SYNOPSIS

NAME OF SPONSOR/COMPANY:	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
The R.W. Johnson Pharmaceutical Research Institute (RWJPRI) NAME OF FINISHED PRODUCT: TOPAMAX® (topiramate) NAME OF ACTIVE INGREDIENT(S): 2,3:4,5-Di-*O*-(isopropylidene)-β-D-fructopyranose sulfamate	Volume: 7 Page: 2105	

Protocol No.: CR005461

Title of Study: TOPAMAX (Topiramate) Monotherapy Comparison Trial to Standard Monotherapy in the Treatment of Newly Diagnosed Epilepsy

Investigators: 115 investigators

Study Centre(s): 115 centers

Publication (Reference): none	
Studied Period (years): 12 August 1997 - 29 February 2000	**Phase of development:**

Objectives: The objective of this trial was to compare the efficacy and safety of topiramate monotherapy to standard monotherapy (carbamazepine or valproate) in subjects with newly diagnosed epilepsy.

Methodology: This randomized, double-blind, parallel, multicenter, multinational trial compared the efficacy and safety of topiramate monotherapy to standard monotherapy (carbamazepine, CBZ, or valproate, VPA) in subjects with newly diagnosed epilepsy. The trial included three phases: baseline, double-blind, and blinded extension. Only the data collected through the end of the double-blind phase are included in this report. Eligibility was assessed during the baseline phase, which lasted for up to seven days. At the end of this phase, the investigators assigned each subject to either CBZ or VPA treatment branch, based on the clinical evaluation of the subject and the type of seizures the subject experienced. Within each branch, subjects were randomly assigned in equal proportions to one of the three treatment groups: topiramate 100 mg/day (TPM 100), topiramate 200 mg/day (TPM 200), or standard therapy (either CBZ 600 mg/day or VPA 1,250 mg/day). The double-blind phase was divided into two periods: titration (approximately 35 days) and stabilization (of variable duration). For subjects receiving a baseline AED, that AED was tapered off by the end of Week 5 of titration, while the dose of study medication was gradually increased. During stabilization, the dose of study medication remained constant. Subjects remained in the double-blind phase until a decision was made by either the investigator or the subject to i) discontinue, ii) change the study medication or dosing regimen, or iii) add another AED. The protocol-specified reasons for making such decision included ineffective treatment, adverse events, subject choice, loss to follow-up, and death. Subjects completed the double-blind phase either by exiting or by continuing study therapy until the trial was terminated (six months after the last subject was randomized).

Number of Subjects (planned and analyzed): Six hundred subjects with newly diagnosed epilepsy were to be enrolled in this trial. A total of 621 subjects were randomized; of those, 613 subjects contributed data after randomization and were included in the intent-to-treat analysis.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were at least six years of age, weighed at least 30 kg, had been diagnosed with epilepsy, and had at least one unprovoked seizure within three months before entering the study. The subjects had either no history of AED use or had received a single AED for no longer than six weeks.

Test Product, Dose and Mode of Administration, Batch No.: TPM was supplied in tablets for the CBZ branch (25-mg, 2 batches; 50-mg, 2 batches) and in capsules for the VPA branch (25-mg, 6 batches; 50-mg, 12 batches; see Table 3). TPM was administered in two divided doses. The treatment began in a twice-a-day regimen, which was subsequently changed to a three-times-a-day regimen, where a matching placebo was substituted for the afternoon TPM dose.

SYNOPSIS (CONTINUED)

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Duration of Treatment: Duration of double-blind therapy was variable for individual subjects (median duration, 244 days; range, 2-806 days). Subjects received double-blind treatment until i) exit for protocol-specified reasons, ii) planned study termination (6 months after randomization of the last subject), or iii) withdrawal for protocol violations.

Reference Therapy, Dose and Mode of Administration, Batch No.: VPA (divalproex sodium) was supplied in 250-mg capsules (27 batches); CBZ was supplied in 200-mg tablets (8 batches). Placebo was supplied in tablets for the CBZ branch (25-mg, 2 batches; 50-mg, 5 batches; 200-mg, 5 batches) and in capsules for the VPA branch (4 batches; see Table 3). The treatment with both CBZ and VPA began in a twice-a-day regimen; as the doses increased, the subjects were switched to a three-times-a-day regimen.

Criteria for Evaluation:

Efficacy: Efficacy assessment was based on similarity between topiramate treatment (TPM 100/200) and standard treatment (CBZ/VPA) with respect to the clinical utility endpoint (time to exit), and efficacy endpoints (seizure freedom during the last six months of the double-blind phase and time to first seizure).

Safety: Safety was evaluated on the basis of treatment-emergent adverse events, clinical laboratory tests, measurements of vital signs and body weight, and physical examination findings.

Statistical Methods: The primary efficacy analysis compared TPM 100 and TPM 200 with respect to the time to first seizure from Day 15. In further analyses, TPM 100 and TPM 200 were pooled within each branch for comparison with standard AEDs with respect to the time to exit, proportion of seizure-free subjects during the last six months of the double-blind phase, and time to first seizure. Kaplan-Meier estimates were calculated for time to first seizure from Day 15, time to exit, and time to first seizure. All analyses were stratified by branch. The differences in the Kaplan-Meier curves between TPM 100/200 and CBZ/VPA at selected time points were estimated by 95% confidence intervals (CI), using the method of Laird and Mosteller. Heterogeneity between branches was tested using Cochran's test. Consistency of the treatment effects with respect to demographic/baseline characteristics was assessed using Cox's proportional hazards model.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: TPM monotherapy, administered at the doses of 100 mg/day or 200 mg/day, was at least as efficacious as the physician's preferred AEDs in reducing seizures among adults and children with newly diagnosed epilepsy. TPM treatment and standard treatment were comparable with respect to all clinical utility and efficacy endpoints, i.e., i) time to exit, ii) proportion of subjects free of seizures during the last six months of the double-blind phase, and iii) time to first seizure. The 95% CIs for the differences between the two treatments with respect to each of these endpoints were narrow and included zero. After six months of therapy, the retention rates on the study could be up to 5.7% higher in the subjects receiving standard treatment, compared with those receiving topiramate; on the other hand, topiramate monotherapy could have an advantage of up to 10.4% over the physician's preferred standard AED. Seizure-free rates during the last six months of therapy could be only up to 6.1% higher in the standard treatment group, but up to 10.6% higher in the topiramate treatment group.

SAFETY RESULTS: The most common treatment-emergent adverse events reported across study treatments were neuropsychiatric in nature. Dizziness, somnolence, difficulty with memory, anxiety, hypoesthesia, and asthenia were reported at similar rates across all study treatments. The TPM-treated subjects experienced higher incidences of paresthesia, anorexia, insomnia, depression, and nervousness. Some neuropsychiatric adverse events were reported at lower rates by the subjects treated with TPM 100, compared to those treated with TPM 200. Adverse events reported at higher incidences in CBZ-treated subjects included nausea, rash, abdominal pain and menstrual disorder. Alopecia and tremor occurred primarily in the subjects receiving VPA. Weight decrease was reported at similar rates in the TPM- and CBZ-treated subjects; weight increase was reported mostly in the VPA group.

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SAFETY RESULTS (Continued):

Table A: Incidence of The Most Common[a] Treatment-Emergent Adverse Events (Intent-to-Treat Population; Protocol CR005461)

Body System	TPM 100 (N=210)		TPM 200 (N=199)		CBZ (N=126)		VPA (N=78)	
Preferred Term	No.	%	No.	%	No.	%	No.	%
Neuropsychiatric								
Paraesthesia	52	25	66	33	5	4	2	3
Headache	52	25	36	18	37	29	14	18
Fatigue	43	20	45	23	36	29	14	18
Dizziness	28	13	24	12	20	16	8	10
Somnolence	26	12	25	13	18	14	12	15
Anorexia	23	11	27	14	6	5	3	4
Depression	16	8	21	11	5	4	2	3
Insomnia	21	10	14	7	4	3	1	1
Difficulty with Concentration /Attention	9	4	22	11	5	4	1	1
Tremor	6	3	2	1	3	2	13	17
Other Body Systems								
Upper respiratory tract infection	37	18	34	17	19	15	9	12
Nausea	15	7	28	14	25	20	11	14
Weight Decrease	20	10	24	12	10	8	1	1
Infection Viral	13	6	20	10	10	8	4	5
Rash	13	6	7	4	13	10	4	5
Alopecia	9	4	4	2	3	2	11	14
Weight Increase	4	2	4	2	3	2	9	12

[a] Adverse events that occurred in at least 10% of subjects in any of the treatment groups

No deaths were reported in the double-blind phase of the study. Serious adverse events were reported for 15 subjects (7%) treated with TPM 100, 17 subjects (9%) treated with TPM 200, 8 subjects (6%) receiving CBZ, and 4 subjects (5%) receiving VPA. Most of these events were transient and were considered by the investigators to be of doubtful or no relationship to the study medication. Five TPM-treated subjects and two VPA-treated subjects discontinued the study treatment due to serious adverse events.

Tolerability of topiramate monotherapy was at least as good as that of the physician's preferred AEDs, based on 95% CIs for the difference between the treatments in rates of discontinuation due to adverse events. This rate was lower among the subjects receiving TPM 100 (19%), compared to the other treatments, where it ranged from 23% in subjects receiving VPA to 28% in subjects receiving TPM 200. Neuropsychiatric adverse events, such as fatigue, paresthesia, somnolence, anorexia, and mood problems, were most likely to contribute to discontinuation of TPM therapy. These events were usually reported at lower rates in TPM 100 than in TPM 200 group. In the subjects receiving standard AEDs, common reasons for the discontinuation of therapy included rash and gastrointestinal adverse events (CBZ group), and alopecia, tremor, weight increase, and thrombocytopenia (VPA group).

There were no clinically important changes or abnormalities in vital sign measurements or in laboratory tests of liver function, renal function, and hematologic parameters.

CONCLUSION: The results of this study demonstrate that topiramate, administered as monotherapy at the doses of 100 or 200 mg/day, was efficacious in the treatment of adults and children with newly diagnosed epilepsy. The global clinical utility and efficacy of topiramate were at least as good as those of the physician's treatment of choice in a broad range of epilepsy syndromes. The safety and tolerability profile of topiramate 100 mg/day compared favorably with those of topiramate 200 mg/day. Overall, topiramate monotherapy was well tolerated and did not present any unexpected or unusual safety risks.

Date of the report: 26 OCTOBER 2000

SYNOPSIS (CONTINUED)

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