Janssen Research & Development

Clinical Study Report Synopsis
[Protocol TOPMAT-MIGR-002; Phase 3]

RWJ-17021-000 (Topiramate)

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- Information has been removed or redacted to protect commercially confidential information.
- Aggregate data have been included, with any direct reference to an individual patient or study subject excluded.
- 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.: PRI/TOP-INT-48 (TOPMAT-MIGR-002) **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: 1 March 2001 to 4 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. and Canada 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 study. Only subjects with an established history of migraine with or without aura according to International Headache Society (IHS) criteria were eligible to enter the study. 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 483 subjects were randomized; of these, 468 contributed efficacy data during the double-blind phase and were included in the intent-to-treat analyses, and 466 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, and 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 in a 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. D99LK0222), and was administered orally twice a day, except during the first week of titration.		

SYNOPSIS (CONTINUED)

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Criteria for Evaluation:

Pharmacokinetics: Topiramate plasma concentrations were collected at 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 that topiramate treatment group; 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 analyzed using the Tukey-Ciminera-Heyse trend test (a step-down procedure that assumes a monotone dose-response relationship). The same model and unadjusted pairwise comparisons were used to analyze the primary efficacy endpoint and the secondary efficacy endpoints of the change in: average monthly migraine attack rate, average monthly migraine days, average monthly migraine duration, average migraine severity, average monthly rate of rescue medication use, and average severity of migraine-associated symptoms. 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. 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 was dose dependent, averaging 2.5 µg/mL in the TPM 50 group, 3.7 µg/mL in the TPM 100 group, and 5.9 µg/mL in the TPM 200 group.

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS (Continued)

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≤0.008), 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 primary efficacy analysis. 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.

Summary of Primary Efficacy and Key Secondary Efficacy Endpoints
(Study TOPMAT-MIGR-002: Intent-to-Treat Population)

Efficacy Endpoint	PBO	TPM 50 mg/day		TPM 100 mg/day		TPM 200 mg/day	
Migraine Period Rate	**-1.1**	**-1.4**	**NS**	**-2.1**	*****	**-2.4**	******
Responder Rate, %	23%	39%	*	49%	**	47%	**
Onset of Action (at Month 1)	-0.3	-0.8	NS	-1.2	*	-1.6	*
Migraine Attack Rate	-1.0	-1.2	NS	-1.8	*	-1.7	*
Rescue Medication Use (Days)	-1.0	-1.4	NS	-2.1	*	-2.2	*
Migraine Days	-1.3	-1.7	NS	-2.6	*	-2.9	**

NS= denotes nominal p value of >0.05; * denotes nominal p value of ≤0.05; ** denotes nominal p values of ≤0.001; 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.

Examination of the dose-response relationship in terms of the primary efficacy endpoint showed no statistically significant difference between TPM 100 and TPM 200 (p=0.426), but each was different from TPM 50 (TPM 50 vs. 200: p=0.006 and TPM 50 vs. 100: p=0.049) 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 ≤0.010). 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 in days, and migraine days. A statistically significant difference from placebo for migraine duration was found only in the TPM 200 group (p=0.007) and for migraine severity only in the TPM 100 group (p=0.037). There were no statistically significant differences found between placebo and any topiramate treatment groups in the analysis of severity of migraine-associated symptoms (nausea, photophobia, and phonophobia). *SF-36:* Statistically significant improvements in the SF-36 Role Physical domain were found in the TPM 100 (p=0.022) and 200 (p=0.017) groups compared with placebo, but not in the TPM 50 group versus placebo (p=0.228). The comparisons between topiramate and placebo for the SF-36 Vitality domain were not statistically significant for any treatment group. *MSQ:* The comparisons between topiramate and placebo on the MSQ domains of Role Restrictive and Role Prevention were statistically significant for all comparisons (all p values ≤0.019). *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 neurologic or psychiatric in nature. In all body systems, paresthesia, hypoesthesia, fatigue, diarrhea, taste perversion, and weight decrease were reported more often in the TPM 50, TPM 100, and TPM 200 groups versus the placebo group. Paresthesia was reported at a higher incidence in the TPM 100 and 200 groups versus the TPM 50 group. Some events, such as anorexia, difficulty with memory, anxiety and confusion occurred at lower incidences in the placebo and TPM 50 groups than in the TPM 100 and 200 groups.

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Incidence of the Most Common[a] Treatment-Emergent Adverse Events by Preferred Term
(Study TOPMAT-MIGR-002: Safety Population)

Body System Preferred Term	Placebo (N=113) n (%)	TPM 50 mg/day (N=117) n (%)	TPM 100 mg/day (N=119) n (%)	TPM 200 mg/day (N=117) n (%)
Central & Peripheral Nervous System				
Paresthesia	5 (4)	40 (34)	59 (50)	57 (49)
Dizziness	14 (12)	10 (9)	10 (8)	12 (10)
Hypoesthesia	0	9 (8)	13 (11)	12 (10)
Psychiatric				
Anorexia	9 (8)	9 (8)	16 (13)	17 (15)
Difficulty with memory	4 (4)	6 (5)	12 (10)	18 (15)
Somnolence	10 (9)	9 (8)	8 (7)	14 (12)
Other body systems				
Fatigue	10 (9)	22 (19)	17 (14)	21 (18)
Upper respiratory tract infection	12 (11)	17 (15)	14 (12)	14 (12)
Diarrhea	4 (4)	12 (10)	13 (11)	14 (12)
Nausea	8 (7)	13 (11)	12 (10)	11 (9)
Sinusitis	9 (8)	13 (11)	7 (6)	15 (13)
Taste perversion	0	13 (11)	10 (8)	16 (14)
Injury	9 (8)	4 (3)	8 (7)	14 (12)
Weight decrease	3 (3)	7 (6)	13 (11)	11 (9)

[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 study. There were 2 subjects in the placebo group and 4 topiramate-treated subjects with nonfatal serious adverse events. Only 1 of the serious adverse events (renal calculus in the TPM 100 group) was considered probably related to topiramate and no subjects discontinued topiramate therapy due to serious adverse events.

The number of subjects in the safety population who discontinued due to any adverse event was 14 (12%) in the placebo group and 20 (17%), 32 (27%), and 26 (22%) 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, fatigue, nausea, abdominal pain, somnolence, difficulty with memory, difficulty with concentration and attention, insomnia, diarrhea, confusion, dizziness, and language problems.

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. 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.

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 the mean reduction in the average monthly migraine period rate, migraine days, migraine attack rate, rate of 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 health related quality of life. Overall, the safety and tolerability profile was comparable between topiramate 100 mg/day and 200 mg/day, and topiramate 50 mg/day was better tolerated than topiramate 100 and 200 mg/day. All doses were safe and adverse events were similar to those seen in other topiramate monotherapy studies. Topiramate did not present any unusual or unexpected safety risks in subjects with migraine.

Date of the report: 04 OCTOBER 2002