CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-505/S-002
20-844/S-010

CLINICAL PHARMACOLOGY BIOPHARMACEUTICS REVIEW

JUN 3 1998

Topamax™ (topiramate)
NDA 20-505
(S001, S002, S003)
Submission Date: July 31, 1997
Reviewer: Iftekhar Mahmood, Ph. D.

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TOPAMAX (topiramate) Tablets were approved on December 24, 1996 for the adjunctive treatment for adults with partial onset seizures. The Sponsor RW Johnson plan to market topiramate for 3 new treatment indications: partial onset seizures in children, Lennox-gastaut syndrome, and generalized tonic-clonic seizures. In support of these 3 new indications, four randomized, placebo-controlled, double blind studies were conducted to evaluate the safety and efficacy of topiramate. Topiramate is available as 25, 50, 100, 200, and 300 mg tablets.

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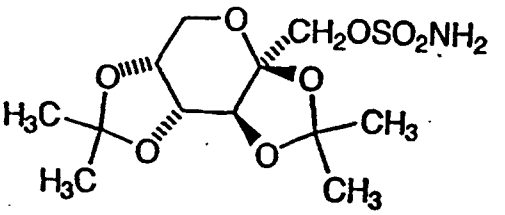
Summary of Topiramate Pharmacokinetics (previous Tablet NDA)



Topamax™ (topiramate) is a chemical compound classified as a sulfamate-substituted monosaccharide, claimed by the Sponsor to be an antiepileptic. Chemically Topamax is designated as 2, 3:4,5-bis-O-(1-methylethylidene)-b-D-fructopyranose sulfamate.

Topiramate is rapidly and well-absorbed after oral administration. Following 400 mg multiple oral dosing every 12 hours, peak plasma concentration of 27 µg/mL is reached in about two hours. There is no effect of food on the bioavailability of topiramate. The volume of distribution of topiramate following 100 to 1200 mg oral dose ranged from 0.55 l/kg to 0.8 l/kg. Plasma protein binding of topiramate is about 17 percent. Topiramate is not extensively metabolized. At least six minor inactive metabolites formed through hydroxylation or hydrolysis of the isopropylidene groups and glucuronidation have been identified from plasma and urine of humans. About 70% of the dose of topiramate is excreted unchanged in human urine. The mean elimination half-life of topiramate in humans is approximately 21 hrs. Oral clearance is approximately 29 ml/min in humans following oral administration. Clearance of topiramate is not affected by age (18-67 years), gender or race. The mean renal clearance of topiramate is 14 ml/min. Multiple q 12h dosing of 50 and 100 mg doses of topiramate for at least 14 days results in topiramate C_{max} and AUC values that increased in a linear and dose-proportional manner.

The pharmacokinetics of topiramate is affected by renal impairment. Oral clearance decreased by 56% in the severe group (creatinine clearance <30 ml/min/1.73m^2) and by 46% in the moderate group (creatinine clearance 30-69 ml/min/1.73m^2) as compared to normals. Topiramate is effectively removed from the plasma by hemodialysis.

In three multicenter clinical studies designed to compare the safety and efficacy of different doses of topiramate (200-1000 mg/day) in patients with refractory partial epilepsy, the median percent reduction in seizure rate increases with increasing plasma topiramate concentrations up to 5.2 µg/mL. At plasma topiramate concentrations above 5.2 µg/mL, a decrease from the peak seizure rate reduction is observed.

Summary of the Present NDA

In this NDA the main objective of the Sponsor is to evaluate the safety and efficacy of topamax tablets for the treatment of partial onset seizures in children, Lennox-gastaut syndrome, and generalized tonic-clonic seizures. The Sponsor has submitted 3 studies. A pharmacokinetic and pharmacodynamic study which relates the plasma concentration and 50% reduction in seizure in the group of patients with partial onset seizures (in children), Lennox-gastaut syndrome, and generalized tonic-clonic seizures. The results of this study indicate that median percent reduction and percent responders were greatest in the mid-range plasma topiramate concentrations $\geq$3.2 to $\leq$5.4 µg/mL. There was no correlation between percent reduction in the average monthly partial onset seizure rate and plasma topiramate concentration or the average monthly seizure rate for all seizures (Study #1).

The remaining 2 studies deal with the bioequivalence studies which were submitted in the original NDA and were reviewed (Studies #2&3). A study describing the pharmacokinetics of topamax in children was also reviewed but has not been submitted in this NDA. For the benefit of the reader the pharmacokintics of topamax in children has also been included in this review (Study #4)

Labelling Comments

The Sponsor is requested to make following changes in their labelling:

1. Under **Pediatric Pharmacokinetics please add:**

2. Under **Oral Contraceptive Pharmacokinetics please add:**

Recommendation:

From a pharmacokinetic point of view this NDA is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. The Sponsor is requested to incorporate all the 'Labelling' changes.

Please convey the Labelling Comments to the Sponsor.

Iftekhar Mahmood, Ph.D. 1S1

RD/FT initialed by Chandra Sahajwalla, Ph.D._ 1S1

Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

CPB Briefing: June 2, 1998

CC: NDA 20-505, HFD-120, HFD-860 (Mahmood, Sahajwalla, Malinowski), HFD-340 (Viswanathan), CDR (Barbara Murphy) and FOI (HFD-19) files.

Study # 1

Study #1: Pharmacokinetic and Pharmacodynamic Relationships:

Pediatric partial onset seizures (Protocol YP):

This was a multicenter, randomized, double-blind, placebo-controlled trial to compare the safety and efficacy of different topiramate doses in pediatric patients with partial onset seizures with or without secondary generalized seizures. Total daily doses of 125 mg, 175 mg, 225 mg, and 400 mg based on subject's body weight to approximate a dosage of 6 mg/kg per day as adjunctive therapy were given to 86 subjects. As part of inclusion criteria, subjects were required to have at least six partial onset seizures during the baseline phase, with at least one partial onset seizure occuring during each 28-day period, while being maintained on a stable regimen of one or two standard AEDs. The double-blind phase consisted of a 56-day titration period and a 56-day stabilization period. Blood samples for determination of topiramate plasma concentrations were obtained on days1, 15, and 29 of the titration period and on days 43, 57, 85, and 113 of the stabilization period. Concentrations of topiramate were determined by a validated capillary gas chromatography method.

Percent reduction in seizure rate was defined as:

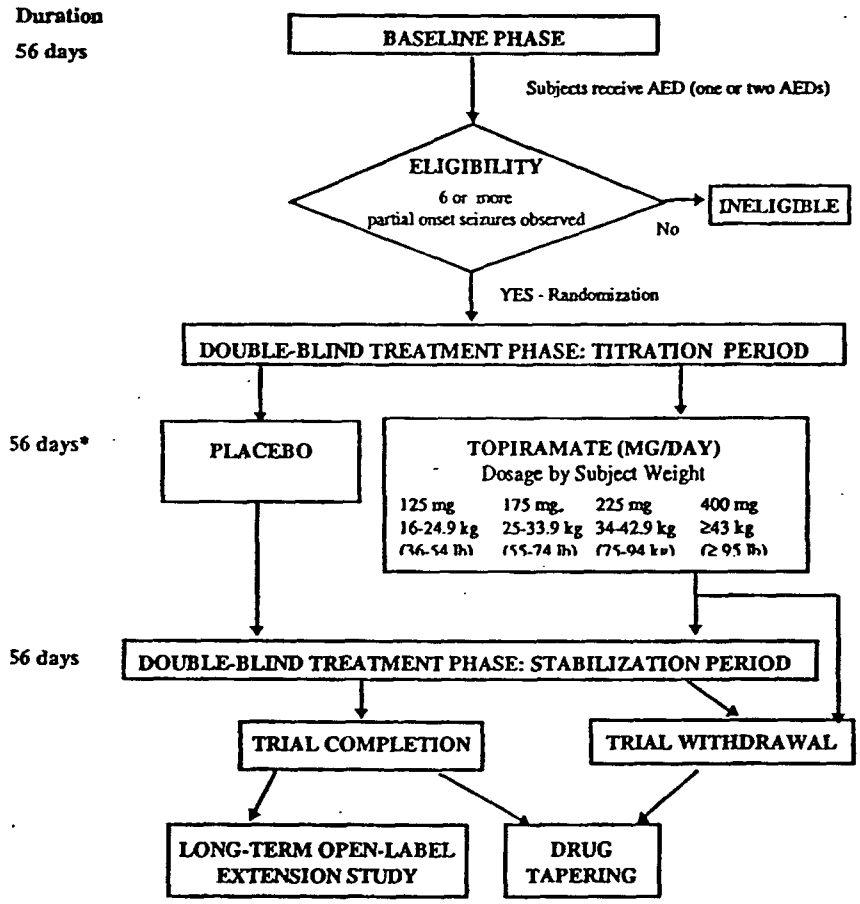
$$\text{Seizure rate} = 100*(B-S)/B$$

Where B = baseline seizure rate and S= stabilization period seizure rate.

The average monthly seizure rate for a time period was calculated as the total number of seizures reported during the period divided by the number of days in the period multiplied by 28. The baseline seizure rate was calculated as the average monthly seizure rate for the pretreatment period. The subjects were declared responders if there was a 50% or greater reduction in seizure frequency. The stabilization seizure rate was defined for each subject as the average monthly seizure rate over the portion of the stabilization period completed by that subject. The percent reduction in seizure rate was plotted against the mean plasma topiramate concentration. Kendall's correlation coefficients for these two variables were calculated for all subjects and for males and females separately.

The mean plasma concentration of topiramate for the entire period of the trial was 3.6 ± 1.98 µg/mL. Median percent reduction and percent responders were greatest in the mid-range plasma topiramate concentrations stratum ≥ 3.2 to ≤ 5.4 µg/mL. There was no correlation between percent reduction in the average monthly partial onset seizure rate and plasma topiramate concentration ($\tau_b = 0.067$, $p= 0.537$) or the average monthly seizure rate for all seizures ($\tau_b = 0.082$, $p= 0.452$).

Figure 6: Study Design for Protocol YP



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

Table 20: Changes in Plasma Concentrations of Concomitant AEDs From the Baseline Phase to the Double-Blind Phase (Randomized Subjects With Available Data; Protocol YP)

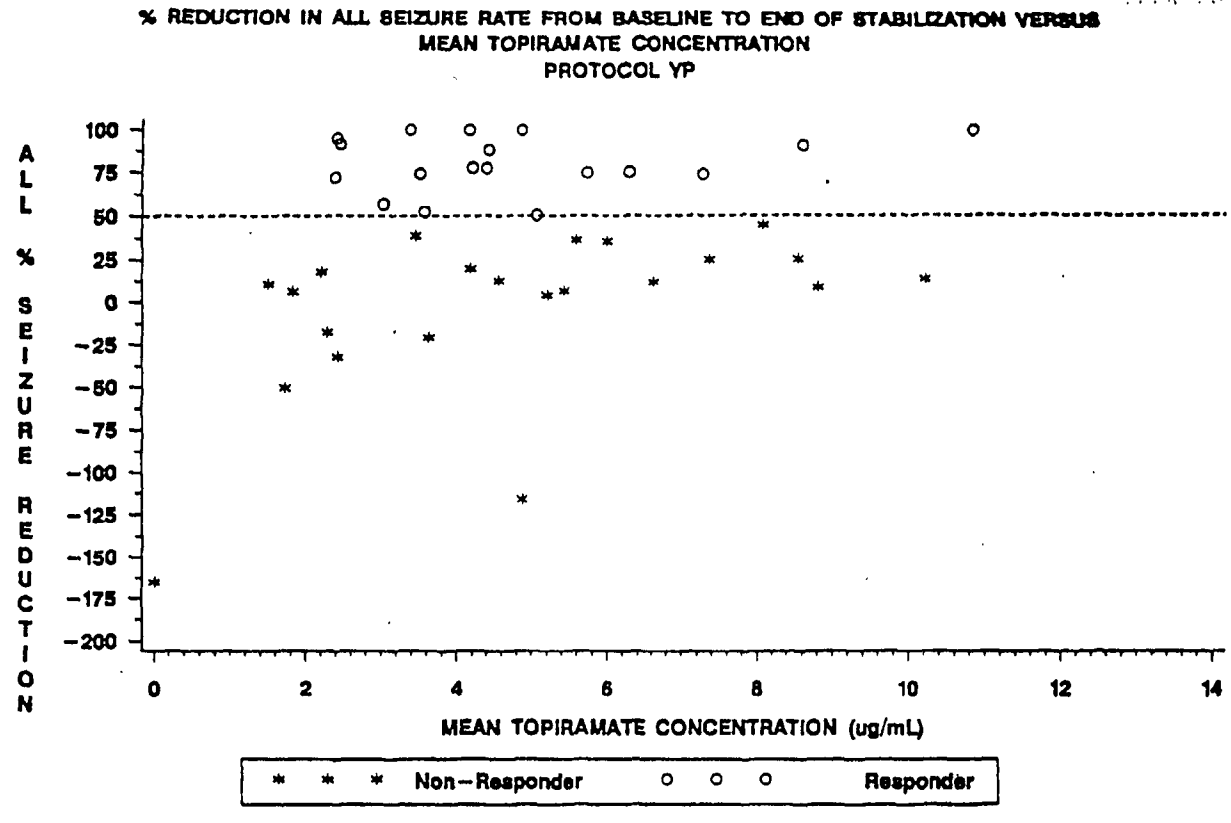
	Placebo						Topiramate						
		Baseline Mean (SD)			Mean Change (SD)			Baseline Mean (SD)			Mean Change (SD)		
Concomitant AED	N	(μg/mL)		N	(μg/mL)		N	(μg/mL)		N	(μg/mL)		p-value*
Carbamazepine	26	9.3	(2.49)	25	-0.3	(1.60)	25	8.9	(2.46)	25	-0.8	(2.18)	0.428
Valproic Acid	12	75.6	(40.34)	10	-4.2	(16.28)	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

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

Table 21: Percent 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

Percent Reduction in All Seizure Rate from Baseline to End of Stabilization Versus Mean Topiramate Concentration - Protocol YP



One subject with Topiramate concentration of 8.1 and % seizure reduction of −586 was not presented.

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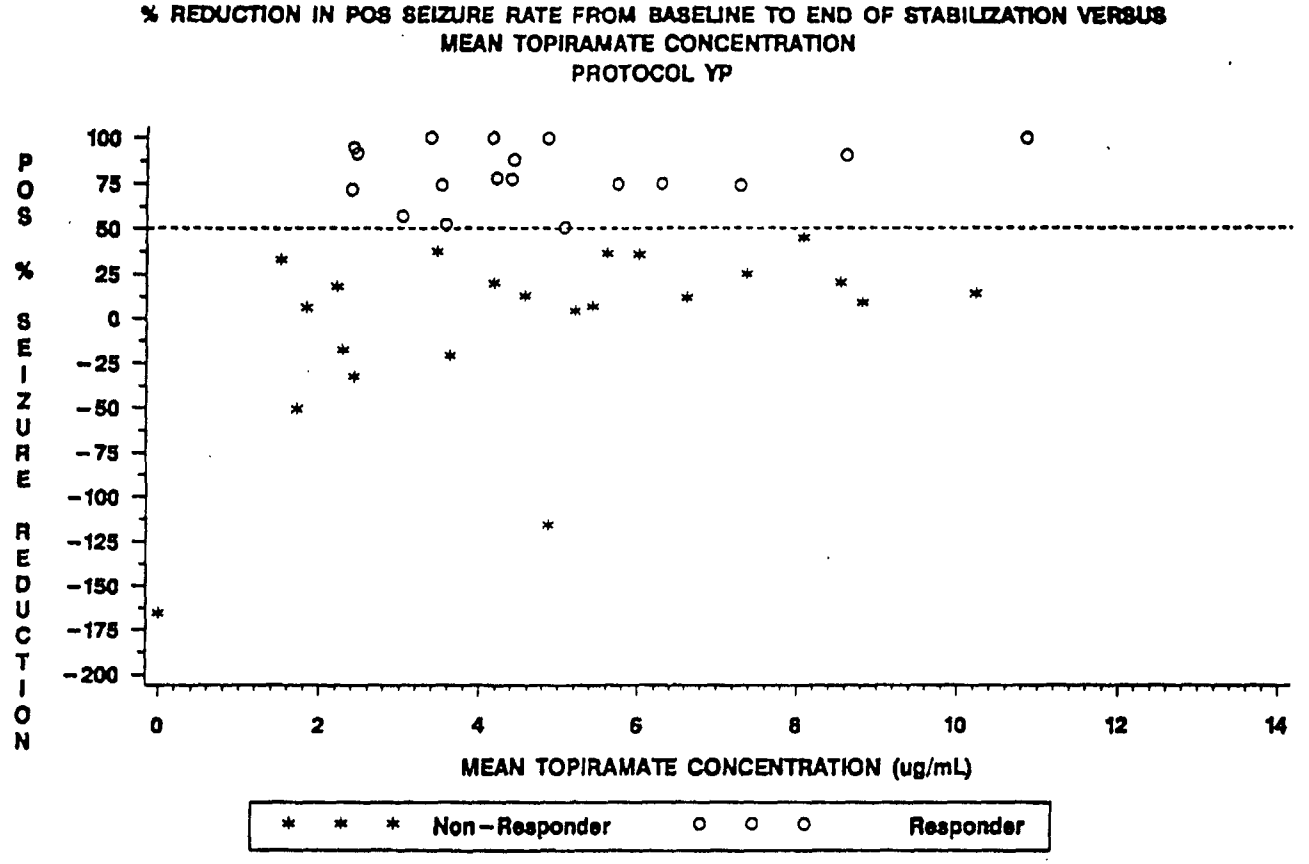
Appendix 5.1

Percent Reduction in POS Seizure Rate from Baseline to End of Stabilization Versus Mean Topiramate Concentration - **Protocol YP**



One subject with Topiramate concentration of 8.1 and % seizure reduction of −586 was not presented.

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Lennox-Gastaut Syndrome in adults and children (Protocol YL):

This was a multicenter, randomized, double-blind, placebo-controlled trial to compare the safety and efficacy of topiramate doses in patients with Lennox-Gastaut Syndrome (n =98). There were 40 children and 8 adults in topamax treated group. Total daily dose was 6 mg/kg (maximum of 600 mg daily)as an adjunct. As part of inclusion criteria, subjects were required to have at least 60 seizures during the month before entering baseline phase, while being maintained on a stable regimen of one or two standard AEDs. The trial included a baseline phase (4 weeks) and a double blind treatment phase (11 weeks). Blood samples for determination of topiramate plasma concentrations were obtained on days 1, 2, and 3 of the titration period and on days 4, 5, and 6 of the maintenance period. The percent reduction in seizure rate was plotted against the steady state topiramate plasma concentration. Kendall's correlation coefficients for these two variables were calculated for all subjects and for males and females separately.

The mean plasma concentration of topiramate for the entire period of the trial was 4.0 ± 2.23 μg/mL. There was no correlation between percent reduction in seizure rate and plasma topiramate concentration.

Figure 7: Study Design for Protocol YL

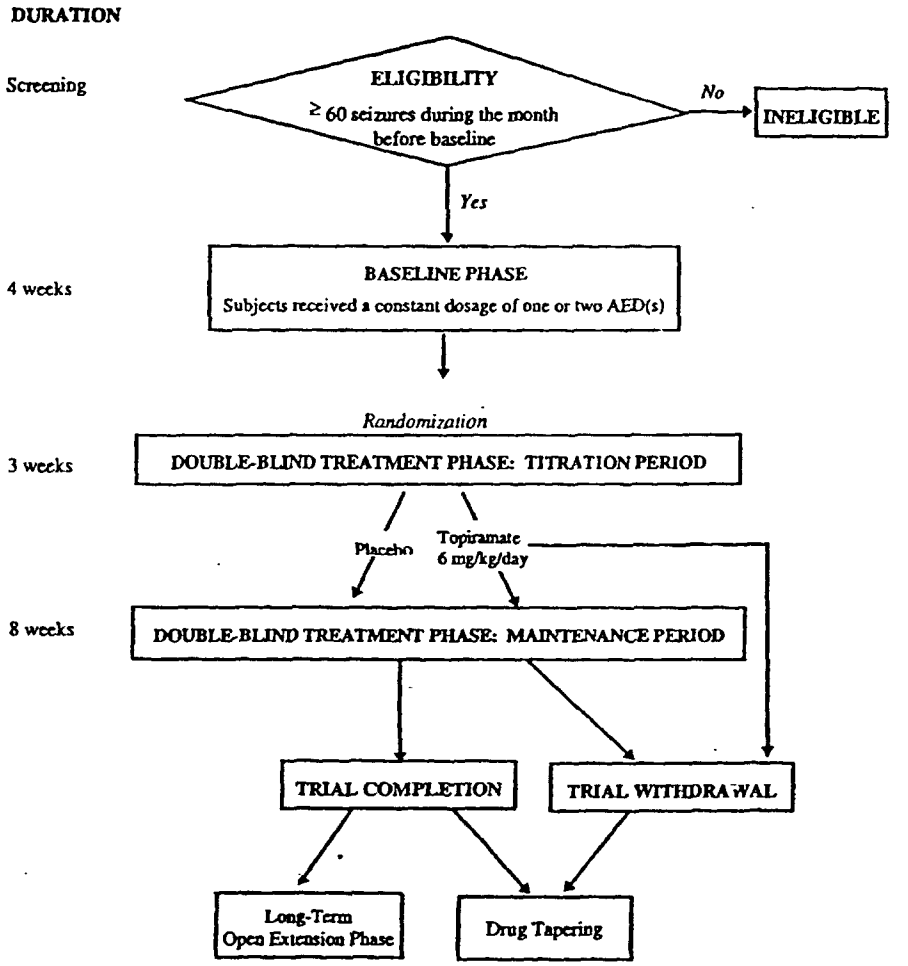


Table 22: Changes in Plasma Concentrations of Concomitant AEDs from the Baseline Phase to the Double-Blind Phase
(Randomized Subjects With Available Data; Protocol YL)

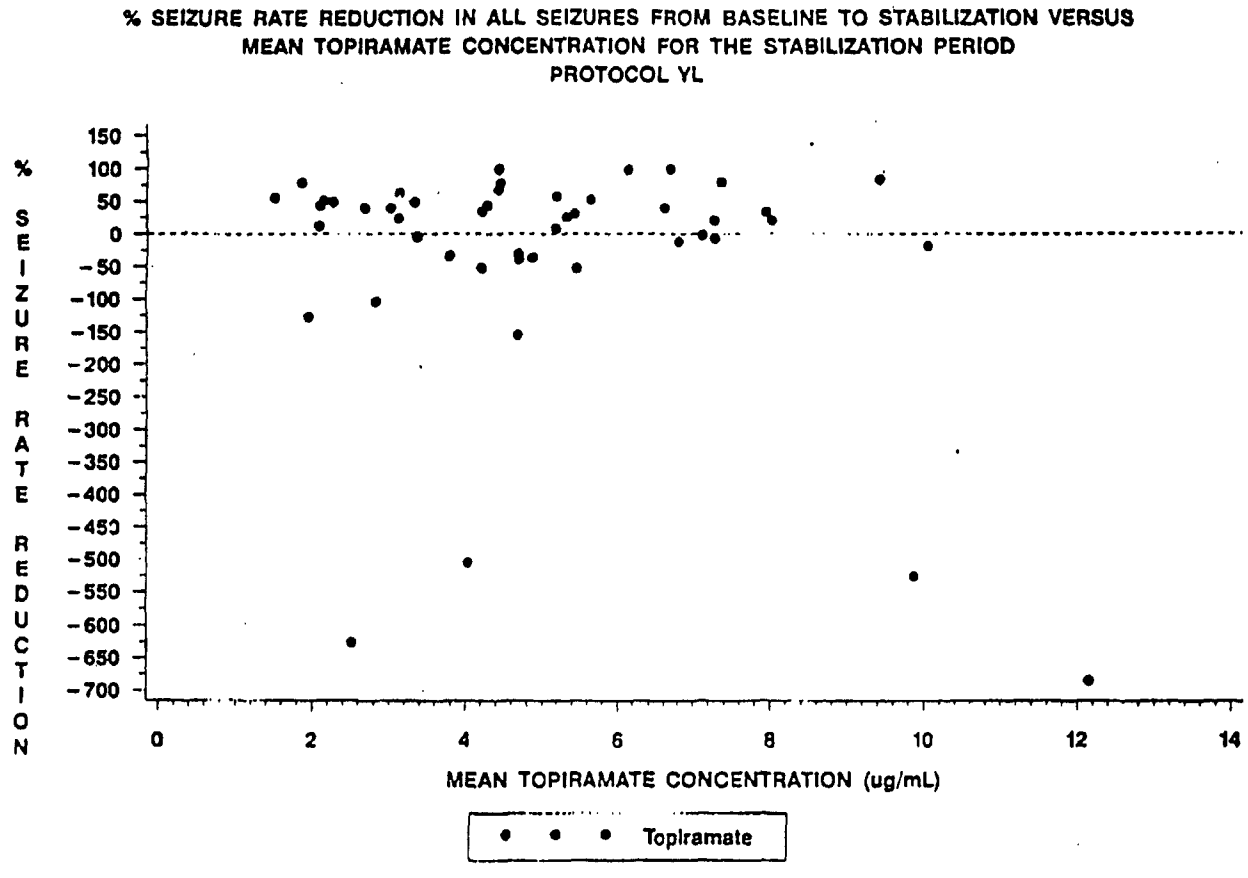
	Placebo				Topiramate				
Concomitant AED	N	Baseline Mean (SD) (µg/mL)	N	Mean Change (SD) (µg/mL)	N	Baseline Mean (SD) (µg/mL)	N	Mean Change (SD) (µg/mL)	P-value*
Valproic acid	35	100.8 (33.77)	35	-0.7 (25.79)	33	106.1(35.78)	32	-4.6 (15.83)	0.466
Phenytoin	9	13.3 (8.46)	8	-1.5 (2.69)	11	12.2 (5.86)	11	-0.1 (4.35)	0.429
Lamotrigine	8	8.5 (3.93)	8	0.9 (2.24)	8	5.4 (4.80)	7	-1.6 (3.25)	0.115
Felbamate	7	81.3 (30.76)	7	-2.4 (6.86)	6	63.6 (26.62)	6	5.7 (10.78)	0.131
Clonazepam	9	20.2 (20.10)	7	-0.8 (5.46)	7	24.8 (18.40)	6	-9.1 (10.74)	0.101
Carbamazepine	5	8.3 (4.70)	3	0.6 (1.55)	8	7.9 (2.88)	8	-0.7 (0.77)	0.102

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

Table 23: Percent Seizure Rate Reduction and Percent Treatment Responders by Plasma Topiramate Concentration Stratum
(All Available Plasma Samples During Maintenance; Protocol YL)

Seizure Type Plasma Topiramate Stratum (µg/mL)	N	Median Percent Reduction	Responders No.	Responders %
All Seizures				
< 3.80	16	39.5	4	25
3.80 to < 5.66	16	16.9	4	25
≥ 5.66	16	20.5	5	31
Drop Attacks (Tonic-Atonic Seizures)				
< 3.80	14	34.5	4	29
3.80 to < 5.66	16	22.1	4	25
≥ 5.66	16	26.7	6	38

Plot of Percent Seizure Rate Reduction for All Seizures from Baseline to Stabilization Versus Mean Topiramate Concentration for the Stabilization Period - Protocol YL



Primary Generalized Tonic-Clonic seizures in adults and children

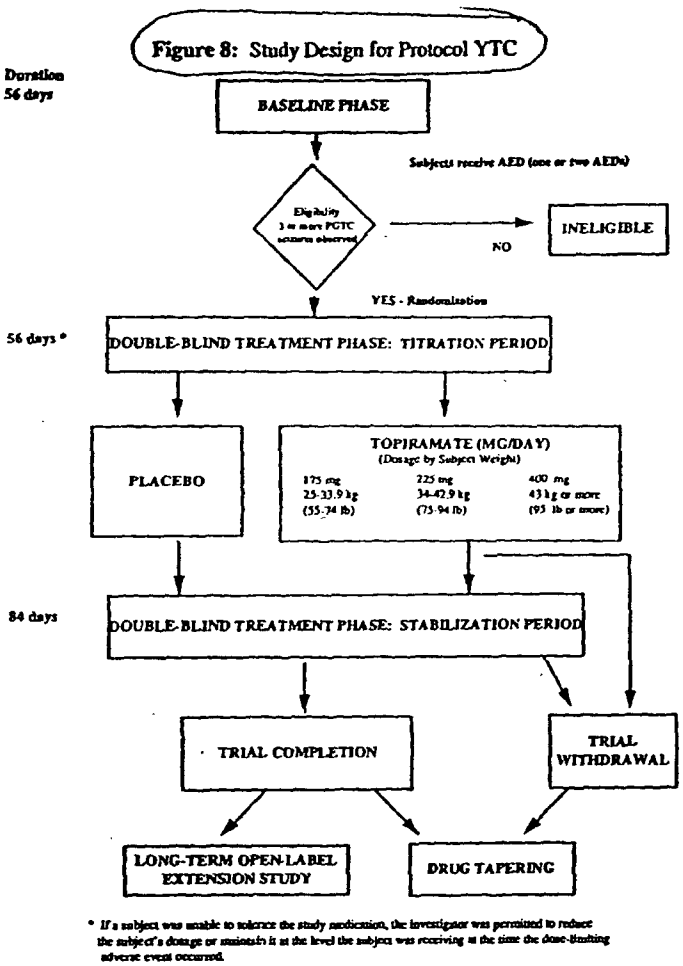
(Protocols YTC and YTC-E):

Protocol YTC:

This was a multicenter, randomized, double-blind, placebo-controlled trial to compare the safety and efficacy of different topiramate doses as adjunctive therapy in patients with Primary Generalized Tonic-Clonic (PGTC) seizures with or without other generalized seizure subtypes. Total daily doses of 175 mg, 225 mg, and 400 mg based on subject's body weight to approximate a dosage of 6 mg/kg per day as adjunctive therapy were given to 72 subjects. As part of inclusion criteria, subjects were required to have at least 3 PGTC seizures during the baseline phase, with at least one PGTC seizure occuring during each 28-day period, while being maintained on a stable regimen of one or two standard AEDs. The titration period consisted of an initial 28-day interval and two 14-day intervals and a 84-day stabilization period. Blood samples for determination of topiramate plasma concentrations were obtained on days 1, 29, and 43 of the titration period and on days 57, 85, 113 and 141 of the stabilization period. The percent reduction in PGTC seizure rate was plotted against the mean plasma topiramate concentration. Kendall's correlation coefficients for these two variables were calculated for all subjects.

The mean plasma concentration of topiramate for the entire period of the trial was 5.1 ± 2.51 µg/mL. There was no significant correlation ($\tau_b = 0.189$, $p = 0.118$) between percent reduction in the average monthly PGTC seizure rate and plasma topiramate concentration. There was a significant but weak correlation between percent reduction in the average monthly seizure rate based on all seizures and plasma topiramate concentration ($\tau_b = 0.257$, $p = 0.032$).

A diagrammatic representation of the study design is presented in Figure 8.



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

Table 24: Changes in Plasma Concentrations of Concomitant AEDs From the Baseline Phase to the Double-Blind Phase
(Randomized Subjects With Available Data: Protocol YTC)

	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]
Valproic Acid	20	94.2 (28.94)	20	0.4 (16.05)	20	96.4 (40.20)	19	-1.5 (14.11)	0.696
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	1.2 (7.36)	9	21.0 (11.83)	7	-3.4 (8.02)	0.294

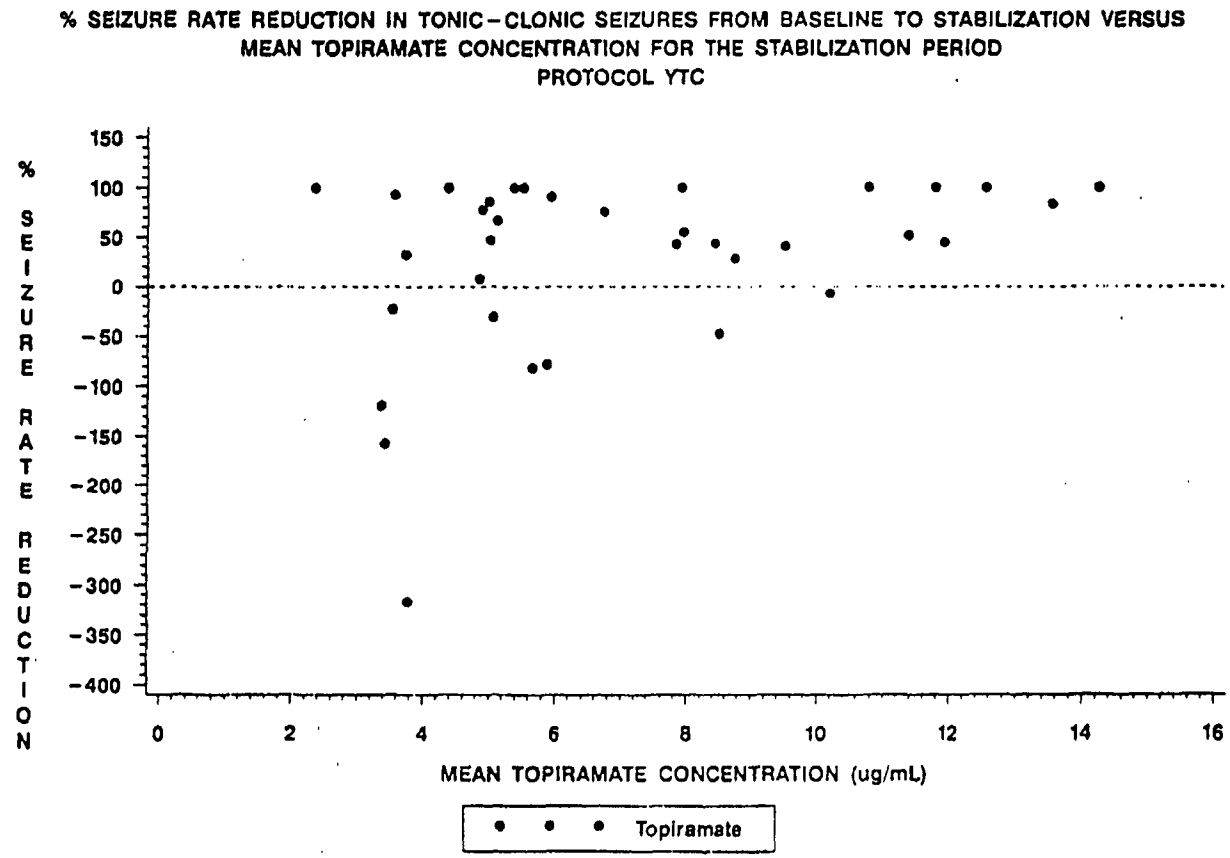
[a] One-way ANOVA comparing topiramate with placebo with respect to mean change from baseline.

Table 25: 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.	Responders %
PGTC Seizures				
<5.04 µg/Ml	12	39.5	5	42
5.04 to <8.46 µg/mL	12	60.8	7	58
≥8.46 µg/Ml	11	51.5	6	55
All Seizures				
<5.04 µg/mL	12	2.9	4	33
5.04 to <8.46 µg/mL	12	59.0	7	58
≥8.46 µg/Ml	11	51.5	7	64

Appendix 15.2

Plot of Percent Seizure Rate Reduction for PGTC Seizures Versus Mean Plasma Topiramate Concentration - Protocol YTC



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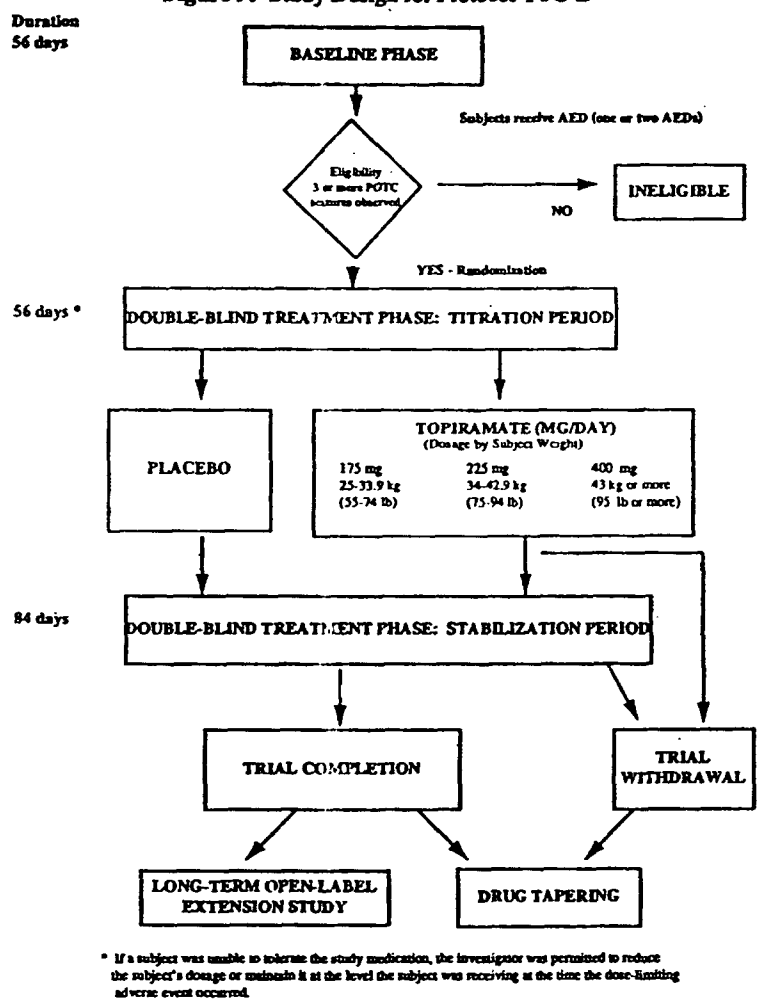
Protocol YTC-E:

This trial was conducted in Europe and the USA whereas Protocol YTC was conducted in Costa Rica and the USA. The design and sample size of protocol YTC-E is similar to protocol YTC. No significant correlation between percent reduction in the average monthly PGTC seizure rate ($\tau_b = 0.113$, p= 0.382) or in all seizure rate ($\tau_b = 0.140$, p= 0.263) and plasma topiramate concentration was found.

The combined data analysis from protocols YTC and YTC-E indicated that except for the weak but statistically significant correlation between plasma topiramate concentration and efficacy in the <16 year old group (PGTC and all seizures) and among females (all seizures), no other statistically significant correlation were found.

Figure 9: Study Design for Protocol YTC-E



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

Table 26: 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	-0.20 (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 27: Percent Seizure Rate Reduction and Treatment Responders by Plasma Topiramate Concentration Stratum
(All Available Plasma Samples During Stabilization; Protocol YTC-E)

	Median Reduction		Treatment Responders	
Seizure Type/ Plasma Topiramate Stratum	N	Reduction %	N	%
PGTC Seizures				
<5.01 μg/mL	9	25.1	4	44
≥5.01 to <9.67 μg/mL	11	68.5	8	73
≥9.67 μg/mL	11	35.3	4	36
All seizures				
<5.01 μg/mL	10	24.6	4	40
≥5.01 to <9.67 μg/mL	11	50.0	6	55
≥9.67 μg/mL	11	40.0	5	45

Appendix 19.2

Plot of Percent Reduction in Tonic-Clonic Seizure Rate from Baseline to Stabilization Versus Mean Topiramate Concentration - Protocol YTC-E

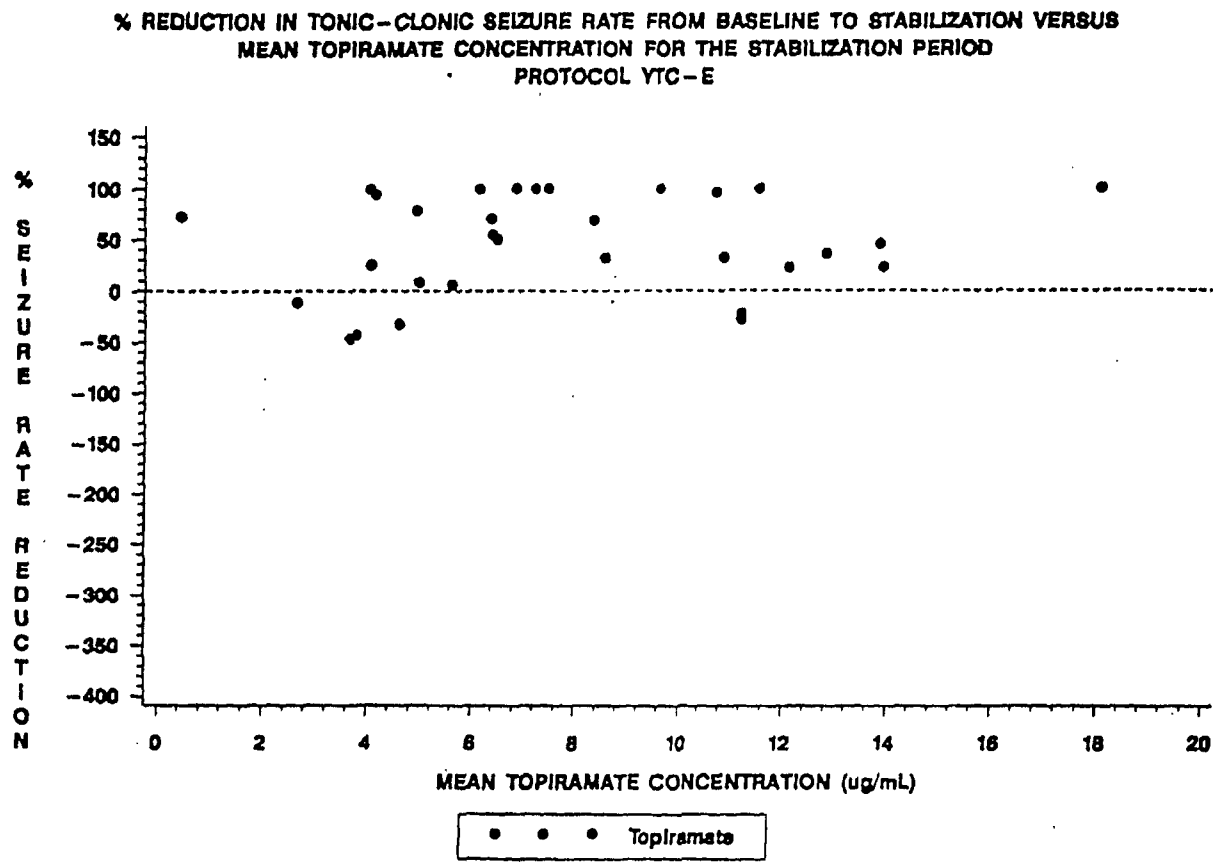


Table 17: Steady-State Plasma Concentrations of Topiramate as a Function of Age
(Overall Pediatric Population: Topiramate-Treated Subjects in Double-Blind Studies, Protocols YL, YP, YTC, and YTC-E Combined)

AGE (YEARS)	N[a]	STEADY-STATE PLASMA TOPIRAMATE CONCENTRATION (µg/mL) MEAN (SD)	MEDIAN	RANGE	MEDIAN AVERAGE STABILIZATION DOSE (mg/kg/day)
≤7	36	5.1 (3.7)	4.4	0.0 - 18.1	5.9
8 - 11	30	5.3 (2.3)	5.2	1.8 - 9.9	5.8
12-16	30	5.9 (2.8)	4.9	2.3 - 12.2	6.0
>16	61	6.9 (3.4)	5.7	0.5 - 14.3	4.9

[a] One subject in the ≤7 group, one subject in the 8-11 group, and 9 subjects in the >16 group are not included because they did not have concentration measurements during the stabilization period.

Table 18: Steady-State Plasma Concentrations of Topiramate as a Function of Age and Gender
(Overall Pediatric Population: Topiramate-Treated Subjects in Double-Blind Studies, Protocols YL, YP, YTC, and YTC-E Combined)

AGE (Years)	SEX	N[a]	STEADY STATE PLASMA TOPIRAMATE CONCENTRATION (µg/mL) MEAN (SD)	MEDIAN	RANGE	MEAN AVERAGE STABILIZATION DOSE (mg/kg/Day)
≤7	MALE	19	5.2 (3.7)	4.7	0.0 - 13.6	6.0
	FEMALE	17	5.0 (3.9)	4.4	1.7 - 18.1	5.8
8 - 11	MALE	20	5.6 (2.6)	5.3	2.0 - 9.9	5.8
	FEMALE	10	4.8 (1.5)	4.8	1.8 - 6.8	5.8
12 - 16	MALE	14	6.0 (3.0)	5.1	2.5 - 12.2	6.0
	FEMALE	16	5.8 (2.8)	4.6	2.3 - 10.8	6.1
>16	MALE	32	6.7 (3.3)	5.4	2.4 - 14.3	4.1
	FEMALE	29	7.2 (3.5)	6.2	0.5 - 14.0	5.7

[a] One subject in the ≤7 group, one subject in the 8-11 group, and 9 subjects in the >16 group are not included because they did not have concentration measurements during the stabilization period.

Table 19: Steady-State Plasma Concentrations of Topiramate as a Function of Age and AED Enzyme-Inducer Status
(Overall Pediatric Population: Topiramate-Treated Subjects in Double-Blind Studies, Protocols YL, YP, YTC, and YTC-E Combined)

AGE (Years)	TYPE OF AED[a]	N[b]	STEADY STATE PLASMA TOPIRAMATE CONCENTRATION (µg/mL) MEAN (SD)	MEDIAN	RANGE	MEDIAN AVERAGE STABILIZATION DOSE (mg/kg/Day)
≤7	No Inducer	16	6.6 (4.3)	5.7	1.5 - 18.1	5.7
	Inducer	20	4.0 (2.8)	3.1	0.0 - 12.9	6.1
8 - 11	No Inducer	12	7.2 (1.7)	7.2	4.7 - 9.9	6.0
	Inducer	18	4.1 (1.8)	3.8	1.8 - 8.1	5.6
12 - 16	No Inducer	11	6.6 (3.3)	6.4	2.3 - 12.2	5.9
	Inducer	19	5.5 (2.5)	4.8	2.5 - 10.8	6.1
>16	No Inducer	19	10.0 (3.1)	11.2	4.9 - 14.3	4.8
	Inducer	42	5.5 (2.5)	5.0	0.5 - 11.9	5.2

[a] AED enzyme inducers included carbamazepine, ethotoin, phenobarbital, and phenytoin
[b] One subject in the ≤7 group, one subject in the 8-11 group, and 9 subjects in the >16 group are not included because they did not have concentration measurements during the stabilization period.

Table 28: Mean Changes in Plasma Concentrations of Concomitant AEDs from Baseline to the Double-Blind Phase in Protocols YTC and YTC-E Combined
(Randomized Subjects With Available Data)

		Placebo		Topiramate		
Concomitant AED	Evaluation	N	Mean (SD)	N	Mean (SD)	p-Value[a]
Valproic acid (µg/mL)	Baseline	33	85.6 (30.20)	32	116.1 (120.41)	
	Change	33	2.6 (15.10)	27	-8.9 (47.22)	0.193
Carbamazepine (µg/mL)	Baseline	23	9.0 (2.72)	24	9.8 (5.92)	
	Change	22	0.6 (1.08)	22	-0.9 (1.82)	0.002
Lamotrigine (µg/mL)	Baseline	26	12.3 (27.15)	19	5.6 (3.56)	
	Change	22	0.6 (1.79)	19	0.2 (1.42)	0.530
Phenytoin (µg/mL)	Baseline	20	23.3 (21.16)	22	18.4 (17.56)	
	Change	20	-0.5 (6.04)	19	-0.6 (5.83)	0.968
Phenobarbital (µg/mL)	Baseline	10	39.2 (30.63)	15	25.4 (19.85)	
	Change	10	1.1 (6.16)	13	-1.4 (7.12)	0.381
Gabapentin (µg/mL)	Baseline	6	9.1 (4.37)	11	8.4 (5.44)	
	Change	6	-0.8 (2.22)	8	-0.5 (1.99)	0.807

[a] p-Value for difference in mean change from baseline in placebo and topiramate groups, determined by one-way analysis of variance.

Table 29: Percent Seizure Rate Reduction and Treatment Responders by Plasma Topiramate Concentration Stratum in Protocols YTC and YTC-E Combined
(All Subjects With Plasma Samples During Stabilization)

Seizure Type		Median Percent	Responders	
Plasma Topiramate Stratum	N	Reduction	No.	%
PGTC Seizures				
<5.04 µg/mL	22	28.7	9	41
5.04 to <8.53 µg/mL	21	68.5	15	71
≥8.53 µg/mL	23	44.6	10	43
All Seizures				
<5.04 µg/mL	23	8.9	8	35
5.04 to <8.53 µg/mL	21	53.9	13	62
≥8.53 µg/mL	23	51.5	12	52

Table 30: Percent Seizure Rate Reduction and Treatment Responders by Sex and Plasma Topiramate Concentration Stratum in Protocols YTC and YTC-E Combined (All Subjects With Plasma Samples During Stabilization)

Seizure Type / Plasma Topiramate Stratum	N	Median Percent Reduction	Responders No.	Responders %
PGTC Seizures				
Female				
<5.13 µg/mL	10	16.5	3	30
5.13 to <8.53 µg/mL	13	68.5	9	69
≥8.53 µg/mL	11	44.8	5	45
Male				
<5.02 µg/mL	6	34.9	3	50
5.02 to <8.46 µg/mL	14	65.3	9	64
≥8.46 µg/mL	12	44.0	5	42
All Seizures				
Female				
<5.13 µg/mL	10	2.9	2	20
5.13 to <8.53 µg/mL	13	52.0	8	62
≥8.53 µg/mL	11	51.5	6	55
Male				
<5.04 µg/mL	7	8.9	3	43
5.04 to <8.53 µg/mL	14	60.0	8	57
≥8.53 µg/mL	12	50.2	6	50

Table 31: Percent Seizure Rate Reduction and Treatment Responders by Age and Plasma Topiramate Concentration Stratum in Protocols YTC and YTC-E Combined (All Subjects With Plasma Samples During Stabilization)

Seizure Type / Plasma Topiramate Stratum	N	Median Percent Reduction	Responders No.	Responders %
PGTC Seizures				
≤16 years				
<4.09 µg/mL	4	-5.3	1	25
4.09 to <8.41 µg/mL	6	46.4	3	50
≥8.41 µg/mL	5	68.5	3	60
>16 years				
<5.04 µg/mL	17	46.7	8	47
5.04 to <8.61 µg/mL	16	83.2	11	69
≥8.61 µg/mL	18	44.7	8	44
All Seizures				
≤16 years				
<4.09 µg/mL	4	-6.9	0	0
4.09 to <8.41 µg/mL	6	37.6	3	50
≥8.41 µg/mL	5	54.0	3	60
>16 years				
<5.04 µg/mL	18	35.3	8	44
5.04 to <8.61 µg/mL	16	66.0	9	56
≥8.61 µg/mL	18	51.5	10	56

Table 32: Mean Changes in Plasma Concentrations of Concomitant AEDs from Baseline to Double-Blind Phase
(Overall Pediatric Population: Topiramate-Treated Subjects in Double-Blind Studies, Protocols YL, YP, YTC and YTC-E Combined)

		Placebo		Topiramate		
Concomitant AED	Evaluation[a]	N	Mean (SD)	N	Mean (SD)	p-Value[b]
Carbamazepine (µg/mL)	Baseline	31	9.1 (2.71)	31	8.7 (2.55)	
	Change	29	-0.1 (1.64)	31	-0.7 (1.96)	0.186
Clonazapam (µg/L)	Baseline	10	20.4 (20.8)	7	24.9 (18.37)	
	Change	9	-2.1 (7.56)	7	-8.5 (9.91)	0.162
Felbamate (µg/mL)	Baseline	9	72.1 (38.0)	7	62.3 (24.6)	
	Change	7	-2.4 (6.86)	7	4.3 (10.5)	0.182
Gabapentin (µg/mL)	Baseline	6	4.2 (2.10)	12	7.0 (4.05)	
	Change	6	-0.3 (0.35)	12	-0.4 (2.14)	0.957
Lamotrigine (µg/mL)	Baseline	16	5.3 (3.12)	16	6.1 (4.77)	
	Change	16	0.9 (1.69)	15	-0.9 (2.30)	0.020
Phenobarbital (µg/mL)	Baseline	18	27.3 (9.99)	13	26.9 (13.9)	
	Change	17	1.7 (6.80)	13	-1.1 (6.01)	0.253
Phenytoin (µg/mL)	Baseline	19	15.3 (7.85)	18	11.7 (6.70)	
	Change	19	-0.7 (3.28)	18	0.71 (3.76)	0.227
Primidone (µg/mL)	Baseline	13	6.2 (4.51)	6	8.4 (6.27)	
	Change	10	0.5 (1.83)	6	2.1 (4.67)	0.345
Valproic acid (µg/mL)	Baseline	44	93.9 (36.8)	44	102.3 (38.6)	
	Change	42	-0.9 (23.6)	42	-7.1 (17.0)	0.167

[a] Change is mean change for subjects with measurements at baseline and at the end of the double-blind phase.
[b] p-Value for difference in mean change from baseline in placebo and topiramate groups, determined by one-way analysis of variance.

VIII. LABELING

No substantive pharmacokinetic labeling changes are proposed to be added to the TOPAMAX® (topiramate) Tablets label from these supplemental NDAs. Minor editorial changes and rewording of pharmacokinetic information is made in the proposed label. Please refer to Item 4C of this supplemental NDA for the proposed annotated labeling.

IX. LITERATURE SURVEY

Only one abstract relevant to the pharmacokinetics of topiramate in the three new indications, considered in these three Supplemental New Drug Applications, has been published in the literature. This abstract reports the

E. INTEGRATED ANALYSIS OF CONCOMITANT PLASMA AED CONCENTRATIONS FOR DOUBLE BLIND TRIALS (PROTOCOLS YP,[10] YL,[11] YTC,[12] AND YTC-E[13])

The concomitant plasma AED concentrations from Protocols YL, YP, YTC and YTC-E were combined for an integrated analysis. Values obtained for the plasma concentrations of each AED across the double-blind phase (both titration and stabilization periods) were averaged for each subject to compare changes from baseline during placebo and topiramate treatments. In Table 32, mean changes in plasma concentrations from baseline to the double-blind period are shown for those AEDs used by at least five pediatric subjects in each treatment group. In comparisons between groups, the only AED showing a statistically significant difference between groups for change in plasma concentration was lamotrigine, which showed a mean decrease of 0.9 mg/L (from a baseline value 6.1 mg/L) among topiramate-treated subjects and a mean increase of 0.9 mg/L (from a baseline value of 5.3 mg/L) among placebo-treated subjects. Any difference in the therapeutic effect due to the change in lamotrigine concentration would therefore be expected to favor placebo rather than topiramate treatment. Overall, the data in Table 24 may be interpreted as indicating that the therapeutic efficacy seen for topiramate relative to placebo treatment in the double-blind studies was not mediated through changes in plasma AED concentrations. Also, the concentrations of the AEDs at baseline and during double-blind treatment were sufficiently similar in each treatment group to allow a fair assessment of adverse events for topiramate adjunctive therapy as compared to placebo adjunctive therapy. Finally, given the small changes in concomitant AED concentrations and their comparability in topiramate-treated and placebo-treated subjects, these data provide no evidence of significant drug interactions in terms of an effect of topiramate on other AEDs.

3. Studies Evaluating Concomitant AED Concentration Change, Relating Plasma Concentrations of Topiramate to Clinical Efficacy and Safety Measurements (Pharmacokinetic/Pharmacodynamic Correlations), and Evaluation of Topiramate Concentrations by Subgroup

Plasma concentrations of concomitant AEDs and topiramate determined from subjects during the double-blind phase of the four double-blind studies (Protocols YP, YL, YTC, and YTC-E)[10,11,12,13] were analyzed for change in concomitant antiepileptic drug concentration with the addition of topiramate therapy, and the relationship of plasma concentrations of topiramate to clinical safety and efficacy measurements (pharmacokinetic/pharmacodynamic correlations), respectively. In addition, topiramate concentrations in different subgroups (e.g., age, sex) were evaluated. These analyses are provided in Section VII. of this technical summary.

Overall, the results from these analyses showed that changes in plasma concentration of each concomitant AED from the baseline phase to the double-blind phase were clinically insignificant, and indicate that the topiramate effects observed in these studies were not mediated through changes in plasma concentrations of concomitant AED(s). There was no consistent relationship between efficacy and plasma topiramate concentration. For pediatric subjects, each of the seven neuropsychiatric adverse events–somnolence, anorexia, fatigue, nervousness, difficulty with memory, difficulty with concentration/attention, and aggressive reaction–for which the incidence in the topiramate group was at least five percent greater than in the placebo group in the four double-blind trials that included pediatric subjects, there was no apparent relationship between the plasma concentration of topiramate and the occurrence of the adverse event. Topiramate mean and median steady-state concentrations at the target dose of approximately 6 mg/kg in most subjects were lower in the pediatric subjects than in adults, even though the median mg/kg dose was slightly higher in the pediatric subjects. These results are consistent with the pediatric and adult data compared in Study EPPD-001.

Study #2: Comparative bioavailability of topiramate from two 100 mg tablet formulations (formula #1 and 37) administered in the fasted state to healthy male subjects (MS 212).

The objective of this single dose study was to compare the 100 mg market image tablets (formula #37, Batch # R4539, manufactured at _____ , Date of Mfg: July, 1991) and 100 mg tablets used in clinical trials (formula #1, Batch # R4504, manufactured at _____ Date of Mfg: Febraury, 1991). The clinical trial was conducted from October 12, 1991 to November 9, 1991.

The study was a randomized, complete, two-way crossover. Eighteen healthy male subjects who took part in this study (age ranging from 20 to 31 years, weight ranging from 153 to 190 lbs), received a 100 mg oral dose of topiramate as one tablet on each dosing day, separated by a three-week washout period. Seven ml venous blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, 36, 48, 60, 72, 84, 96, 120, 144, and 168 hours. Plasma samples were analyzed for topiramate by validated _____ sing 500 µl plasma, the limit of detection was 0.1 µg/mL.

Results:

The pharmacokinetic parameters C_{max}, T_{max}, AUC (0-infinity), oral clearance (CL/F), and half-life of topiramate from the two treatments are summarized in the following table.

PK parameters	Treatment A (Formula #1) (Clinical reference)	Treatment B (Formula #37) (Test)
$T_{1/2}$ (hrs)	39.1 ± 11.7	39.0 ± 8.1
C_{max} (µg/ml)	1.5 ± 0.3	1.5 ± 3.1
T_{max} (hrs)	2.9 ± 2.6	2.9 ± 2.6
$AUC_{(0\text{-inf})}$ (µg.h/ml)	58.6 ± 9.5	59.5 ± 10.4
CL/F (ml/min)	29.2 ± 5.0	28.9 ± 5.8

Mean ± SD

Statistical comparisons of AUC and Cmax by ANOVA indicated that there were no significant differences between the two treatments. The two, one-sided tests procedure showed that the 90% confidence intervals for AUC and C_{max} of the market image tablet (B) were within ± 20% of the mean values for treatment A. T_{max} for both treatments was comparable (2.9 hrs). Therefore, it can be concluded that the market image tablet is bioequivalent to the tablet used in the clinical trials. The following table summarizes the market vs clinical bioequivalence study of topiramate 100 mg tablet.

90% Confidence Interval for the ratio of the two treatment means on log scale

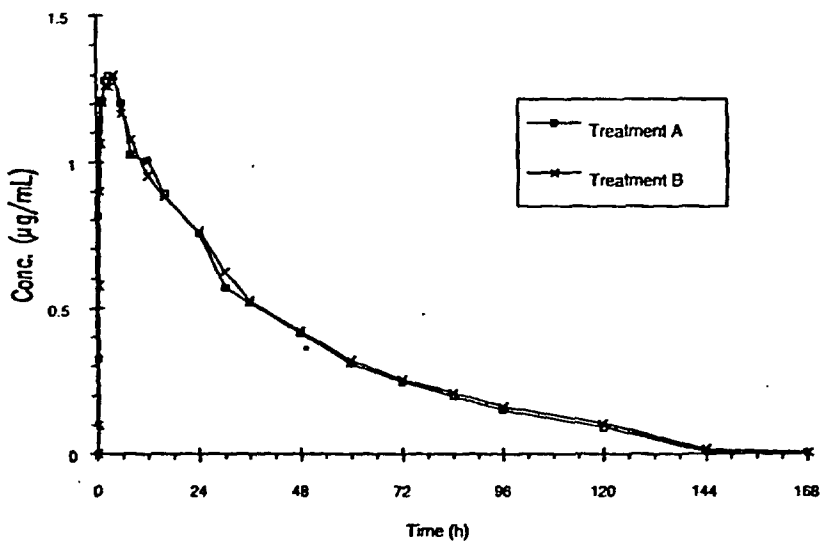
		90% Confidence Interval
Parameter	Lower limit (%)	Upper limit (%)
AUC (0-t)	96.8	107.5
AUC (0-inf)	96.2	106.8
C_{max}	89.9	104.6

Ratio = mean for market/mean for clinical

Conclusions:

The market image 100 mg tablet is bioequivalent to the 100 mg tablet used in the clinical trials.

Figure 4: Mean Topiramate Plasma Concentrations, 100 mg Tablet Bioequivalence Study
(Protocol MS-212)



Study #3: Comparative bioavailability of topiramate from a 100 mg tablet formulation (formula #1) a 400 mg tablet formulation (formula #36) administered as a 400 mg dose in the fasted state to healthy male subjects (MS 213).

The objective of this study was to compare the bioavailability of topiramate between the 100 mg tablet (formula #1,Batch # R4504, manufactured at _____ _____ used in clinical trials and the 400 mg tablet (formula #36, Batch # R4541, manufactured at _____ Date of Mfg: July, 1991) administered at an equal 400 mg dosage to healthy male subjects under fasted conditions.

The study was a randomized, complete, two-way crossover. Eighteen healthy male subjects took part in this study in a crossover fashion separated by a three-week washout period between treatments.

Treatment A: A single oral 400 mg dose as four 100 mg tablets of clinical trial (formula #1) with 240 ml of water following a 10-h overnight fast.

Treatment B: A single oral 400 mg dose as one 400 mg tablet of market image (formula #36) with 240 ml of water following a 10-h overnight fast.

Ten ml blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, 36, 48, 60, 72, 84, 96, 120, 144, and 168 hours. Plasma samples were analyzed for topiramate by validated _____ _____. The limit of detection was 0.5 µg/mL.

Results:

The pharmacokinetic parameters C_{max}, T_{max}, AUC (0-infinity), oral clearance (CL/F), and half-life of topiramate from the two treatments are summarized in the following table.

PK parameters	Treatment A (Formula #1) (4 X 100 mg tablets) (Clinical reference)	Treatment B (Formula #36) (1 X 400 mg tablets) (Test)
AUC (0-t) (µg.h/ml)	276.5 ± 38.8	268.4 ± 62.3
AUC(0-inf) (µg.h/ml)	302.1 ± 42.5	293.0 ± 64.9
C_{max} (µg/ml)	8.2 ± 1.3	7.8 ± 1.4
T_{max} (hrs)	2.0 ± 1.7	2.3 ± 1.4
CL/F (ml/min)	24.0 ± 3.5	26.4 ± 10.8
$T_{1/2}$ (hrs)	27.2 ± 4.3	28.1 ± 5.3

Statistical comparisons of AUC and Cmax by ANOVA indicated that there were no significant differences between the two treatments. The two, one-sided tests procedure showed that the 90% confidence interval for AUC and Cmax of the market image tablet were within ± 20% of the mean values for treatment A. T_{max} for both treatments was comparable (approximately 2 hrs). Therefore, it can be concluded that 1 X 400 mg market image tablet is bioequivalent to 4 X 100 mg tablets used in the clinical trials. The following table summarizes the market vs clinical bioequivalence study of topiramate.

90% Confidence Interval for the ratio of the two treatment means on log scale

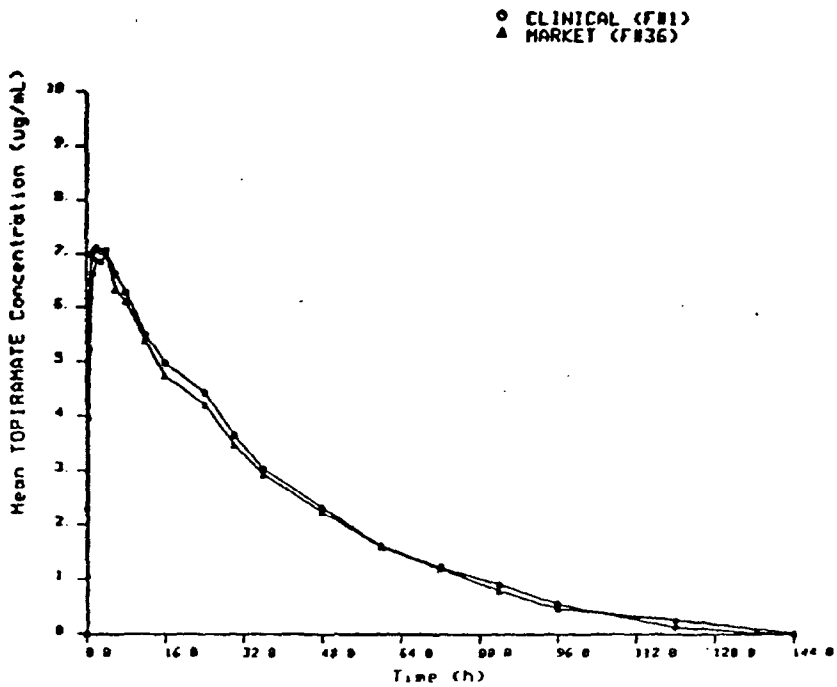
		90% Confidence Interval
Parameter	Lower limit (%)	Upper limit (%)
$AUC_{(0\text{-}t)}$	85.7	104.6
$AUC_{(0\text{-}inf)}$	87.1	103.7
C_{max}	84.6	103.1

Ratio = mean for market/mean for clinical

Conclusion:

One 400 mg market image tablet is bioequivalent to 4 X 100 mg clinical trial tablets.

Figure 5: Mean Topiramate Plasma Concentrations, 400 mg Tablet Bioequivalence Study
(Protocol MS-213)



Study #14

V. PHARMACOKINETICS OF TOPIRAMATE IN PEDIATRIC SUBJECTS

Pharmacokinetic data on topiramate use in pediatric subjects were obtained in one pharmacokinetic study (Protocol EPPD-001).[9] In addition, steady-state plasma levels of topiramate and concomitant AEDs were determined in the double-blind phases of the four double-blind studies that included pediatric subjects (Protocols YL, YP, YTC, and YTC-E).[10,11,12,13] Plasma topiramate concentrations in the double-blind studies were examined for dependence on age and sex.

A. PHARMACOKINETIC STUDY IN PEDIATRIC SUBJECTS WITH EPILEPSY

Pharmacokinetic Profiles in Children

In Protocol EPPD-001,[9] the pharmacokinetics of topiramate were assessed in 18 subjects with seizures inadequately controlled on one or two standard AEDs. Subjects were stratified according to three age groups: 4 to 7 years, 8 to 11 years, and 12 to 17 years. Demographic data are summarized in Table 13.

Table 13: Demographic Characteristics
(All Subjects; Protocol EPPD-001)

	Age Group (Years)			
	4 - 7 (N= 6)	8 - 11 (N=6)	12 - 17 (N=6)	Total (N=18)
Age (years)				
Mean (SD)	5.5 (1.05)	9.7 (1.21)	15.0 (1.90)	10.1 (4.22)
Median	5.5	9.5	15.0	9.5
Range	4 - 7	8 - 11	12 - 17	4 - 17
Gender				
Males/Females	6/0	4/2	3/3	13/5
Weight (kg)				
Mean (SD)	20.1 (3.5)	33.8 (6.1)	64.6 (30.8)	39.5 (25.7)
Median	21.5	33.2	54.1	33.2
Range	14.2-23.4	27.3-41.1	39.5-123.2	14.2-123.2

During a two-week baseline period, the background AED regimen was stabilized. Thereafter, subjects received ascending topiramate dosage regimens of 1, 3, 6, and 9 mg/kg/day administered in q12h intervals for one

week each. Blood samples were collected after one week of treatment at the 1, 3, and 9 mg/kg/day dosage levels for determination of plasma topiramate pharmacokinetic profiles.

Topiramate pharmacokinetics were found to be linear in 4 to 17 year-old subjects (Table 14). Peak plasma concentrations (C_{max}) increased in proportion to dose and generally were achieved in approximately one to two hours across all ages and dosage groups. Oral plasma clearance (CL/F) of topiramate was independent of dose.

Table 14: Mean (SD) Steady-State Plasma Topiramate Pharmacokinetic Parameters in Pediatric Subjects
(All Subjects; Protocol EPPD-001)

	Ages 4 - 7 (q12h Dosing Unless Indicated Otherwise)			Ages 8 - 11 (q12h Dosing Unless Indicated Otherwise)			Ages 12 - 17 (q12h Dosing)		
Parameter	Target[a] Dose 1 mg/kg (N=6)	Target Dose 3 mg/kg (N=6)	Target[b] Dose 9 mg/kg (N=5)	Target Dose 1 mg/kg (N=5)	Target Dose 3 mg/kg (N=6)	Target Dose 9 mg/kg (N=6)	Target Dose 1 mg/kg (N=6)	Target Dose 3 mg/kg (N=6)	Target Dose 9 mg/kg (N=6)
C_{max} (µg/mL)	2.32 (0.64)	3.91 (2.16)	10.55 (1.91)	2.74[c] (0.77)	4.29 (1.49)	11.50 (3.13)	1.72 (0.68)	5.28 (2.47)	12.37 (4.61)
t_{max} (h)	1.8 (1.2)	1.2 (0.5)	1.0 (0.7)	0.8[c] (0.4)	2.8 (2.2)	2.2 (1.6)	1.0 (0.6)	1.1 (0.7)	1.8 (1.2)
AUC_{0-t} (µg·h/mL)	23.5 (9.1)	30.7 (18.9)	78.5 (29.5)	21.2[d] (8.2)	40.7 (16.2)	102.7 (34.8)	14.7 (8.6)	48.2 (30.0)	111.1 (54.8)
CL/F (mL/min)	19.5 (5.6)	18.8 (6.4)	22.0 (7.2)	22.2[d] (8.6)	23.4 (9.0)	25.0 (8.1)	48.3 (33.6)	47.3 (33.1)	50.1 (34.7)

[a] q24h topiramate therapy.
[b] Data from Subject 13 excluded from analysis as outlier data.
[c] N = 2 for C_{max} and t_{max} - includes only q12h topiramate-treated subjects.
[d] N = 5 for AUC_{0-t} and CL/F (all subjects, excluding Subject 4). Subject 4 data excluded from analysis because subject received an additional dose during the sampling interval

Dose- and weight-normalized estimates of pharmacokinetic parameters are shown in Table 15. Analysis of variance revealed no statistically significant differences (>0.05) among target doses or age groups for the dose- and weight-normalized plasma C_{max} or $AUC_{0-\tau}$ values or for weight-normalized CL/F values (results presented in Clinical Study Report for Protocol EPPD-001).

Table 15: Mean (SD) Dose-and Weight-Normalized Steady-State Plasma Topiramate Pharmacokinetic Parameters (All Subjects; Protocol EPPD-001)

Parameter	Ages 4 - 7 (q12h Dosing Unless Indicated Otherwise)			Ages 8 - 11 (q12h Dosing Unless Indicated Otherwise)			Ages 12 - 17 (q12h Dosing)		
	Target[a] Dose 1 mg/kg (N=6)	Target Dose 3 mg/kg (N=6)	Target[b] Dose 9 mg/kg (N=5)	Target Dose 1 mg/kg (N=5)	Target Dose 3 mg/kg (N=6)	Target Dose 9 mg/kg (N=6)	Target Dose 1 mg/kg (N=6)	Target Dose 3 mg/kg (N=6)	Target Dose 9 mg/kg (N=6)
C_{max} (µg/mL/400 mg daily dose and 70 kg)	10.37 (2.39)	7.28 (2.36)	6.75 (1.24)	12.63[c] (3.35)	8.15 (3.09)	7.85 (2.65)	10.37 (3.88)	9.85 (3.73)	8.62 (2.99)
AUC_{0-t} (µg·h/mL/200 mg dose and 70 kg)	51.5 (12.8)	56.1 (19.8)	50.5 (20.0)	85.5[d] (40.8)	77.4 (34.4)	70.2 (28.3)	88.9 (50.8)	88.7 (48.9)	77.5 (36.3)
CL/F (mL/min/70 kg)	68.0 (15.7)	65.0 (19.5)	72.9 (22.7)	46.6[d] (22.0)	49.1 (17.3)	52.9 (17.4)	52.9 (34.6)	51.9 (31.5)	52.8 (25.8)

[a] q24h topiramate therapy.

[b] Data from Subject 13 excluded from analysis as outlier data.

[c] N = 2 for C_{max}

[d] N = 5 for AUC_{0-t} and CL/F (all subjects, excluding Subject 4). Subject 4 data excluded from analysis because subject received an additional dose during the sampling interval.

Concomitant AEDs (one or two per subject) represented in this study were the enzyme-inducers phenytoin, carbamazepine, phenobarbital, and ethotoin, and the non-inducers valproic acid and gabapentin. In this 4 to 17 year-old population, weight-normalized topiramate CL/F was found to be higher, and dose- and weight-normalized C_{max} and $AUC_{0-\tau}$ were lower, in subjects receiving enzyme-inducing concomitant AEDs than in subjects not receiving the enzyme inducers (Table 16). Analysis of variance showed the differences between groups for each parameter to be statistically significant.

Subjects who were receiving non-enzyme inducing concomitant AEDs had a mean (±SD) half-life of 15.4 (±2.3) hours and subjects receiving enzyme inducing concomitant AEDs had a mean (±SD) half-life of 7.5 (±2.1) hours. There was no discernible dependence on age within this group of subjects. Differences in these half-life values are in agreement with differences in plasma clearance estimates for the two enzyme induction status groups, respectively.

Table 16: Effect of Concomitant AEDs on Mean (±SD) Dose-Normalized and Weight-Normalized Steady-State Plasma Topiramate Pharmacokinetic Parameters (All Subjects; Protocol EPPD-001)

Parameter	Subjects with Concomitant Enzyme Inducers			Subjects Without Concomitant Enzyme Inducers		
	Target Dose 1 mg/kg (N=11)	Target Dose 3 mg/kg (N=11)	Target[b] Dose 9 mg/kg (N=10)	Target Dose 1 mg/kg (N=5)	Target Dose 3 mg/kg (N=6)	Target Dose 9 mg/kg (N=6)
C_{max} (µg/mL/400 mg daily dose	7.89[a] (1.98)	6.73 (1.81)	6.39 (0.97)	13.98[a] (1.67)	11.65 (2.78)	10.17 (2.58)
t_{max} (h)	0.6[a] (0.3)	1.8 (1.7)	1.5 (1.1)	1.3[a] (0.6)	1.4 (1.4)	1.7 (1.3)
AUC_{0-t} (µg·h/mL/200 mg dose and 70 kg)	52.3[a] (17.2)	51.5 (15.3)	46.6 (9.4)	123.3[a] (35.8)	113.9 (33.3)	100.2 (23.2)
CL/F[d] (mL/min)	69.8 (20.8)	69.2 (17.4)	74.1 (14.9)	29.5[c] (11.0)	31.7 (10.3)	35.1 (9.5)
t½ (h)[e]	7.5 (2.1)			15.4 (2.3)		

[a] N=4 for C_{max} and t_{max} - includes only q12h topiramate-treated subjects.
[b] Data from Subject 13 excluded from analysis as outlier data.
[c] N=4 for C_{max} and t_{max} - includes only q12h topiramate-treated subjects. Subject 4 data excluded; subject received an additional dose.
[d] Weight-normalized only.
[e] Mean (±SD) from 3 and 9 mg/kg target doses

Comparison of Pharmacokinetics in Pediatric and Adult Subjects with Epilepsy

Weight-normalized CL/F values from the pediatric subjects participating in Study EPPD-001 were compared with those from adult subjects receiving adjunctive topiramate therapy (400 mg/day) in earlier topiramate studies (Studies MS-215, MS-216, and MS-218).[14,15,16] This comparison indicated that weight-normalized mean topiramate clearance was higher in children than in adults when the drug was administered adjunctive to enzyme-inducing AEDs (70.1 mL/min/70 kg in children compared to 46.1 mL/min/70 kg in adults) as well as to nonenzyme-inducing AEDs (33.1 mL/min/70 kg in children compared to 22.4 mL/min/70 kg in adults). These results suggest that steady-state plasma topiramate concentrations for the same mg/kg dose may be somewhat lower in children than adults; subsequent findings in the double-blind trials were consistent with these results (see Section V.B.) below) Similar observations have been made for many other drugs, including AEDs.[17,18]

ATTACHMENT E
PROPOSED PRODUCT DISSOLUTION METHOD AND SPECIFICATION