SYNOPSIS

NAME OF FINISHED PRODUCT: TOPAMAX® (topiramate) tablets 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 @@7000fad8004b3c6	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: CR005830 Ti**tle of Study**: Topiramate (RWJ-17021-000) Clinical Trial in Primary Generalized Tonic-Clonic Seizures		
Investigators: 16 investigators		
Study Centres: 16 study centers		
Publication (Reference): None		
Studied Period (years): 15 September 1994 - 12 November 1996		**Phase of development**: 3
Objectives: This trial was designed to evaluate the safety and efficacy of oral topiramate as adjunctive therapy in subjects with uncontrolled primary generalized tonic-clonic (PGTC) seizures (i.e., tonic-clonic seizures considered to be generalized from the onset) with or without other generalized seizure subtypes.		
Methodology: This was a multicenter, randomized, double-blind, placebo-controlled trial that evaluated topiramate total daily (target) dosages of 175, 225, or 400 mg/day based on subject's weight to approximate 6 mg/kg/day (theoretical range: ≤9.3 mg/kg/day) as adjunctive therapy in subjects with PGTC seizures with or without other generalized seizure subtypes. The trial included a baseline phase (approximately 56 days in duration) and a double-blind phase (approximately 140 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). Those 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. Efficacy was evaluated based on the reduction from baseline in average monthly PGTC seizure rate, the primary efficacy variable, and on the reduction from baseline in average monthly seizure rate based on all seizures. Efficacy was also evaluated by the percent of treatment responders (subjects with a ≥50% reduction in average monthly seizure rate) based on PGTC seizures and based on all seizures, and subject's global evaluation of improvement in seizure severity. Safety was evaluated by reported adverse events, clinical laboratory tests, vital sign and body weight measurements, electrocardiograms (ECGs), physical examinations, and neurologic examinations. Subjects (or their parents/legal guardians) completed evaluations on mental status including level of alertness, level of interaction with their environment, ability to perform activities of daily living, 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): Eighty subjects were enrolled; 40 were randomly assigned to each treatment group. All 80 subjects were included in the intent-to-treat analyses of efficacy and safety.		
Diagnosis and Main Criteria for Inclusion: Subjects (≥ 4 years of age; ≥25 kg) enrolled in the trial had PGTC seizures with or without other generalized seizure subtypes. Subjects were to have three or more PGTC seizures during the 56-day baseline phase (with at least one during each 28-day period) while on a stable regimen of one or two AEDs.		
Test Product, Dose and Mode of Administration, Batch No.: In Europe, topiramate was supplied as white 25 mg (911 301, 913 410) and yellow 100 mg (909 301, 916 410, 917 410) tablets. In the United States, topiramate was supplied as white 25 mg (R5993) and yellow 100 mg (R6147) tablets. In this trial, maximum dosages of topiramate based on subjects' weight were 175 mg/day (25 to 33.9 kg), 225 mg/day (34 to 42.9 kg), 400 mg/day (≥43 kg).		
Duration of Treatment: The total duration of double-blind therapy was 140 days, including a 56-day titration period and an 84-day stabilization period.		
Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was supplied as "25 mg" (901 209, 902 209, R6130) and "100 mg" (917 301, R457) tablets to match topiramate tablets in Europe and the United States, respectively.		
Criteria for Evaluation: Efficacy: The efficacy of topiramate in the treatment of PGTC seizures was based on a statistically significant between-group difference with respect to percent reduction in average monthly PGTC seizure rate. Safety: Safety was evaluated by reported adverse events, clinical laboratory tests, vital sign and body weight measurements, ECGs, physical and neurologic examinations, and evaluations of the subject's mental status.		
Statistical Methods: A two-way (with treatment and center as factors) analysis of variance on ranks was used to analyze treatment group differences in percent reduction from baseline seizure rate for both PGTC seizures and all seizures. An additional efficacy assessment compared treatment groups with respect to percent of PGTC responders and responders based on all seizures, stratified by center, using the Cochran-Mantel-Haenszel method. Based on the baseline PGTC seizure rate imbalance between placebo (3.0 seizures/month) and topiramate (5.0 seizures/month), rank-based analysis was also done using baseline PGTC seizure rate as a covariate and PGTC treatment responders were analyzed using logistic regression with treatment, center, and baseline PGTC seizure rate as terms in the model. The global evaluation of improvement in seizure severity was analyzed by exact Wilcoxon rank-sum tests stratified by center and unstratified.		

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SUMMARY - CONCLUSIONS

EFFICACY RESULTS: Efficacy results of this trial consistently favored topiramate over placebo, although treatment comparisons generally did not achieve statistical significance using standard, unadjusted, intent-to-treat analysis. Analyses adjusting for the baseline PGTC seizure rate imbalance favored topiramate more strongly, resulting in a p-value of 0.078 for the primary efficacy variable, percent reduction from baseline in PGTC seizure rate (57.1% vs. 33.2%), and a highly significant difference (p=0.016) for the comparisons of percent responders based on PGTC seizures (54% vs. 35%) (Table 1). In addition, an examination of treatment response using a more rigorous definition, i.e., reduction in seizure rate of ≥75%, revealed a 21% difference in incidence of response statistically favoring topiramate (15% vs. 36%; p=0.040, unadjusted).

Table 1: Summary of the Efficacy Results of the Double-Blind Phase
(All Randomized Subjects; Protocol CR005830)

	Treatment Group		
Efficacy Assessment	Placebo (N=40)	Topiramate (N=40)	p-value
PGTC Seizures			
Primary Variable			
N	39	40	
Median percent reduction from baseline in average monthly seizure rate	33.2	57.1	0.124[a] 0.078[b]
Secondary Variable			
N	39	40	
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 covariates.
[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

Subjects treated with topiramate experienced a greater median percent reduction from baseline for all seizures, 26.0%, in comparison to 12.1% for subjects treated with placebo. The results of this statistical comparison were not significant (p=0.212). A 20% difference in responder rates between treatment groups was observed for all seizures, favoring topiramate (p=0.061). The between-group difference in the percentage of subjects demonstrating a ≥75% seizure rate reduction statistically favored topiramate (5% vs. 30%; p=0.005). An examination of response by seizure type was limited by the small number of patients within most seizure-type categories; only absence and myoclonic seizure rate could be reasonably assessed. Median percent reductions numerically favored topiramate for both absence and myoclonic seizures. Forty-eight percent of the subjects in the topiramate group reported marked or moderate improvement in seizure severity compared to the 33% in the placebo group reporting moderate improvement. None of the subjects treated with placebo reported marked improvement. The difference between treatment groups for this evaluation of global improvement achieved statistical significance (p=0.026). This subjective measure potentially includes changes in seizure severity that are not part of the seizure rate-based efficacy variables.

SYNOPSIS (Continued)

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EFFICACY RESULTS (Continued): The results of the plasma concentration analyses for concomitantly administered AEDs with sufficient subject data for evaluation did not reveal any significant differences between the treatment groups. There was no consistent relationship between efficacy and plasma topiramate concentration

SAFETY RESULTS: In this trial, neuropsychiatric treatment-emergent adverse events of nervousness and anorexia, in addition to vision abnormalities and diarrhea were reported more frequently in the topiramate group than in the placebo group (Table 2). In comparison, aggravated convulsions, injury, and upper respiratory tract infection were reported more frequently in the placebo group. Overall, the neuropsychiatric treatment-emergent adverse event profile was milder compared to that previously reported for topiramate-treated adult subjects with partial onset seizures. In general, this finding may be attributable to the slower titration rate for adults used in this trial compare to that used in the previous trials in adults with partial onset seizures with or without secondarily generalized seizures

Table 2: Incidence of Common[a] Neuropsychiatric Treatment-Emergent Adverse Events
(All Randomized Subjects; Protocol CR005830)

	Placebo (N=40)		Topiramate (N=40)	
Body System/Preferred Term	No.	%	No.	%
Somnolence	7	18	9	23
Headache	8	20	9	23
Fatigue	7	18	8	20
Nervousness	1	3	8	20
Anorexia	2	5	7	18
Confusion	4	10	6	15
Dizziness	6	15	6	15
Insomnia	3	8	5	13
Difficulty with memory (NOS)	2	5	4	10
Aggressive reaction	4	10	3	8
Ataxia	4	10	3	8
Convulsions (aggravated)	6	15	2	5

[a] Treatment-emergent neuropsychiatric adverse events reported by ≥10% of subjects in either treatment group.
NOS = not otherwise specified

One sudden death was reported in the placebo group. Six other subjects in the placebo group and five in the topiramate group prematurely discontinued study treatment. In both treatment groups, the adverse events associated with premature discontinuation were primarily neuropsychiatric signs and symptoms. In addition to the one death, 11 other subjects (seven in the placebo group and four in the topiramate group) reported serious treatment-emergent adverse events that resolved by the end of the study. Eleven subjects (four in the placebo group and seven in the topiramate group) had their dosage of study treatment adjusted because of (primarily) CNS-related adverse events. The majority of these events resolved with dosage reduction—all 11 subjects completed the study following dosage reduction. More subjects in the topiramate group than in the placebo group improved with regard to mental status during the study, i.e., increased alertness, interaction with the environment, activities of daily living, and responsiveness to verbal instructions. No noteworthy hematologic, renal, or liver toxicity was observed (most of the few observed abnormalities were sporadic, transient, and did not lead to alteration in treatment). Except for mild decreases in body weight, there were no noteworthy treatment-related changes in vital signs, ECGs, neurologic or physical examinations.

CONCLUSION: Topiramate at dosages up to 400 mg/day was well-tolerated in this trial of subjects with PGTC seizures with or without other generalized seizure types. Subjects treated with topiramate showed a significant reduction in the severity of seizures as measured by the subject's global evaluation of seizures, but were not significantly different from the placebo group in the rate of all seizures or the rate of PGTC seizures.

Date of the report: 24 June 1997

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