Summary of Topiramate Clinical Trial: Protocol CR005467

NAME OF SPONSOR/COMPANY: The R.W. Johnson Pharmaceutical Research Institute	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: TOPAMAX® (topiramate)	@@7000fad8004b27c	
NAME OF ACTIVE INGREDIENT(S): 2,3:4,5-bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate		

Protocol No.: CR005467
Title of Study: Topiramate Clinical Trial in Children with Partial Onset Seizures

Investigators: 17 investigators

Study Centre(s): 17 centers

Publication (Reference): None

Studied Period (years): 2 June 1994 - 29 May 1996

Phase of development: 3

Objectives: The objective of this trial was to evaluate the safety and efficacy of oral topiramate as adjunctive therapy in pediatric subjects with uncontrolled partial onset seizures with or without secondarily generalized seizures.

Methodology: This was a randomized, double-blind, placebo-controlled trial conducted in the United States and Costa Rica that evaluated topiramate total daily (target) dosages of 125, 175, 225, and 400 mg/day based on subject weight to approximate 6 mg/kg per day as adjunctive therapy in pediatric subjects with uncontrolled partial onset seizures with or without secondarily generalized seizures. The trial consisted of a baseline phase (approximately 56 days in duration) and a double-blind phase (approximately 112 days in duration). During the baseline phase, the number and type of seizures that occurred were monitored while subjects received a constant dosage of one or two antiepileptic drugs (AEDs). Subjects who were eligible for the double-blind phase of the trial were randomized in equal proportions at each center to receive either placebo or topiramate while continuing on their background AED regimen. The primary efficacy variable was reduction from baseline in the average monthly rate for partial onset seizures. Efficacy was also evaluated based on the percent reduction in average monthly seizure rate for all seizures and for secondarily generalized seizures, the percent treatment responders (subjects with a ≥50% reduction in average monthly seizure rate), and on improvement in seizure severity. Safety was evaluated based on treatment-emergent adverse events, clinical laboratory tests, measurements of vital signs, body weight, electrocardiograms (ECGs), physical and neurological examination findings. Parental global evaluations of mental status included level of alertness, level of interaction with the environment, ability to perform the activities of daily living, and responsiveness to verbal requests. Plasma AED concentrations were measured at periodic intervals to assess potential effects of topiramate on background AEDs.

Number of Subjects (planned and analyzed): The planned sample size was approximately 72 subjects. Eighty-six subjects were randomized; 45 subjects received placebo and 41 subjects received topiramate. All 86 subjects were included in the intent-to-treat analyses of safety and efficacy.

Diagnosis and Main Criteria for Inclusion: Pediatric subjects, 2 to 16 years of age, were enrolled in this trial and had partial onset seizures with or without secondarily generalized seizures. During the baseline period subjects were required to have at least six partial onset seizures with at least one seizure occurring during each 28-day period of the 56-day baseline phase while maintained on a stable dose of one or two concomitant AEDs. Subjects had to have a diagnosis of partial epilepsy confirmed by routine electroencephalogram (EEG). Subjects had to weigh at least 16 kg.

Test Product, Dose and Mode of Administration, Batch No.: Topiramate was supplied as 25 (Batches R4568 and R5570) and 100 mg (Batches R5509 and R5512) tablets. Maximum doses based on subject weight: 125 mg/day (16-24.9 kg), 175 mg/day (25 to 33.9 kg), 225 mg/day (34 to 42.9 kg), and 400 mg/day (43 or more kilograms).

Duration of Treatment: The total duration of the double-blind period was 112 days, consisting of a 56-day titration and a 56-day stabilization period.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was supplied as matching 25 mg (Batches R4569 and R5721)and 100 mg (Batch R4567) tablets.

Summary of Topiramate Clinical Trial: Protocol CR005467 (continued)

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Criteria for Evaluation:
Efficacy: The efficacy of topiramate was based on a statistically significant between-group difference (topiramate vs. placebo) with respect to percent reduction in average monthly partial onset seizure rate.
Safety: Safety was evaluated by treatment-emergent adverse events, clinical laboratory tests, measurements of vital signs, body weights, electrocardiograms (ECGs), physical and neurologic examination findings, and parental global evaluations of a subject's mental status.

Statistical Methods: A two-way analysis of variance (with treatment and center as factors) on ranks was used to analyze treatment group differences in percent reduction from baseline seizure rates. The frequency of treatment responders was compared between treatment groups using the Cochran-Mantel-Haenszel test adjusted for centers. The parental global evaluation of improvement in seizure severity was analyzed by the exact Wilcoxon rank-sum test unstratified and stratified by center. All statistical tests were two-sided.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: In pediatric subjects with partial onset seizures, topiramate was effective in reducing the average monthly partial onset seizure rate and in reducing the severity of seizures. The results of intent-to-treat analyses of primary and secondary efficacy variables are presented in the following table.

Table 1: Summary of the Efficacy Results for the Double-Blind Phase
(All Randomized Subjects; Protocol CR005467)

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:			
All seizures	10.5	31.9	0.077[b]
Secondarily 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 a 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.

Topiramate-treated subjects had a median percent reduction in partial onset seizure rate of 33.1% compared with 10.5% for placebo-treated subjects (p=0.034). Topiramate-treated subjects also had a greater median percent reductions compared with placebo in average monthly seizure rate for secondarily generalized seizures and for all seizures. Thirty-nine percent of topiramate-treated subjects were treatment responders compared with 20% of placebo-treated subjects based on 50% or greater reduction in partial onset seizures. Seventeen percent of topiramate-treated subjects and 2% of placebo-treated subjects were treatment responders based on a more rigorous definition of 75% reduction in seizure rate. Based on parental global evaluations, 59% of topiramate-treated and 33% of placebo-treated subjects had an improvement in seizure severity; the between-group difference was statistically significant.

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EFFICACY RESULTS (continued): Plasma concentrations of concomitant AEDs were generally comparable over time between topiramate- and placebo-treated subjects. These results indicate that the topiramate effects observed in this study were not mediated through changes in plasma concentrations of concomitant AEDs.

SAFETY RESULTS: Topiramate dosages up to approximately 9 mg/kg per day were well-tolerated in children with partial onset seizures. Most treatment-emergent adverse events were related to seasonal and childhood illnesses (e.g., upper respiratory tract infection, fever, sinusitis) and occurred at comparable rates in the placebo and topiramate groups. Injury and purpura were reported more often in topiramate-treated than in placebo-treated subjects. Common treatment-emergent neuropsychiatric adverse events that occurred in pediatric subjects with partial onset seizures in this trial are presented in the following table. Fatigue, emotional lability, and difficulty with concentration or attention were reported at higher percentages in topiramate-treated subjects than in placebo-treated subjects.

Table 2: Incidence of Common[a] Treatment-Emergent Neuropsychiatric Adverse Events (All Randomized Subjects; Protocol CR005467)

	Placebo (N=45)		Topiramate (N=41)	
Body System/Preferred Term	No.	%	No.	%
Fatigue	3	7	6	15
Somnolence	6	13	5	12
Anorexia	5	11	5	12
Emotional Lability	2	4	5	12
Difficulty with Concentration/Attention	1	2	5	12
Mood Problems	5	11	4	10
Aggressive Reaction	3	7	4	10
Nervousness	3	7	4	10

[a] Includes neuropsychiatric adverse events reported by ≥10% of subjects in either treatment group.

The majority of treatment-emergent adverse events were mild or moderate in severity. No deaths occurred during the study or within 30 days of completion of the double-blind phase of the trial. Three placebo-treated subjects were hospitalized due to adverse events (aggravated convulsions in two subjects, viral infection in one subject) and one topiramate-treated subject was hospitalized for an adverse event (symptoms associated with constipation). One subject receiving placebo discontinued study medication due to an adverse event (rash) while none of the subjects in the topiramate group discontinued therapy due to an adverse event.

Based on parental global evaluations of mental status, more topiramate-treated subjects had an improvement in alertness, level of interaction with the environment, ability to perform the activities of daily living, and responsiveness to verbal requests than did placebo-treated subjects.

Injury and purpura were reported more often in topiramate-treated than in placebo-treated subjects. Ten (24%) subjects in the topiramate group and 2 (4%) subjects in the placebo group had markedly elevated lymphocytes. Seven (17%) subjects in the topiramate group and 4 (9%) subjects in the placebo group had markedly elevated eosinophil counts. In general, markedly elevated lymphocyte or eosinophil counts represented single transient occurrences and none were considered to represent a clinically relevant, drug-related change. A mild decrease in mean body weight occurred among topiramate-treated subjects; one placebo- and two topiramate-treated subjects reported weight decrease as an adverse event. There were no clinically relevant changes in neurologic or physical examination findings, ECGs, or vital signs.

CONCLUSION:

Topiramate dosages up to approximately 9 mg/kg per day were well-tolerated when administered to pediatric subjects between the ages of two and 16. Topiramate was effective in reducing partial onset seizures.

Date of the report: 27 May 1997

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