SYNOPSIS

NAME OF SPONSOR/COMPANY: The R.W. Johnson Pharmaceutical Research Institute NAME OF FINISHED PRODUCT: TOPAMAX® (topiramate) NAME OF ACTIVE INGREDIENT(S): 2,3:4,5-bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER @@7000fad8004b3c0	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: CR005464 **Title of Study**: A Double-Blind Trial of Topiramate in Subjects with Lennox-Gastaut Syndrome		
Investigators: 12 investigators		
Study Centre(s): 12 study centers		
Publication (Reference): None		
Studied Period (years): 27 July 1993 to 11 April 1996		**Phase of development**: 3
Objectives: The objective of this study was to evaluate the safety and efficacy of topiramate as adjunctive therapy in subjects with Lennox-Gastaut syndrome.		
Methodology: This was a multicenter, randomized, double-blind, placebo-controlled trial conducted in the United States that evaluated a topiramate (TPM) total daily (target) dosage of 6 mg/kg/day (≤600 mg/day) as adjunctive therapy in subjects with Lennox-Gastaut syndrome. The trial included a baseline phase (approximately 4 weeks in duration) and a double-blind treatment phase (approximately 11 weeks in duration). During the 4-week baseline period, the number and type of seizures that occurred were monitored while subjects received a constant dosage of one or two antiepileptic drugs (AEDs). Those subjects who elected to participate in the double-blind phase of the trial were randomized, in equal proportions at each center, to receive either topiramate or placebo while continuing on their background AED regimen. Efficacy was evaluated based on data regarding seizure type and frequency obtained from seizure diaries maintained by each subject, parent, or legal guardian for the duration of the trial and on a parental global evaluation of improvement in seizure severity. Safety was evaluated by reported adverse events, clinical laboratory tests, vital sign measurements, body weights, electrocardiograms (ECGs), physical examinations, and neurologic examinations. Parents completed evaluations of the subject's mental status including level of alertness, level of interaction with the environment, ability to perform the activities of daily living (ADL), and responsiveness to verbal requests. In addition, 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 for this trial was approximately 80 subjects. Ninety-eight subjects entered the double-blind phase of the study; 50 were randomly assigned to receive placebo and 48 were randomly assigned to receive topiramate. All 98 subjects were included in the intent-to-treat analyses of efficacy and safety.		
Diagnosis and Main Criteria for Inclusion: Subjects in this study were 12 months of age or older and had Lennox-Gastaut syndrome characterized by EEG recordings showing slow spike-and-wave patterns. Atypical absence seizures and drop attacks (i.e., tonic-atonic seizures) were required among other seizure types that could include tonic-clonic, myoclonic, and minor-motor. Subjects were required to have had at least 60 seizures during the month before baseline.		
Test Product, Dose and Mode of Administration, Batch No.: Topiramate was supplied as 25 (Batch R4568) and 100 mg (Batches R4561, R5509, and R5512) tablets. The total daily (target) dosage was 6 mg/kg per day administered b.i.d. in equal oral doses.		
Duration of Treatment: The total duration of double blind therapy was 11 weeks, including a three-week titration period and an eight-week maintenance period. The total daily dosage was 6 mg/kg per day administered b.i.d. in equal doses.		
Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was supplied as 25 (Batch R4569) and 100 mg (Batch R4567) matching tablets.		
Criteria for Evaluation: Efficacy: The efficacy of topiramate in the treatment of Lennox-Gastaut syndrome was based on a statistically significant between-group difference (topiramate vs. placebo) with respect to either one of two variables: i) percent reduction in the average monthly seizure rate for all seizure types or ii) a compound variable consisting of percent reduction in drop attacks (tonic-atonic seizures) and the parental global evaluation of improvement in seizure severity.		

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Criteria for Evaluation (continued): Safety: Safety was evaluated by reported adverse events, clinical laboratory tests, vital sign measurements, body weights, electrocardiograms (ECGs), physical examinations, neurologic examinations, and parental evaluations of the subject's mental status.

Statistical Methods: A two-way (with treatment and investigator as factors) analysis of variance on ranks was used to analyze treatment group differences in percent reduction from baseline seizure rate. The parental global evaluation of improvement in seizure severity was analyzed by exact Wilcoxon rank-sum tests with and without stratification by center.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: The results of the intent-to-treat analysis of primary and secondary efficacy variables are presented in the following table:

Summary of the Efficacy Results for the Double-Blind Phase
(All Randomized Subjects; Protocol CR005464)

Efficacy Assessment	Placebo	TPM	p-value
Primary Variables			
EITHER			
1) percent reduction in seizure rate for all seizures	8.8	20.6	0.430[c]
OR			
2) each component of a compound variable consisting of:			
• percent reduction in drop attacks	-5.1	14.8	0.041[c]
AND			
• parental global evaluation of seizure severity[a]	28	52	0.037[d] 0.059[e]
Secondary Variables			
Percent treatment responders:[b]			
All seizures	16	17	0.930[f]
Drop attacks (tonic-atonic seizures)	14	28	0.071[f]

[a] Percent of subjects who were minimally, much, or very much improved from baseline.
[b] A treatment responder is defined as a subject whose seizure rate was reduced by 50% or more during the double-blind phase.
[c] TPM vs.placebo; two factor (treatment center) ANOVA on ranks.
[d] TPM vs. placebo; Wilcoxon-rank sum test unstratified.
[e] TPM vs. placebo; Wilcoxon-rank sum test stratified by center.
[f] TPM vs. placebo; Cochran-Mantel-Haenszel test stratified by center.

For all seizure types combined, the median percent reduction from baseline in the average monthly seizure rate was 20.6% for subjects in the topiramate group and 8.8% for the placebo group; this difference was not statistically significant. The median percent reduction in average monthly rate for drop attacks – the first component of the compound efficacy variable – was 14.8% for topiramate compared with an increase in average monthly seizure rate of 5.1% for placebo (p=0.041). The second component of the compound efficacy variable – the parental global evaluation of improvement in seizure severity – also favored topiramate over placebo; 52% of subjects in the topiramate group experienced an improvement in the severity of their seizures compared with 28% of subjects in the placebo group. The p-value for this comparison was 0.037 or 0.059 depending on the method of analysis. The improvement in both components of the compound variable demonstrates the effectiveness of topiramate in reducing the severity of the seizures associated with Lennox-Gastaut syndrome and the number of drop attacks, the most severe seizure type associated with Lennox-Gastaut syndrome.

For all seizures, the percentage of treatment responders (i.e., subjects achieving a 50% or greater seizure rate reduction) was the same for topiramate- and placebo-treated subjects; 17% of topiramate-treated and 16% of placebo-treated subjects were treatment responders. For drop attacks, a greater number of subjects in the topiramate group (28%) achieved a 50% or greater reduction in drop attacks than in the placebo group (14%).

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SUMMARY - CONCLUSIONS (Continued)

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 6 mg/kg per day were well-tolerated. The most common adverse events associated with topiramate were neuropsychiatric in nature and included somnolence, anorexia, nervousness, personality disorder, fatigue, and dizziness. Weight decrease occurred in five (10%) subjects in the topiramate group and none in the placebo group.

Common[a] Treatment-Emergent Neuropsychiatric Adverse Events
(All Randomized Subjects; Protocol CR005464)

Body System/	Placebo (N=50)		Topiramate (N=48)	
Preferred Term	No.	%	No	%
Somnolence	11	22	20	42
Anorexia	10	20	19	40
Nervousness	5	10	10	21
Personality Disorder (Behavior problems)	5	10	10	21
Fatigue	2	4	9	19
Insomnia	4	8	5	10
Dizziness	0	0	5	10

[a] Treatment-emergent neuropsychiatric adverse events reported by 10% or more subjects in either treatment group.

There were no deaths during the study and none of the subjects discontinued prematurely due to an adverse event. Three topiramate-treated subjects were hospitalized during the study; none of the events leading to hospitalization (aggravated convulsions; gastroesophageal reflux; and pneumonia, otitis media, sinusitis, and vomiting) were considered by the investigators to be related to study medication.

Compared with placebo, topiramate had no effect on the subjects' mental status in terms of improvement in alertness, level of interaction with the environment, ability to perform the activities of daily living, and responsiveness to verbal requests.

There were 2 (4%) placebo-treated subjects and 8 (17%) topiramate-treated subjects with markedly elevated lymphocytes. In general, markedly elevated lymphocytes in topiramate-treated subjects represented single, transient occurrences and were associated with intercurrent infections (e.g., URTI, bronchitis, sinusitis). There were no clinically relevant changes in vital signs, neurologic or physical examination findings, or ECGs.

CONCLUSION: Topiramate dosages of approximately 6 mg/kg per day were well-tolerated when administered to subjects with Lennox-Gastaut syndrome and were effective in reducing the severity of seizures associated with Lennox-Gastaut syndrome and the number of drop attacks (tonic-atonic seizures), the most severe seizure type associated with Lennox-Gastaut syndrome.

Date of the report: 27 May 1997

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