Janssen Research & Development

Clinical Study Report Synopsis
[Protocol TOPMAT-MIGR-001; Phase 3]

RWJ-17021-000 (Topiramate)

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- To disclose as much scientifically useful data as possible, no information other than that outlined above has been removed or redacted.

SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: TOPAMAX® (topiramate) NAME OF ACTIVE INGREDIENT(S): 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: TOPMAT-MIGR-001 **Title of Study:** A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study to Evaluate the Efficacy and Safety of Topiramate in the Prophylaxis of Migraine		
Coordinating Investigator: [redacted] M.D. - [redacted] USA		
Publication (Reference): None		
Study Initiation/Completion Dates: 15 February 2001 to 29 April 2002		**Phase of development:** 3
Objectives: The primary objective of this trial was to evaluate the safety and efficacy of 3 doses of topiramate (50, 100, and 200 mg/day) compared with placebo in migraine prophylaxis. Secondary objectives were to assess the dose-response relationship for topiramate and to evaluate the effect of prophylactic treatment with topiramate compared with placebo on health-related quality of life (HRQOL).		
Methodology: This randomized, double-blind, placebo-controlled, parallel-group, multicenter trial conducted in the U.S. evaluated the efficacy and safety of 3 doses of topiramate (50, 100, and 200 mg/day) versus placebo for migraine prophylaxis. The trial included 5 phases: baseline, double-blind, blinded transition, open-label extension, and taper/exit. 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 up to 42 days and included a 14-day washout and 28-day prospective baseline period. All prophylactic migraine medication was tapered during the washout period. Subjects recorded headache (migraine and non-migraine) information in headache records during the trial. Only subjects with an established history of migraine with or without aura according to International Headache Society (IHS) criteria were eligible to enter the trial. Eligibility was also determined based on the number of i) migraine periods (based on migraine information classified according to subject's own judgment and defined as the length of time between the onset and cessation of painful migraine symptoms that could last up to, but no longer than, 24 hours), and ii) headache days (migraine and non-migraine) during the prospective baseline period. Subjects with 3 to 12 migraine periods, but no greater than 15 headache days were eligible for randomization in equal proportions to 1 of 4 treatment groups: topiramate 50 mg/day (TPM 50), topiramate 100 mg/day (TPM 100), topiramate 200 mg/day (TPM 200), or placebo. The double-blind phase was divided into 2 periods: titration (8 weeks) and maintenance (18 weeks). Study medication began at a daily dose of 25 mg/day and was titrated upwards in weekly increments of 25 mg/day until either the assigned dose or maximum tolerated dose was achieved. During maintenance, the dose of study medication was to remain constant; however, a total of 2 dose reductions were allowed during the double-blind phase. Subjects were considered to have completed the double-blind phase if they completed all 26 weeks of double-blind treatment (i.e., 8 weeks of titration and 18 weeks of maintenance). At the end of treatment, regardless of the phase, study medication was tapered during a 2-week taper/exit phase.		
Number of Subjects (planned and analyzed): Four hundred eighty subjects with an established history consistent with migraine were to be enrolled in this trial. A total of 487 subjects were randomized; of these, 469 contributed efficacy data during the double-blind phase and were included in the intent-to-treat analyses and 473 contributed safety data during the double-blind phase and were included in the safety analyses.		
Diagnosis and Main Criteria for Inclusion: Eligible subjects were between 12 and 65 years of age, had an established history (at least 6 months) consistent with migraine based on IHS criteria. Subjects must have failed no more than 2 previous adequate regimens of prophylactic medications for recurrent migraine episodes. Eligible subjects had 3 to 12 migraine periods and no more than 15 headache days during the prospective baseline period, and were not receiving any concomitant prophylactic medication for migraine.		
Test Product, Dose and Mode of Administration, Batch No.: Topiramate was supplied as 25-mg tablets (Bulk Batch No. D99LL0245). Topiramate was administered orally twice a day (b.i.d.) in equally divided doses, except during the first week of titration.		
Duration of Treatment: The planned duration of double-blind treatment was 26 weeks.		
Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was supplied as tablets matching topiramate (Bulk Batch No. D99K0222), and was administered orally b.i.d., except during the first week of titration.		

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Criteria for Evaluation:

Pharmacokinetics: Topiramate plasma concentrations were collected at up to 2 time points (once during the titration and once during the maintenance period) after dosing began.

Efficacy: The primary efficacy assessment was based on the comparison of topiramate to placebo with respect to change in the monthly (28-day) migraine period rate averaged over the entire double-blind phase versus the rate at baseline. The following endpoints were included in the secondary efficacy evaluation: i) responder rate (response defined as at least a 50% reduction in average monthly migraine period rate); ii) onset of action for a treatment group was defined as the earliest monthly time point a statistically significant difference in the primary efficacy endpoint was detected between placebo and topiramate treatment groups; iii) change in number of monthly migraine attacks (classified according to an algorithm based on IHS criteria); iv) change in the average monthly rate of rescue medication use; v) change in number of migraine days per month; and vi) HRQOL measured in subjects 18 years of age or older by 2 of the Medical Outcomes Short Form-36 (SF-36) domains (Vitality, Role Physical) and 2 of the Migraine-Specific Questionnaire (MSQ) domains (Role Restrictive, Role Prevention). Other efficacy variables included monthly migraine duration; types of headache; average migraine severity; and severity of migraine-associated symptoms.

Safety: Safety was evaluated on the basis of treatment-emergent adverse events (including abnormal findings in physical examinations), clinical laboratory tests, measurements of vital signs, body weight and BMI, and neurologic examination findings.

Statistical Methods: The primary efficacy endpoint, the change in average monthly migraine period rate, was analyzed using a linear model with baseline value as a covariate and analysis center and treatment as factors. Statistical significance of the treatment effect was assessed using the Tukey-Ciminera-Heyse trend test (a step-down procedure that assumes a monotonic dose-response relationship). The same model and unadjusted pairwise comparisons were used to analyze the primary efficacy endpoint and secondary efficacy endpoints of the change in: average monthly migraine attack rate, average monthly migraine days, and average monthly rate of rescue medication use. The Cochran-Mantel-Haenszel pairwise test was used to assess treatment differences in the proportion of responders. The onset of action was determined for a topiramate treatment group by evaluating the monthly pairwise comparison between the treatment group and placebo in the cumulative monthly migraine period rate. The average migraine duration, types of headache, average migraine severity, and severity of migraine-associated symptoms were summarized for each treatment group. Between-group differences in the HRQOL endpoints were analyzed using a mixed-effects piecewise linear regression model. Possible associations between the changes in the primary efficacy endpoint and HRQOL endpoints were examined using a Spearman's rank correlation analysis. Plasma topiramate concentrations were summarized descriptively for each dose group. The percent change in body weight from baseline to the end of the double-blind phase was analyzed using a linear model with treatment as a factor; comparisons between placebo and each topiramate group were performed using unadjusted pairwise comparisons.

SUMMARY – CONCLUSIONS

PHARMACOKINETICS: The plasma concentrations of topiramate at the final visit were dose dependent, averaging 2.4 µg/mL in the TPM 50 group, 3.8 µg/mL in the TPM 100 group, and 5.4 µg/mL in the TPM 200 group.

EFFICACY RESULTS: The results of the primary efficacy analysis demonstrated statistically significant differences between placebo and TPM 100 and 200 in the change from baseline to the double-blind phase in the average monthly migraine period rate (p values <0.001), indicating that topiramate at dosages of 100 and 200 mg/day was effective in migraine prophylaxis. TPM 50 was not shown to be statistically different from placebo based on the change from baseline in average monthly migraine period rate. The treatment effect for the primary and key secondary efficacy variables and the analysis results are summarized in the table below. All statistical comparisons are relative to the placebo group.

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Summary of Primary Efficacy and Key Secondary Efficacy Endpoints
(Study TOPMAT-MIGR-001: Intent-to-Treat Population)

Efficacy Endpoint	PBO	TPM 50 mg/day		TPM 100 mg/day		TPM 200 mg/day	
Migraine Period Rate	**-0.8**	**-1.3**	**NS**	**-2.1**	******	**-2.2**	******
Responder Rate, %	23%	36%	*	54%	**	52%	**
Onset of Action (at Month 1)	0.0	-0.9	*	-1.0	*	-1.6	**
Migraine Attack Rate	-0.7	-1.3	NS	-1.9	**	-2.1	**
Rescue Medication Use (days)	-0.9	-1.5	NS	-2.0	**	-2.1	**
Migraine Days	-1.0	-1.6	NS	-2.7	**	-2.6	**

NS= denotes nominal p value of p>0.05; * denotes nominal p-value of ≤0.05; ** denotes nominal p value of ≤0.01; all tests were 2 sided and all values are the least squares mean changes from baseline to the double-blind phase except for the Responder Rate, see text for definitions and analysis methods.

Because of a statistically significant treatment-by-baseline interaction (p=0.043), a transformation of the primary efficacy endpoint to a percent reduction in average monthly migraine period rate from baseline to the double-blind phase was performed for each subject, and analyzed using a 2-way analysis of variance on ranks. Results of this analysis indicated that the percent reductions in average monthly migraine period rate were statistically significantly larger in all 3 topiramate groups compared with the placebo group (p values of 0.048, <0.001, and <0.001 for comparisons involving the TPM 50, TPM 100, and TPM 200 groups, respectively).

Examination of the dose-response relationship in terms of the mean change from baseline in average monthly migraine period rate showed no statistically significant difference between TPM 100 and TPM 200 (p=0.799), but each was different from TPM 50 (TPM 50 vs. 100: p=0.020, and TPM 50 vs. 200: p=0.012). The effect of TPM 100 and 200, measured by the onset of action, was shown to begin at Month 1 and remained statistically significant until the end of the double-blind phase. Greater proportion of responders, measured by the responder rate, were found in the TPM 50, TPM 100, and TPM 200 groups compared to placebo (all p values ≤0.036). Many of the secondary findings were consistent with the primary analysis in that, statistically significant differences were found between placebo and TPM 100 and TPM 200, but not TPM 50, with respect to the average monthly: migraine attack rate, rate of rescue medication use, and migraine days. *SF-36:* The comparisons between topiramate and placebo for the SF-36 Role Physical and Vitality domains were not statistically significant for any dosage group. *MSQ:* The comparisons between topiramate and placebo on the MSQ domain of Role Restrictive were statistically significant for all comparisons (all p values ≤0.035) and on the domain of Role Prevention for the TPM 100 group (p=0.045). *SF-36 and MSQ Correlation Analysis:* All correlations between the changes in SF-36 and MSQ measures and the primary efficacy endpoint were statistically significant.

SAFETY RESULTS: The most common (reported by at least 10% of subjects in any treatment group) treatment-emergent adverse events reported in the topiramate groups were related to the central and peripheral nervous system or psychiatric in nature. In all body systems, paresthesia, language problems, anorexia, anxiety, difficulty with memory, difficulty with concentration/attention, mood problems, nervousness, taste perversion, and weight decrease were reported more often in the TPM 50, TPM 100, and TPM 200 groups versus the placebo group.

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Incidence of the Most Common[a] Treatment-Emergent Adverse Events by Preferred Term
(Study TOPMAT-MIGR-001: Safety Population)

Body System Preferred Term	Placebo (N=116) n (%)	TPM 50 mg/day (N=118) n (%)	TPM 100 mg/day (N=126) n (%)	TPM 200 mg/day (N=113) n (%)
Central and Peripheral Nervous System				
Paresthesia	8 (7)	43 (36)	59 (47)	53 (47)
Dizziness	13 (11)	9 (8)	10 (8)	14 (12)
Language problems	1 (1)	7 (6)	10 (8)	15 (13)
Psychiatric				
Anorexia	5 (4)	13 (11)	16 (13)	16 (14)
Difficulty with memory	3 (3)	11 (9)	9 (7)	14 (12)
Difficulty with concentration/attention	1 (1)	3 (3)	5 (4)	11 (10)
Body as a Whole				
Fatigue	12 (10)	11 (9)	14 (11)	20 (18)
Injury	11 (9)	16 (14)	9 (7)	8 (7)
Gastrointestinal System				
Nausea	14 (12)	8 (7)	20 (16)	16 (14)
Diarrhea	8 (7)	8 (7)	14 (11)	17 (15)
Respiratory System				
Upper respiratory tract infection	14 (12)	14 (12)	19 (15)	14 (12)
Sinusitis	12 (10)	10 (8)	16 (13)	10 (9)
Special Senses				
Taste perversion	2 (2)	23 (19)	13 (10)	16 (14)
Metabolic and Nutritional				
Weight decrease	1 (1)	6 (5)	12 (10)	13 (12)
Vision				
Abnormal vision	3 (3)	7 (6)	2 (2)	11 (10)

[a] Adverse events that were reported by at least 10% of the subjects in any treatment group.

There were no deaths reported in the double-blind phase of this trial. There were 4 subjects in the placebo group and 6 topiramate-treated subjects with serious adverse events. Only 1 of the serious adverse events (renal calculus) was considered to be related to topiramate; this was the only serious adverse event that led to premature discontinuation of topiramate therapy.

The number of subjects in the safety population who discontinued due to any adverse event was 12 (10%) in the placebo group and 21 (18%), 25 (20%), and 39 (35%) in the TPM 50, 100, and 200 groups, respectively. The most common (occurring in ≥2% of all topiramate-treated subjects) events leading to discontinuation of topiramate therapy included paresthesia, hypoesthesia, anxiety, insomnia, aggravated depression, difficulty with memory, nervousness, confusion, dizziness, language problems, fatigue, nausea, and diarrhea.

There were no clinically important changes or abnormalities in vital sign measurements, neurologic examinations, or in laboratory tests of liver function, renal function, and hematologic parameters. A reduction in body weight was observed in the topiramate treatment groups. All topiramate groups exhibited greater mean weight loss compared with the placebo group and statistically significantly greater percent decreases from baseline to the end of the double-blind phase were found in the TPM 50, TPM 100, and TPM 200 groups compared to placebo.

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CONCLUSION: The results of this study demonstrated that topiramate at doses of 100 and 200 mg/day was effective in migraine prophylaxis as measured by a mean reduction in the average monthly migraine period rate, migraine days, migraine attack rate, rescue medication use, and a 50% or greater decrease in the average monthly migraine period rate (responder rate). The effect of topiramate 100 and 200 mg/day in migraine prophylaxis was shown to begin at Month 1. The effect of topiramate 50 mg/day was seen in a statistically significantly higher responder rate compared with placebo. There were no statistically significant differences between the topiramate 100 and 200 mg/day groups with respect to the primary efficacy endpoint; however, each of these groups was found to be more effective than topiramate 50 mg/day. Topiramate 50, 100, and 200 mg/day showed a positive effect on 1 measure of health-related quality of life and a second measure showed a positive effect from topiramate 100 mg/day. The safety and tolerability profile demonstrated that, in general, topiramate 50 mg/day and topiramate 100 mg/day were better tolerated than topiramate 200 mg/day. All doses were safe and adverse events were similar to those seen in topiramate monotherapy studies. Topiramate did not present any unusual or unexpected safety risks in subjects with migraine.

Date of the report: 31 OCTOBER 2002