Janssen Research & Development

Clinical Study Report Synopsis
[Protocol TOPMAT-MIGR-003; Phase 3]

RWJ-17021-000 (Topiramate)

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SYNOPSIS

NAME OF SPONSOR/COMPANY:	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
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	Volume: Page:	

Protocol No.: PRI/TOP-INT-47 (TOPMAT-MIGR-003)
Title of Study: A Randomized, Double-Blind, Parallel Group, Dose-Response Study to Evaluate the Efficacy and Safety of Two Doses of Topiramate Compared to Placebo and Propranolol in the Prophylaxis of Migraine.

Coordinating Investigator: [redacted] M.D. - [redacted] Germany

Publication (Reference): None

Study Initiation/Completion Dates: 17 April 2001 to 11 April 2002 | **Phase of development:** 3

Objectives: The primary objective of this trial was to evaluate the safety and efficacy of 2 doses of topiramate (100 and 200 mg/day) compared to placebo in migraine prophylaxis. Secondary objectives were to assess the dose-response relationship for topiramate, to evaluate the relative efficacy of topiramate in migraine prophylaxis compared with propranolol, 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, parallel-group, multicenter trial conducted in 13 countries outside the U.S. evaluated the efficacy and safety of 2 doses of topiramate (100 and 200 mg/day) versus placebo and propranolol 160 mg/day for migraine prophylaxis. The trial included 4 phases: baseline, core double-blind, blinded extension, and taper/exit. Only the data collected through the end of the core 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 and 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 100 mg/day (TPM 100), topiramate 200 mg/day (TPM 200), propranolol 160 mg/day, or placebo. The core double-blind phase was divided into 2 periods: titration (8 weeks) and maintenance (18 weeks). For subjects assigned to receive TPM, the initial daily dose was topiramate 25 mg/day, while for subjects assigned to receive propranolol, the initial daily dose was propranolol 20 mg/day. The dose of study medication was titrated upwards in weekly increments of 25 mg/day for TPM and 20 mg/day for propranolol 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 core double-blind phase. Subjects were considered to have completed the core double-blind phase if they completed all 26 weeks of core 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 an up to 7-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 575 subjects were randomized; of these, 568 contributed efficacy data after randomization and were included in the intent-to-treat population for the efficacy analyses and 570 contributed to 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 12 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 capsules (Batch No. R10676, R10679, R10681, R10829). Topiramate was administered orally twice a day, except during the first week of titration.

Duration of Treatment: The planned duration of core double-blind treatment was 26 weeks.

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Reference Therapy, Dose and Mode of Administration, Batch No.: Propranolol was supplied as matching capsules (each containing 2, 10-mg tablets) (Batch No. R10662, R10684, R10832), while placebo was supplied as matching capsules (Batch No. R10682, R10834, R10835, R10836, R10837). Both reference therapies were administered orally twice a day, except during the first week of titration.

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 core 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 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 for the diagnosis of migraine); iv) change in the average monthly rate of rescue medication use; v) change in number of migraine days per month; and vi) HRQOL measured 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. Efficacy of topiramate relative to that of propranolol was evaluated with respect to the primary efficacy variable and all secondary variables except the onset of action.

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, 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. Treatment comparisons between the topiramate groups and placebo were assessed by a step-down procedure, where at each step, the Tukey-Ciminera-Heyse trend test was performed 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, rate of 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 each topiramate treatment group by evaluating the monthly pairwise comparison between the topiramate treatment group and placebo in the cumulative monthly migraine period rate. The onset of action was determined for each topiramate treatment group by comparing to the placebo group 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 topiramate dose group. . Summary statistics and 95% confidence intervals were examined for the comparison between the topiramate and propranolol treatment groups. The percent change in body weight from baseline to the end of the core double-blind phase was analyzed using a linear model with treatment as a factor; differences between placebo and each topiramate group were evaluated using unadjusted pairwise comparisons.

SUMMARY – CONCLUSIONS

PHARMACOKINETICS: The plasma concentrations of topiramate at the final visit were dose-dependent, averaging 3.4 µg/mL in the TPM 100 group and 5.1 µg/mL in the TPM 200 group.

EFFICACY RESULTS: A statistically significant monotonic dose-response relationship with respect to the change from baseline to the core-double blind phase in the average monthly migraine period rate was not observed among the placebo, TPM 100, and TPM 200 groups due to the high dropout rate in the TPM 200 group and therefore the difference between the TPM 200 group and placebo was not considered statistically significant. Consequently, the predefined step down procedure analysis stopped with no further testing.

SYNOPSIS (CONTINUED)

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EFFICACY RESULTS (Continued): Based on pairwise comparisons, the TPM 100 group had a greater reduction in the average monthly migraine period rate compared to the placebo group (p=0.011). Comparison of mean changes between the topiramate groups showed that the TPM 100 group had a greater reduction than the TPM 200 group in average monthly migraine period rate from baseline to the double-blind phase. Topiramate at a dose of 100 mg/day was effective compared to placebo in the prophylaxis of migraine as measured by the mean reduction in migraine days (p = 0.026), rate of rescue medication use (p = 0.029), and a 50% or greater decrease in the average monthly migraine period rate (responder rate; p = 0.010). The effect of topiramate 200 mg/day was seen in a statistically significantly higher responder rate compared with placebo (p = 0.028). The onset of the effect of topiramate 100 mg/day in reduction of average migraine period rate was shown to begin at Month 1. Plots of the cumulative response rate showed that no matter how the cutoff for a responder was defined, the TPM 100 and 200 groups had a consistently higher response rate than the placebo group. In a dose response analysis, the TPM 100 group showed better efficacy than the TPM 200 group. The difference between the TPM 100 and TPM 200 groups marginally approached significance (p = 0.072). There was no statistically significant difference in the average monthly migraine attack rate between either topiramate group and placebo. The average monthly migraine duration decreased from baseline by 0.8 days in the TPM 100 group and 0.5 days in the TPM 200 group, compared with a decrease of 0.4 days in the placebo group. Analysis of HRQOL measures showed no statistically significant improvements in the SF-36 Role Physical or Vitality domains for either of the topiramate groups compared with placebo. The TPM 100 group showed a significant improvement in the MSQ Role Restrictive and Role Prevention domains while the TPM 200 group showed no significant improvements for these domains.

Summary of Primary Efficacy and Key Secondary Efficacy Values: Topiramate vs. Placebo
(Study TOPMAT-MIGR-003: Intent-to-Treat Population)

Efficacy Endpoint	Placebo	TPM 100 mg/day		TPM 200 mg/day	
Migraine Period Rate	**-0.8**	**-1.6**	*****	**-1.1**	**NS**
Responder Rate, %	22%	37%	*	35%	*
Onset of Action (at Month 1)	0.0	-0.7	*	-0.7	NS
Migraine Attack Rate	-0.8	-1.1	NS	-1.1	NS
Rescue Medication Use (Days)	-0.8	-1.5	*	-0.9	NS
Migraine Days	-1.1	-1.8	*	-1.3	NS

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

The comparisons between the topiramate groups and the propranolol group for the primary and secondary efficacy variables are shown below. Topiramate 100 mg/day was shown to be comparable to propranolol (160 mg/day) in the mean reduction of the average monthly migraine period rate, migraine attack rate, rate of rescue medication use, and migraine days. The TPM 100 group was similar to the PROP 160 group with respect to the decrease in average monthly migraine period rate (both decreased by 1.6). The TPM 100 and PROP 160 groups had similar decreases in migraine attack rate, rate of rescue medication use, and number of migraine days. The PROP 160 group had a higher responder rate than the TPM 100 group (43% and 37%, respectively).

Summary of Primary Efficacy and Key Secondary Efficacy Values: Topiramate vs. Propranolol
(Study TOPMAT-MIGR-003: Intent-to-Treat Population)

Efficacy Endpoint	TPM 100 mg/day	TPM 200 mg/day	PROP 160 mg/day
Migraine Period Rate	**-1.6**	**-1.1**	**-1.6**
Responder Rate, %	37%	35%	43%
Migraine Attack Rate	-1.1	-1.1	-1.3
Rescue Medication Use (Days)	-1.5	-0.9	-1.6
Migraine Days	-1.8	-1.3	-1.9

All values are the least squares mean changes from baseline to the core double-blind phase except for the responder rate, see text for definitions and analysis methods.

The mean reductions in the severity of migraines and migraine-associated symptoms (nausea, photophobia, and phonophobia) were comparable among all treatment groups and the propranolol group. Statistically significant improvements in the SF-36 Vitality domain were found in the TPM 200 group (p=0.003) compared with propranolol but not in the TPM 100 group. There were no statistically significant differences in the SF-36 Role Physical, or MSQ Role Restrictive and Role Prevention domains for either topiramate group versus propranolol.

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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. There were no deaths in the core double-blind phase of this trial. There were 5 subjects in the placebo group, 2 in the PROP 160 group, and 10 topiramate-treated subjects (8 and 2 in the TPM 100 and TPM 200 group, respectively) with serious adverse events, however, 1 of the events in the TPM 100 group was reported as a serious adverse event in error. Three topiramate-treated subjects discontinued due to serious adverse events that were considered possibly or very likely to be related to topiramate. Within the safety population, limiting adverse events occurred most frequently in the TPM 200 group (44%), and in 28%, 20%, and 10% of subjects in the TPM 100, PROP 160, and placebo groups, respectively. The most common (occurring in ≥2% of subjects in either topiramate group) events leading to discontinuation of topiramate therapy included difficulty with concentration and attention, difficulty with memory, mood problems, insomnia, anorexia, depression, anxiety, paresthesia, hypoesthesia, vertigo, language problems, headache, dizziness, fatigue, asthenia, nausea, abdominal pain, diarrhea, weight decrease, dyspepsia, taste perversion, and abnormal vision. There were no clinically important changes in clinical laboratory tests of liver function, renal function, and hematologic parameters or abnormalities in vital sign measurements or neurologic examinations. The safety profile of topiramate 100 mg/day was comparable to propranolol 160 mg/day.

Incidence of the Most Common[a] Treatment-Emergent Adverse Events by Preferred Term
(Study TOPMAT-MIGR-003: Safety Population)

Body System Preferred Term	**Placebo** (N=143) n (%)	**TPM 100 mg/day** (N=141) n (%)	**TPM 200 mg/day** (N=144) n (%)	**PROP 160 mg/day** (N=142) n (%)
Central & Peripheral Nervous System				
Paresthesia	9 (6)	77 (55)	81 (56)	17 (12)
Dizziness	9 (6)	13 (9)	14 (10)	17 (12)
Psychiatric				
Anorexia	8 (6)	24 (17)	20 (14)	4 (3)
Difficulty with concentration/Attention	6 (4)	13 (9)	22 (15)	7 (5)
Insomnia	14 (10)	10 (7)	14 (10)	18 (13)
Depression	9 (6)	9 (6)	15 (10)	6 (4)
Other Body Systems				
Fatigue	22 (15)	27 (19)	35 (24)	31 (22)
Nausea	11 (8)	19 (13)	25 (17)	18 (13)
Abdominal pain	11 (8)	16 (11)	16 (11)	11 (8)
Diarrhea	4 (3)	16 (11)	15 (10)	4 (3)
Upper respiratory tract infection	21 (15)	21 (15)	16 (11)	25 (18)
Taste perversion	2 (1)	7 (5)	20 (14)	0

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

CONCLUSION: A statistically significant monotonic dose-response relationship in change from baseline to the core double-blind phase in average monthly migraine period rate was not observed among the placebo, TPM 100, and TPM 200 groups due to a high drop out rate in the TPM 200 group, however, the findings of this study demonstrated that topiramate at a dose of 100 mg/day was superior to placebo. TPM 100 was also shown to be effective compared to placebo in the prophylaxis of migraine as measured by the mean reduction in the average monthly migraine days, rate of rescue medication use, and a 50% or greater decrease in the average monthly migraine period rate (responder rate). The TPM 100 and PROP 160 groups were similar with regard to change from baseline to core double-blind phase in average monthly migraine period rate and other secondary efficacy variables. Topiramate 200 mg/day had a statistically significantly higher responder rate compared with placebo. The tolerability profiles demonstrated that topiramate 100 mg/day was better tolerated than topiramate 200 mg/day, and was comparable to propranolol 160 mg/day. No unusual or unexpected safety risks were found with topiramate therapy in subjects with migraine.

Date of the report: 27 November 2002