled primary generalized tonic-clonic seizures	Topiramate	40	17/23 39W/1B	29.2 7 to 60 9/31
			175 mg	2		
			225 mg	1		
			400 mg	37		
			Placebo	40	21/19 40W	29.1 12 to 46 2/38
			175 mg	1		
			225 mg	0		
			400 mg	39		
			(140 days)			

[a] W = White; B = Black; H = Hispanic

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

	Protocol YTC				Protocol YTC-E				YTC/YTC-E		
	Placebo (N=41)		Topiramate (N=39)		Placebo (N=40)		Topiramate (N=40)		Placebo (N=81)		Top (N
Reason	N	%	N	%	N	%	N	%	N	%	N
Limiting Adverse Event	1	2	1	3	7	18	5	13	8	10	6
Subject Choice	1	2	2	5	0	0	2	5	1	1	4
Lost to Follow-up[b]	1	2	0	0	1[c]	3	0	0	2	2	0
Other[b]	0	0	2	5	3	8	2	5	3	4	4
Total Discontinued	3	7	5	13	11	28	9	22	14	17	14
Total Completed	38	93	34	87	29	72	31	78	67	83	65

[a] 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 52 (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 in the placebo group and Subjects 39 (no PGTC seizures during baseline) and 236 (subject stopped taking all treatments and did not return to clinic) in the to group.

Age, Weight, Height, and Average Monthly Seizure Rate
(Randomized Subjects; Protocols YTC and YTC-E)

	Protocol YTC		Protocol YTC-E		YTC/YTC-E Combined	
	Placebo (N=41)	Topiramate (N=39)	Placebo (N=40)	Topiramate (N=40)	Placebo (N=81)	Topiramate (N=79)
yr)						
No. (%)	13 (32)	8 (21)	2 (5)	9 (23)	15 (19)	17 (22)
No. (%)	28 (68)	31 (79)	38 (95)	31 (77)	66 (81)	62 (78)
	25.6	26.8	29.1	29.2	27.3	28.0
	13.38	12.82	8.69	12.44	11.37	12.60
n	26.0	25.0	29.0	30.0	28.0	29.0
	3 to 50	5 to 59	12 to 46	7 to 60	3 to 50	5 to 60
ıt (kg)						
9; No. (%)	6 (15)	5 (13)	1 (3)	4 (10)	7 (9)	9 (11)
9; No. (%)	2 (5)	1 (3)	0 (0)	2 (5)	2 (2)	3 (4)
lo. (%)	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
n	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
	159.1	166.1	170.3	166.6	164.3	166.3
	19.44	17.21	8.83	17.15	16.29	17.04
	161.0	168.0	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
e Avg. 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 159.5	0.5 to 299.9	0.5 to 297.7
ures						
	2000.9	91.1	422.3	604.5	1221.4	351.0
	12347	214.7	1799	2880	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 10876.0	1.5 to 18232.0	1.0 to 79109.0	1.0 to 18232.0

[a] 28 days. Monthly rate based on prospective baseline data.

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

	Protocol YTC				Protocol YTC-E				YTC/YTC-E Combined			
	Placebo (N=41)		Topiramate (N=39)		Placebo (N=40)		Topiramate (N=40)		Placebo (N=81)		Topiramate (N=79)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Sex												
Male	21	51	24	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 AED[a]												
Valproic acid[b]	20	49	19	49	23	58	22	55	43	53	41	52
Carbamazepine	9	22	11	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	5	13	4	5	13	16
Lorazepam	3	7	4	10	2	5	5	13	5	6	9	11
Clonazepam	6	15	6	15	2	5	1	3	8	10	7	9
Gabapentin	3	7	5	13	4	10	4	10	7	9	9	11
Clobazam	0	0	0	0	1	3	4	10	1	1	4	5
Diazepam	4	10	3	8	0	0	1	3	4	5	4	5
Ethosuximide	3	7	1	3	1	3	3	8	4	5	4	5
Clorazepate dipotassium	1	2	3	8	0	0	0	0	1	1	3	4
Felbamate	2	5	2	5	0	0	0	0	2	2	2	3
Methylphenobarbital	2	5	0	0	0	0	2	5	2	2	2	3
Mephenytoin	0	0	1	3	0	0	0	0	0	0	1	1
Vigabatrin	0	0	0	0	1	3	1	3	1	1	1	1
Methsuximide	1	2	0	0	1	3	0	0	2	2	0	0
Primidone	6	15	0	0	2	5	0	0	8	10	0	0
One Background AED	9	22	9	23	11	27	9	23	20	25	18	23
Two Background AEDs	22	54	19	49	22	55	23	57	44	54	42	53
> Two Background AEDs	10	24	11	28	7	18	8	20	17	21	19	24
Baseline Seizure Type[c]												
Tonic-Clonic	40[d]	98	39	100	40	100	39[d]	98	80[d]	99	78[d]	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	19	15	19
Atypical absence	4	10	2	5	3	8	7	18	6	7	9	11
Drop attack	5	12	2	5	3	8	1	3	8	10	3	4
Other[e]	1	2	1	3	2	5	2	5	3	4	3	4
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	72	56	71

[a] Individual subjects may have received more than one background AED.
[b] Includes valproate semisodium.
[c] Individual subjects may have had a history of more than one seizure type.
[d] Subject 161 in Protocol YTC and Subject 39 in Protocol YTC-E did not experience a PGTC seizure during either the baseline or the double-blind phase.
[e] 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 prolonged/uncertain seizure types categorized as "other". Additional information for Subjects 60 and 225 (placebo) and Subject 235 (topiramate) was unavailable.

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

	Protocol YTC			Protocol YTC-E			YTC/YTC-E Combined		
ment	N	Median	Range	N	Median	Range	N	Median	Range
ge Daily Dosage (mg/kg/day)[1]									
o[2]	41	4.3	0.6 to 7.3	40	3.3	0.5 to 5.7	81	3.7	0.5 to 7.3
imate	39	3.7	1.3 to 6.3	40	3.6	0.6 to 10.7[3]	79	3.7	0.6 to 10.7[3]
mum Daily Dosage (mg/kg/day)[4]									
o[2]	41	6.3	0.6 to 9.3	40	4.8	0.5 to 7.9	81	5.3	0.5 to 9.3
imate	39	5.3	2.1 to 8.5	40	5.2	0.6 to 14.2[3]	79	5.3	0.6 to 14.2[3]

ect's average dosage (mg/kg) over the entire double-blind phase.
ts based on administration of "25 mg" and "100 mg" placebo tablets that matched topiramate tablets.
subjects (Subjects 14, 24, 217, 222, and 257) in the topiramate group received greater than the protocol-specified based on their baseline weight.
ect's 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)

	Protocol YTC			Protocol YTC-E			YTC/YTC-E Combined		
ment	N	Median	Range	N	Median	Range	N	Median	Range
ge Daily Dosage (mg/kg/day)[1]									
o[2]	39	5.9	3.0 to 9.1	37	4.9	0.9 to 7.6	76	5.3	0.9 to 9.1
imate	38	5.1	1.7 to 8.5	38	5.1	0.8 to 14.0[3]	76	5.1	0.8 to 14.0[3]
mum Daily Dosage (mg/kg/day)[4]									
o[2]	39	6.3	3.1 to 9.3	37	4.9	1.5 to 7.9	76	5.4	1.5 to 9.3
imate	38	5.3	2.1 to 8.5	38	5.3	0.8 to 14.2[3]	76	5.3	0.8 to 14.2[3]

ect's average dosage (mg/kg per day) over the stabilization period.
ts based on administration of "25 mg" and "100 mg" placebo tablets that matched topiramate tablets.
subjects (Subjects 14, 24, 217, 222, and 257) in the topiramate group received greater than the protocol-specified based on their baseline weight.
ect's maximum dosage (mg/kg per day) over the stabilization period.

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

		Number Randomized to Double-Blind Study Drug			
		Topiramate (mg/day by weight category)			
Number Enrolled in Baseline Phase	Placebo	175 (25 - 33.9 kg)	225 (34 - 42.9 kg)	400 (≥ 43 kg)	Overall
103	41	5	1	33	90
87	40	2	1	37	80
190	81	7	2	70	160

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

	Protocol YTC			Protocol YTC-E			YTC/YTC-E Comb		
Treatment Group Target Dose	N	Median	Range	N	Median	Range	N	Median	Range
Placebo[1]									
175 mg/day	6	174.0	146.2 to 175.0	1	174.7	--	7	174.7	146.2 t
225 mg/day	2	203.8	182.7 to 225.0	0	--	--	2	203.8	182.7 t
400 mg/day	31	398.8	298.2 to 400.0	36	388.9	60.0 to 400.0	67	392.4	60.0 to
Topiramate									
175 mg/day	4	174.3	173.0 to 175.0	2	174.9	174.7 to 175.0	6	174.9	173.0 t
225 mg/day	1	225.0	--	1	224.1	--	2	224.5	224.1 t
400 mg/day	33	393.8	155.7 to 400.0	35[2]	388.5	50.0 to 475.3[3]	68	389.8[2]	50.0 to

[1] Results based on administration of "25 mg" and "100 mg" placebo tablets that matched topiramate tablets.
[2] Three subjects (Subjects 217, 222, 257) in the topiramate group whose weights were <43 kg were assigned a 400 mg/day target dosage.
[3] 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)

	Protocol YTC[a]				Protocol YTC-E[a]				YTC/YTC-E Combined[a]			
Double-Blind Therapy	Placebo (N=41)		Topiramate (N=39)		Placebo (N=40)		Topiramate (N=40)		Placebo (N=81)		Topiramate (N=79)	
(Days)	N	%	N	%	N	%	N	%	N	%	N	%
1 to 133	5	12	6	15	9	23	9	23	14	17	15	19
134 to 140	11	27	8	21	6	15	6	15	17	21	14	18
141 to 147	12	29	13	33	13	32	15	38	25	31	28	35
148 to 154	8	20	7	18	7	18	5	12	15	19	12	15
≥155	5	12	5	13	5	12	5	12	10	12	10	13
Mean (SD)	138.8 (29.30)		139.9 (25.42)		128.4 (39.97)		129.3 (36.90)		133.6 (35.15)		134.5 (31.00)	
Median	141.0		142.0		141.0		141.0		141.0		141.0	
Range	1 to 176		48 to 197		4 to 176		24 to 169		1 to 176		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 trials

Table 9: Treatment Responders[1] for the Double-Blind Phase Based on PGTC Seizures
(All Randomized Subjects With PGTC Seizures; Protocols YTC and YTC-E)

	Protocol YTC			Protocol YTC-E			YTC/YTC-E Combined		
		Treatment Responders			Treatment Responders			Treatment Responders	
Treatment	N	No.	%	N	No.	%	N	No.	%
Placebo	40	8	20	40	14	35	80	22	28
Topiramate	39	22	56	39	21	54	78	43	55
p-value		0.001[2]			0.102[3]			0.001[4]	
		<0.001[5]			0.016[6]			<0.001[5]	

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

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

	Protocol YTC		Protocol YTC-E		YTC/YTC-E Combined	
Percent Reduction	Placebo (N=40)	Topiramate (N=39)	Placebo (N=40)	Topiramate (N=39)	Placebo (N=80)	Topiramate (N=78)
100	5	13	10	8	8	10
≥75	13	33	15	36	14	35
≥50	20	56	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

[a] 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[a] - Completer Analysis
(All Subjects With PGTC Seizures Who Completed Double-Blind Therapy; Protocols YTC and YTC-E)

	Protocol YTC			Protocol YTC-E			YTC/YTC-E Combined		
ment	N	Median	25th to 75th Percentile	N	Median	25th to 75th Percentile	N	Median	25th to 75th Percentile
bo	37	9.3	-28.1 to 46.4	29	33.8	12.5 to 61.8	66	27.1	-12.5 to 49.8
amate	34	64.2	-3.7 to 85.6	31	60.0	21.0 to 86.8	65	60.7	10.9 to 85.6
lue			0.003[b]			0.094[b]			0.002[c]
			0.005[d]			0.059[d]			0.001[e]

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

Table 12: Treatment Responders[a] 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)

	Protocol YTC			Protocol YTC-E			YTC/YTC-E Combined		
		Treatment Responders			Treatment Responders			Treatment Responders	
Treatment	N	No.	%	N	No.	%	N	No.	%
Placebo	37	7	19	29	9	31	66	16	24
Topiramate	34	21	62	31	16	52	65	37	57
p-value		<0.001[b]			0.084[b]			<0.001[b]	
		<0.001[c]			0.017[d]			<0.001[d]	

[a] Subjects with 50% or greater reduction from baseline.
[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.
[d] 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[a] Based on All Seizures
(All Randomized Subjects; Protocols YTC and YTC-E)

	Protocol YTC			Protocol YTC-E			YTC/YT	
Treatment	N	Median	25th to 75th Percentile	N	Median	25th to 75th Percentile	N	Median
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[b]		

[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 protocol) ANOVA on ranks.

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

	Protocol YTC			Protocol YTC-E			YTC/YTC-E Co	
		Treatment Responders			Treatment Responders			Treatr Respon
Treatment Group	N	No.	%	N	No.	%	N	No.
Placebo	41	7	17	40	8	20	81	15
Topiramate	39	18	46	40	16	40	79	34
p-value		0.003[b]			0.061[b]			0.001[c]

[a] Subjects with 50% or greater reduction from baseline.
[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[a]
(All Randomized Subjects; Protocols YTC and YTC-E)

	Protocol YTC		Protocol YTC-E		YTC/YTC-E Combined	
Percent Reduction	Placebo (N=41)	Topiramate (N=39)	Placebo (N=40)	Topiramate (N=40)	Placebo (N=81)	Topiramate (N=79)
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

[a] Tabulated numbers are percent of subjects in treatment group.

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

	Protocol YTC		Protocol YTC-E		YTC/YTC-E Combined	
Seizure Type	Placebo	Topiramate	Placebo	Topiramate	Placebo	Topiramate
Absence	4.1 (N=17)	52.8 (N=18)	-16.1 (N=24)	-6.6 (N=17)	-10.9 (N=41)	-3.4 (N=35)
Myoclonic	-401.2 (N=14)	51.8 (N=9)	5.5 (N=14)	15.2 (N=15)	-15.3 (N=28)	39.5 (N=24)
Tonic	-1.0 (N=10)	28.0 (N=9)	-55.2 (N=7)	76.7 (N=8)	-20.9 (N=17)	49.3 (N=17)

[a] Efficacy summaries by seizure type are based specific generalized seizure types experienced by subjects at any time during the trial.

Table 19: Global Evaluation of Improvement in Seizure Severity
(All Randomized Subjects; Protocols YTC and YTC-E)

Improvement Rating (Score)	Protocol YTC Placebo (N=41) N	%	Protocol YTC Topiramate (N=39) N	%	Protocol YTC-E Placebo (N=40) N	%	Protocol YTC-E Topiramate (N=40) N	%	Overall Placebo (N=81) N	%	Overall Topiramate (N=79) N	%
Worse (0)	4	10	3	8	3	8	4	10	7	9	7	9
None (1)	12	29	11	28	20	50	14	35	32	40	25	32
Minimal (2)	8	20	7	18	8	20	0	0	16	20	7	9
Moderate (3)	12	29	9	23	5	13	6	15	17	21	15	19
Marked (4)	3	7	8	21	0	0	13	33	3	4	21	27
Not Assessed	2	5	1	3	4	10	3	8	6	7	4	5
p-value			0.490[a]				0.026[a]				0.020[a]	
			0.388[b]				0.024[b]				0.017[b]	

[a] Wilcoxon rank-sum test stratified by center.
[b] Wilcoxon rank-sum test unstratified.

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 Placebo (N=38) N	%	Protocol YTC Topiramate (N=34) N	%	Protocol YTC-E Placebo (N=29) N	%	Protocol YTC-E Topiramate (N=31) N	%	YTC/YTC-E Combined Placebo (N=67) N	%	YTC/YTC-E Combined Topiramate (N=65) N	%
Worse (0)	4	11	3	9	3	10	2	6	7	10	5	8
None (1)	12	32	8	24	14	48	11	35	26	39	19	29
Minimal (2)	8	21	7	21	7	24	0	0	15	22	7	11
Moderate (3)	11	29	8	24	4	14	5	16	15	22	13	20
Marked (4)	3	8	8	24	0	0	12	39	3	4	20	31
Not Assessed	0	0	0	0	1	3	1	3	1	1	1	2
p-value			0.259[a]				0.009[a]				0.005[a]	
			0.212[b]				0.009[b]				0.005[b]	

[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 No. of Subjects PL	TPM	PGTC Seizures Median % Seizure Rate Reduction PL	TPM	PGTC Seizures Percent Responder[a] PL	TPM	All Seizures No. of Subjects PL	TPM	All Seizures Median % Seizure Rate Reduction PL	TPM	All Seizures Percent Responder[a] PL	TPM
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 No. of Subjects PL	TPM	Protocol YTC Median % Seizure Rate Reduction PL	TPM	Protocol YTC Percent Responders[a] PL	TPM	Protocol YTC-E No. of Subjects PL	TPM	Protocol YTC-E Median % Seizure Rate Reduction PL	TPM	Protocol YTC-E Percent Responders[a] PL	TPM	Protocols YTC and YTC-E Combined No. of Subjects PL	TPM	Protocols YTC and YTC-E Combined Median % Seizure Rate Reduction PL	TPM	Protocols YTC and YTC-E Combined Percent Responders[a] PL	TPM
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