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 IV OF THE DOSSIER Volume: 1 Page: 17	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: CR005470

Title of Study: Single-Center Topiramate Monotherapy Trial

Investigator: Rajesh Sachdeo, MD.

Study Centre(s): University of Medicine and Dentistry of New Jersey, New Brunswick, NJ; USA.

Publication (Reference): Sachdeo RC, Reife RA, Lim P, Pledger G. Topiramate monotherapy for partial onset seizures. Epilepsia 1997; 38:294-300.

Studied Period (years): 04 September 1992 through 20 January 1995 | **Phase of development:** 3

Objectives: The primary objective of the study was to evaluate the safety and efficacy of topiramate monotherapy in subjects with partial onset seizures with or without secondarily generalized seizures.

Methodology: This was a single center, randomized, double-blind, parallel group study conducted in the United States to evaluate topiramate (TPM) at oral dosages of 100 and 1000 mg/day as monotherapy in subjects with refractory partial onset seizures. The trial included an 8-week baseline phase during which eligibility for study entry was determined, a 1-week open-label therapy phase during which subjects received 100 mg TPM daily, and a double-blind treatment phase consisting of two periods, a 5-week conversion period and an 11-week monotherapy period. During the conversion period, baseline AED(s) were gradually discontinued and, for subjects in the 1,000 mg/day group, TPM was titrated to the assigned 1,000 mg/day dosage or the maximum tolerated dosage, if less. Subjects remained in the double-blind phase until they completed the planned 16-week double-blind phase (successes) or reached any of the four exit criteria designed to correspond to therapeutic failure and to ensure subject safety: i) a doubling of the average monthly (28-day) seizure frequency compared to baseline; ii) a doubling of the highest two-day seizure frequency that occurred during baseline; iii) a single generalized seizure if none occurred during the baseline phase; iv) or prolongation of generalized seizure duration (serial seizures or status epilepticus) as compared to the baseline phase seizure duration and requiring intervention. Efficacy was evaluated on the basis of data regarding seizure type and frequency obtained from seizure diaries maintained by each subject for the duration of the trial, and on investigator and subject global evaluations of clinical response to study medication. Safety assessment was based on reported adverse events, clinical laboratory tests, serum gastrin concentrations, investigator and subject global evaluations of tolerability of study medication, neuropsychologic tests, neurologic examinations, vital sign measurements, body weights, and physical examinations. Plasma topiramate and concomitant AED concentrations were measured at periodic intervals.

Number of Subjects (planned and analyzed): 48 planned and analyzed.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were at least 14 years of age with an unequivocal history of frequent partial onset seizures with or without secondarily generalized seizures and a recent history of maintenance on a single standard AED at therapeutic plasma concentrations, or two standard AEDs — one at therapeutic plasma concentrations and one at a concentration no more than 50% of the therapeutic lower limit. For entry into the open-label phase of the trial, subjects were required to have an average of at least four partial seizures per month while being maintained on a constant AED dosage during the eight-week baseline phase. An EEG or CCTV/EEG consistent with a focal seizure disorder and a CT scan or MRI confirming the absence of a progressive lesion were required.

Test Product, Dose and Mode of Administration, Batch No.: Topiramate tablets (100 mg), target dosages of 100 mg/day and 1000 mg/day administered orally, Batch Nos. R4561 and R5509.

SYNOPSIS (CONTINUED)

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Duration of Treatment: All subjects received 100 mg/day TPM during the 1-week open-label phase. Thereafter, 24 subjects received 100mg/day TPM and 24 subjects received up to 1,000 mg/day during the 16-week double-blind phase.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo tablets (100 mg) taken orally in combination with topiramate for a 16-week double-blind phase. Batch No. R4567.

Criteria for Evaluation: Efficacy: The primary efficacy variable was time-to-exit during double-blind treatment. Secondary variables included investigator and subject global evaluations of clinical response to study medication. Plasma topiramate and concomitant AED concentrations were measured. Safety: Safety evaluations included assessments of the incidence and severity of adverse events, clinical laboratory tests, serum gastrin concentrations, vital sign measurements, body weights, investigator and subject global evaluations of tolerability of study medication, neuropsychologic tests, neurologic examinations, and physical examinations.

Statistical Methods: The analyses included all randomized subjects (i.e., intent-to-treat). The between-group difference in time-to-exit, the primary efficacy variable, was compared using the log rank test. Fisher's exact test was used for a between-group comparison of the number of subjects completing the study. Between-group differences in investigator and subject global evaluations of improvement were tested using the Wilcoxon rank sum test. Average plasma topiramate concentrations over time were plotted for each treatment group and mean plasma TPM concentrations of those who exited (failures) and those who did not (successes) were summarized.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS: In the 1,000 mg/day topiramate dosage group, 13 (54%) of 24 subjects were successes, i.e., reached and completed the monotherapy period without meeting any of the four exit criteria, compared to four (17%) of 24 subjects in the 100 mg/day dosage group (Table A).

Table A: Summary of Efficacy Results for the Double-Blind Phase
(All Randomized Subjects; Protocol CR0054)

	TPM 100 mg/day (N=24)		TPM 1,000 mg/day (N=24)		
	N	%	N	%	p-value
Successes[a]	**4**	**17**	**13**	**54**	**—**
≥50% Reduction	3	13	11	46	—
≥75% Reduction	2	8	6	25	—
100% Reduction	0	0	3	13	—
Failures[b]	**20**	**83**	**9**	**38**	**0.005**[d]
Dropouts	**0**	**0**	**2**	**8**	**—**
Global Evaluations of Clinical Response to Study Medication[c]					
Investigator Evaluation	8	33	20	83	<0.001[e]
Subject Evaluation	11	46	21	88	0.002[e]

[a] Percent reduction in average monthly seizure rate is provided only for subjects who completed the study without exiting (i.e., successes).
[b] Subjects meeting an exit criterion.
[c] Number and percent of subjects with minimal, moderate, or marked improvement.
[d] Fisher's exact test.
[e] Wilcoxon rank sum test.

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EFFICACY RESULTS (continued): The time-to-exit was statistically significantly greater for the topiramate. 1,000 mg/day group compared with the topiramate 100 mg/day dosage group (log rank test; p=0.002). Among subjects who successfully completed double-blind therapy, a reduction in seizure rate of 50% or greater from baseline to the end of double-blind therapy was observed for 11 (46%) subjects in the 1,000 mg/day group compared to three (13%) subjects treated with 100 mg/day. Among subjects in the 1,000 mg/day group, six (25%) had a seizure reduction of 75% or greater and three were seizure-free during the entire double-blind phase.

Overall, improvement was found in 83% vs. 33% of the 1,000 mg/day- and 100 mg/day-treated subjects based on the investigator's assessment; overall improvement rates in the two dosage groups were 88% vs. 46% based on the subject's assessment. Statistical comparisons for both global assessments favored the 1,000 mg/day dosage group ($p \leq 0.002$).

SAFETY RESULTS: The incidence of adverse events was similar between the two topiramate groups, with the exception of the incidence of anorexia (42% in the 1000 mg/day group vs. 13% in the 100 mg/day group); the difference may be due in part to the longer duration of treatment of subjects in the 1000 mg/day group. The most frequently reported adverse events were paresthesia, fatigue, anorexia, dizziness, and headache (Table B).

Table B: Incidence of the Most Common[a] Treatment-Emergent Adverse Events (All Randomized Subjects; Protocol CR005470)

Body System	TPM 100 mg/day (N=24)		TPM 1.000 mg/day (N=24)	
Preferred Term	No.	%	No.	%
CNS-Related				
Paresthesia	15	63	14	58
Fatigue	8	33	11	46
Anorexia	3	13	10	42
Dizziness	6	25	6	25
Headache	6	25	6	25
Insomnia	5	21	4	17
Confusion	5	21	3	13
Nervousness	4	17	2	8
Other Body Systems				
Upper Respiratory Infection	4	17	5	21
Dyspnea	0	0	4	17
Nausea	6	25	4	17

[a] Reported by ≥15% of subjects in either dosage group across the open-label and double-blind phases of the trial.

One subject in each dosage group reported a renal calculus. No deaths occurred during the study and no serious or potentially serious adverse events were reported. Four subjects discontinued TPM due to adverse events, three during open-label 100 mg/day TPM treatment and one after randomization to the 1,000 mg/day TPM group. Consistent with other topiramate trials, mild weight loss (5%-7% average) was noted over time. No clinically noteworthy findings were reported based on clinical laboratory tests, vital signs, neurologic examinations, and physical examinations.

CONCLUSION: Topiramate monotherapy was effective in the treatment of refractory partial epilepsy with or without secondarily generalized seizures. Topiramate 1000 mg/day was statistically superior to topiramate 100 mg/day for all efficacy variables and was well tolerated.

Date of the report: 09 June 95

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